IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Krause et al.
U.S. Patent No.:	9,114,166
Issue Date:	August 25, 2015
Appl. Serial No.:	14/558,182
Filing Date:	December 2, 2014
Title:	FORMULATION OF HUMAN ANTIBODIES FOR TREATING TNF-α ASSOCIATED DISORDERS

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PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 9,114,166 PURSUANT TO 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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1003	U.S. Prosecution History S.N. 14/558,182 (U.S. Patent 9,114,166).
1004	U.S. Prosecution History S.N. 10/222,140 (Abandoned).
1005	Supplemental Amendment and Response, filed February 13, 2012 in U.S. Prosecution History S.N. 10/525,292 (U.S. Patent 8,216,583).
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I. INTRODUCTION

Coherus BioSciences Inc. ("Petitioner" or "Coherus") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 of claims 1–4, 6–10, 13–16, 23–26, and 28 of U.S. Patent No. 9,114,166 ("the '166 patent"). Review should be instituted because there is a reasonable likelihood that Coherus will prevail with respect to at least one challenged claim.

A. The '166 Patent is Overbroad and Unpatentable

Claim 1 of the '166 patent stakes a claim to:

- A stable liquid aqueous pharmaceutical formulation
- comprising 50 mg/ml of the light chain and heavy chain variable regions of an anti-TNFα antibody (the IgG_1 antibody D2E7), and
- a buffer system;
- where the formulation is isotonic and suitable for subcutaneous injection, and
- has a pH range between 4.0 and 8.0.

The breadth of this claim is remarkable as it recites nothing more than a desired outcome (a stable formulation) that would essentially cover ***any*** pH buffered liquid subcutaneous formulation containing 50 mg/ml of the IgG_1 antibody D2E7. The requirements for tonicity and buffered pH control over an expansive range lend nothing to patentability. Based on the state of the art as of the priority date (August 16, 2002), these were conventional and routinely

optimized attributes of all physiologically-acceptable liquid pharmaceutical formulations intended for subcutaneous injection. (EX1002 ¶¶64, 80–82.)

In fact, a liquid subcutaneous formulation lacking isotonicity or having a pH outside the range of claim 1 would have been unusual. (*See* EX1025 at 182 ("If a protein drug is to be administered … subcutaneously … there are strict isotonicity and pH considerations ….").) These attributes deserve no inventive credit toward the achievement of stability. Nor can the challenged dependent claims cure the overbreadth of claim 1, as they merely represent a list of the most commonly used excipients and conventional pH ranges that were routinely optimized by persons skilled in the art. Elucidation of the appropriate pH range for a stabilized antibody in solution was (and still is) a standard and routine step completed in the early stages of protein formulation development. (EX1002 ¶91.)

Applying the basic teachings in the art, a person of ordinary skill in the art ("POSA") would have had a reasonable expectation of success in attaining the '166 patent's claimed formulations because the prior art provided compelling motivation to produce the formulations and taught precisely how to do it. (*Id.* ¶¶84, 129, 148-150.)

1. The Challenged Claims are Obvious

The administration of the IgG_1 antibody "D2E7" to treat rheumatoid arthritis was described in prior art publications. One of these, the van de Putte abstract,

reported the results of a D2E7 clinical trial and taught that 20 mg, 40 mg, and 80 mg fixed-doses of D2E7 were safe and effective in treating rheumatoid arthritis ("RA") when administered weekly by subcutaneous injection for a period of at least six months. (*Id.* ¶¶56, 64–65; EX1007.) From van de Putte, a POSA would have understood that these fixed-dosages of D2E7 had been formulated into stable, isotonic, and appropriately buffered single-use subcutaneous injections. (EX1002 ¶¶64, 83.) Although the volume of each "subcutaneous self-injection" was not disclosed in van de Putte, it was well-known that the standard volume of a subcutaneous injection was 0.5 to 1.0 ml. (*Id.* ¶¶71–73.) A POSA would have applied this standard injection volume to the fixed-dose amounts of D2E7 described in van de Putte and concluded that the claimed formulations of the '166 patent could be and had been achieved. (*Id.* ¶¶75, 148–50.)

The only remaining question was how to make these D2E7 formulations, and, as AbbVie previously recognized, the Relton patent provided the answer. It taught stable, isotonic, subcutaneous formulations containing immunoglobulins at the antibody concentration range of ~1 mg/ml to over 100 mg/ml. (*Id.* ¶¶118–127.) Tellingly, Relton indicated that its teachings were "most preferably" applied to IgG_1 antibodies, the subclass to which D2E7 belongs. (*Id.* ¶119; EX1006 at 3:25–27.) AbbVie has acknowledged these teachings. In European opposition

proceedings to the protein formulation claims in EP1324776, AbbVie[1] argued in June 2010 that Relton anticipated a claim to "[a] stable liquid formulation comprising an immunoglobulin in an amount of at least 80 mg/ml and a salt and/or buffer …" which is for "subcutaneous administration." (EX1020 at 6-7, 10–12 *citing* EX1019 at 20-21) (emphasis added.)

The sole difference between Relton and the challenged claims of the '166 patent is the specific IgG_1 antibody used in the liquid formulations. (EX1002 ¶¶150, 160.) But merely substituting one IgG_1 antibody for another in a formulation does not create a patentable invention. AbbVie claimed in the priority application (filed August 16, 2002) that its liquid formulation would work for *all* antibodies, not just D2E7. (*See* EX1004 at 37 (claim 1 stating "[a] liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of *an antibody* in a buffered solution …" regardless of the antibody subclass and whether it was directed to anti-TNFα) (emphasis added).) It cannot be the case that each IgG_1 antibody substituted into Relton's formulations creates a patentable invention.

[1] The statements were made in June 2010 by Abbott Bioresearch Center Patent Department, which was part of Abbott Laboratories. Abbott owned HUMIRA® at that time. On January 1, 2013, Abbott split into two companies, one of which was AbbVie. (EX1002 ¶23.)

Relton teaches high-concentration, liquid IgG_1 formulations for subcutaneous injection. It discloses exemplary liquid formulations that, based on aggregation data, appear equally stable at antibody concentrations ranging from below the 50 mg/ml concentration claimed in the '166 patent, to concentrations over 100 mg/ml. (EX1002 ¶¶120–27.) Relton states that, due to the low injection volume, the "preferred concentrations for subcutaneous preparations are … in the range of 100 mg/ml to 200 mg/ml …" (EX1006 at 4:18–20.) However, its data tables disclose a broader concentration range, including 50 mg/ml, of stable IgG_1 liquid formulations. (*Id.* at Examples 1–4.) In addition, Relton's formulations include the excipients listed in the challenged dependent claims: namely, sodium chloride as a tonicity agent, polysorbate-80 as a surfactant, a chelating agent, and numerous buffers resulting in formulations with a pH between 4 and 8. (*Id.* at 3:59–60; 4:24–42; Example 4.)

Relton received inadequate critical review during prosecution of the '166 patent. The Examiner relied on Relton to reject the pending claims by stating, incorrectly, that the reference taught liquid formulations that contained an antibody concentration of at least 100 mg/ml. (Relton also taught formulations with concentrations encompassing 50 mg/ml.) *See infra* Section VI (discussion of prosecution history). AbbVie did not dispute the Examiner's description of Relton. Instead, AbbVie narrowed the concentration of D2E7 from the range of 20–150

mg/ml in the pending claims to a concentration of 50 mg/ml. AbbVie offered no explanation as to how the 50 mg/ml D2E7 concentration would distinguish Relton, and the Examiner did not provide any reasons for her decision to allow the amended claims over this reference. Again, there is only ***one*** difference between Relton's formulation components and the challenged claims: the particular IgG_1 antibody (D2E7) recited. Other prior art discussed in this Petition will show that a POSA would have had no reason to suspect that making a stable, buffered, isotonic formulation of D2E7 would have posed any greater difficulty than making a similar formulation of any other IgG_1 antibody.

2. Motivation to Combine van de Putte with Relton

A POSA would have been motivated to combine van de Putte with Relton and arrive at the claimed formulation of the '166 patent because: (i) van de Putte taught that weekly administration of 20, 40, or 80 mg D2E7 by subcutaneous injection was safe and effective in treating patients with RA; and (ii) the art taught the importance of limiting subcutaneous injection volumes to 0.5 to 1.0 ml. (EX1002 ¶71.) With regard to conventional injection volumes, it was well-established in the prior art that a subcutaneous injection should be delivered in a volume of 0.5–1.0 ml to reduce patient discomfort at the injection site. (*See infra* pp. 25-27.) Relton corroborates this, stating that a subcutaneous dose "must be low in volume … approximately 1 ml in volume per dose," and that given this

small volume, "*a concentrated preparation will invariably be necessary*." (EX1006 at 4:12–18 (emphasis added).) Relton further teaches that such formulations would be stable. Based on van de Putte's reported effectiveness of treating RA with a weekly subcutaneous injection containing 20, 40, or 80 mg of D2E7, a POSA would have had compelling motivation to formulate these fixed-doses of D2E7 for subcutaneous injection in an art-preferred volume between 0.5 and 1.0 ml. Doing so would have required the POSA to select a target D2E7 concentration from the range of 20 mg/ml to 160 mg/ml. (EX1002 ¶74.)

Total Dose	**Concentration in 1.0 ml**	**Concentration in 0.5 ml**
20 mg	20 mg/ml	40 mg/ml
40 mg	40 mg/ml	80 mg/ml
80 mg	80 mg/ml	160 mg/ml

After selecting any concentration in this range, a POSA would have applied Relton's teachings to prepare a subcutaneous formulation with that concentration and all the other claim limitations, including the initial elucidation of the pH stability range of D2E7. A POSA would have had a reasonable expectation of success in preparing this formulation. Thus, challenged claims 1–4, 6–10, 13–16, 23–26, and 28 are obvious and unpatentable under 35 U.S.C. § 103. Petitioner respectfully requests the Board to institute *inter partes* review of these claims and to cancel them.

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 '166 patent is the subject of the following judicial or administrative matters, which may affect, or be affected by, a decision in this proceeding: (1) *Amgen Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2015-01514 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 8,916,157, dated June 26, 2015; and (2) *Amgen Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2015-01517 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 8,916,158, dated June 26, 2015. On January 14, 2016, the Board issued decisions denying institution for Case Nos. IPR2015-01514 and IPR2015-01517.

AbbVie is the owner of the following U.S. applications and patents that claim the benefit of the priority of the filing of the '166 patent or that the '166 patent claims priority from: U.S. Patent Nos. 8,216,583; 8,795,670; 8,802,100; 8,802,101; 8,802,102; 8,911,741; 8,916,157; 8,916,158; 8,932,591; 8,940,305; 9,220,781; 9,272,041; 9,272,042; 9,289,497; 9,295,725; 9,302,011; 9,327,032 and U.S. Application Nos. 10/222,140 and 15/095,393.

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

Petitioner 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. Petitioner consents to electronic service at these same email addresses.

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

Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 10-0460 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)

Petitioner certifies that the '166 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR.

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

Petitioner requests *inter partes* review of claims 1–4, 6–10, 13–16, 23–26, and 28 on the ground set forth in the following table and requests that each claim be found unpatentable.

Ground	'166 Patent Claims	Basis for Unpatentability
Ground 1	1–4, 6–10, 13–16, 23–26, and 28	Obvious under 35 U.S.C. § 103 over the combination of van de Putte (EX1007) with Relton (EX1006).

The van de Putte and Relton references are prior art to the '166 patent under 35 U.S.C. § 102(b) because each issued or published more than one year before the earliest potential effective filing date of the '166 patent. The ground for invalidity is described in detail in Section X, *infra*, and is supported by the Declaration of Mark Manning, Ph.D. (EX1002). As a skilled practitioner in the relevant field, Dr. Manning is qualified to provide opinions as to what a POSA would have understood, known, or concluded as of August 16, 2002. (EX1002 ¶¶1–9.) The ground is also supported by Brian Reisetter, Ph.D., a pharmaceutical marketing consultant, who offers an opinion on commercial success. (EX1066.)

V. BACKGROUND

Tumor necrosis factor alpha (TNFα) is a protein made by the body, called a cytokine, that is involved in the regulation of immune cells. (EX1002 ¶18.) An excessive amount of TNFα in the body can lead to inflammation and other symptoms associated with autoimmune diseases, such as RA. A therapeutic strategy for inhibiting or counteracting TNFα activity is to dose patients with an antibody that binds to TNFα with high affinity. (*Id.*) One such antibody is adalimumab (also referred to as "D2E7"). (*Id.* ¶19.) Adalimumab, the active pharmaceutical ingredient in HUMIRA®, is a fully-human recombinant IgG_1 monoclonal antibody. (*Id.* ¶21; EX1011 at 1.)

By August 2002, an antibody designated as D2E7 had been tested in clinical trials. (EX1002 ¶¶54–67 (discussing published reports of D2E7 clinical trials).) Fixed-doses (i.e., total-body doses) of 20, 40, and 80 mg D2E7 had been shown to be safe and effective in treating rheumatoid arthritis when administered weekly by "subcutaneous (s.c.) self injection." (*Id.* ¶¶63–67 (discussing van de Putte and Sorbera).) These promising clinical results provided the motivation to prepare a formulation that would deliver a fixed-dose of D2E7 in a volume suitable for subcutaneous injection. (*Id.* ¶68.) The challenged claims are directed to such subcutaneous formulations of 50 mg/ml D2E7, which also include well-known and routinely used formulation excipients.

When developing a new liquid antibody formulation, a POSA would have first looked for guidance in the published literature to see if liquid formulations already existed for antibodies in the same subclass (here, IgG_1). (*Id.* ¶85.) If any existed, the skilled artisan would have used the formulation details provided in the reference as a guidepost to formulate the protein of interest. That is the situation here. The Relton patent teaches that stable, high concentration (up to and exceeding 100 mg/ml) IgG_1 antibody liquid formulations for subcutaneous dosing can be achieved. A POSA would have been motivated to apply Relton's teachings to the D2E7 antibody and would have had a reasonable expectation of success in making the formulations of the challenged claims. (EX1002 ¶¶118, 129.)

There is nothing special or surprising about the formulations in the challenged claims. (*Id.* ¶¶ 170, 180.) In solution, D2E7 behaves like a typical IgG_1 antibody and there is nothing unexpected about its formulations. Nor is there any described criticality to the claimed 50 mg/ml concentration. The science of rationally designing stable, liquid protein formulations was well-established by August 2002. (*See, e.g.*, EX1002 ¶¶85–86; EX1025 (Carpenter & Manning's RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS).) This rational approach to making stable liquid protein formulations involved determining, early in development, the appropriate physiologically-acceptable and tolerable pH range. (EX1002 ¶¶91–93.) This was done based on pH-stability studies, the protein's

amino acid sequence, and its isoelectric point. (*Id.* ¶¶94–95, 100.) After the pH range was identified, a buffer system was selected to maintain that range, and excipients were picked from a finite list of commonly used and approved materials, such as tonicity agents, surfactants, and chelating agents. (*Id.* ¶103.)

The challenged claims are the expected result of this rational approach. They merely recite art-required formulation properties, along with the most common excipients routinely added to protein formulations. For example, that the claims require an isotonic formulation is not a reflection of creativity or innovation, but of a known requirement that formulations administered to a human subcutaneously must be isotonic. (*Id.* ¶¶80–82; EX1006 at 4:24-25; EX1031 at 317.) Similarly, all the claimed pH ranges reflect routine optimization done to address the art-recognized goal of increasing protein solubility and inhibiting the most common form of chemical instability known to affect IgG_1 antibodies like D2E7. (EX1002 ¶¶89-90; 95-102.) Finally, the D2E7 concentration of 50 mg/ml is not only within the concentration range taught by Relton, but also a predictable design choice that accommodated the standard volume for subcutaneous injections (0.5–1.0 ml). (*Id.* ¶¶118, 133.)

VI. THE '166 PATENT AND ITS PROSECUTION HISTORY

A. The '166 Patent

The '166 patent, entitled "Formulation of Human Antibodies For Treating TNF-α Associated Disorders," is directed to pharmaceutical formulations of antibodies suitable for therapeutic use to inhibit or counteract detrimental human TNFα activity. (EX1001 at 3:14–21). It claims liquid formulations containing a human IgG_1 antibody that includes the variable regions of the light and heavy chains of D2E7 and a buffer system in a physiologically-acceptable pH range of between 4 and 8. (*See id.* at Claim 1.) Certain dependent claims of the '166 patent require that the formulation also include a tonicity agent, a surfactant, and a chelating agent. The patent includes three examples, none of which fall within the scope of any of the challenged claims. (*Id.* at 21:41-24:25; EX1002 ¶169.)

B. The Prosecution History

The '166 patent issued on August 25, 2015, from U.S. Application No. 14/558,182, filed on December 2, 2014, and claims priority to U.S. Application No. 10/222,140, filed on August 16, 2002. The Examiner initially rejected all 30 of the presented claims as being obvious over the Lam '586 patent (EX1012) and the Salfeld '382 patent (EX1013) and also rejected all the claims for obviousness-type double patenting over eleven of the '166 patent's family members. (EX1003 at 116–134 (Feb. 5, 2015, non-final rejection).) In response, AbbVie filed terminal disclaimers and argued that the cited references would not have provided a POSA

with an expectation of successfully making the claimed invention. (*Id.* at 161–172, 179–183 (Feb. 12, 2015, response and disclaimers).)

The Examiner then rejected the pending claims for being obvious over Relton (EX1006) in view of Salfeld (EX1013). (EX1003 at 196–202 (April 29, 2015, non-final rejection).) In response, AbbVie amended the pending D2E7 claim range from 20–150 mg/ml to a 50 mg/ml concentration. (*Id.* at 214 (May 4, 2015, response).) Tellingly, AbbVie did not argue that the Relton and/or Salfeld references failed to provide an expectation of success in making the claimed invention. Nor could it, given AbbVie's own statements in the European opposition to EP1324776 that the same Relton publication anticipated claims directed to similar subject matter. (EX1020 at 6-7, 10–12.) The Examiner then allowed the application, without explaining how the amendment addressed the rejection. (EX1003 at 644 (July 14, 2015, notice of allowance).)

C. Representative Claims and Claim Groupings

The '166 patent includes one broad independent claim directed to an antibody formulation comprising 50 mg/ml of a human IgG_1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody having the light chain variable region and the heavy chain variable region of D2E7, a buffer system with a pH of 4.0 to 8.0, that is isotonic and suitable for single-use subcutaneous injection. (EX1001 at Claim 1.)

Most of the challenged claims limit one of these elements. Claims 2–3 and 14–15 limit the buffer system to an organic acid. Claims 4 and 6–8 limit the pH of the formulation to specific ranges. Claim 9 purports to limit the second element to the D2E7 antibody to the extent not done so in the independent claim. Claims 10 and 16 require the presence of a tonicity agent, and claims 13 and 23 require that tonicity agent be sodium chloride. Claims 24–26 require addition of a surfactant and, specifically, polysorbate-80. Claim 28 requires a chelating agent.

VII. LEVEL OF SKILL IN THE ART

As of August 16, 2002, the education and experience level of a POSA who would be asked to design a pharmaceutical antibody formulation would have had an advanced degree in biology, biochemistry, or chemistry (or a related discipline). This person also would have had at least two years of experience preparing stable formulations of proteins suitable for therapeutic use. (EX1002 ¶42.)

VIII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

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 In re Cuozzo Speed Techs. LLC*, 793 F.3d 1268, 1276–79 (Fed. Cir. 2015). Thus, the words of the challenged claims are given their ordinary and customary meaning as understood by one of skill in the art at the time of the invention in the context of the entire disclosure. *In re Translogic, Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Except as set forth below, the terms in the challenged claims should be given their plain meaning.

A. "Stable"

The preamble to claim 1 recites a "stable" formulation. If the Board decides that the preamble is a limitation and the construction of "stable" is necessary, then it should use the definition provided in the '166 patent as a formulation "in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." (EX1001 at 7:24–65.) This definition reflects that the IgG_1 antibody is sufficiently stable in a liquid formulation administered subcutaneously to a human such that the formulation is biologically effective and not significantly toxic. (*Id.* at 7:15–23 (reading "stable" in the context of the phrase it modifies, i.e., "pharmaceutical formulation").) The definition would include formulations used in clinical trials wherein the D2E7 liquid formulation was given to patients subcutaneously, since a POSA would have understood that it would be improper, and dangerous, to administer an unstable formulation to a patient. (EX1002 ¶45.) Notably, this definition is different, and less stringent, than the stability required for FDA approval.

This common-sense definition is supported by AbbVie's admission that the IgG_1 subcutaneous formulations in Relton are "stable." In its June 2010 opposition

to the EP1324776 patent issued to Genentech (EX1019)[2], AbbVie stated that Relton teaches liquid formulations for subcutaneous administration that "have a low aggregate formation capability," and thus Relton anticipates claims directed to "[a] stable liquid formulation comprising an immunoglobulin …." (EX1020 at 6-7, 10–12 (AbbVie Opposition, dated June 16, 2010, noting that reference "D1" (EX1022, Relton's published PCT application WO 97/45140) anticipates the claimed subject matter.)

B. "Human anti-human Tumor Necrosis alpha (TNFα) IgG_1 antibody"

Many portions of this claim term are defined in the '166 patent. For example, "antibody" refers to "immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds." (EX1001 at 9:38–41.) It defines "human antibody" to mean immunoglobulin molecules "derived from human germline immunoglobulin sequences" (*id.* at 10:47–49), and "human TNFα" is well understood in the art (*id.* at 9:25–33). These definitions should be applied here.

The term "IgG_1" is not defined in the '166 patent. However, a POSA would have known that IgG_1 refers to a specific subclass of the immunoglobulin G

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2 EP1324776 defines "stable" by using essentially the same language as the '166 patent. (Compare EX1019 at ¶ [0044] and EX1001 at 7:24–65.)

antibodies. (EX1002 ¶47.) Relton, for example, indicates that immunoglobulins are divided into classes known as "IgM, IgG, IgA, IgE and IgD." (EX1006 at 3:19–21.) It further indicates that the "class IgG" includes the "sub-classes IgG_1, IgG_2, IgG_3, and IgG_4." (*Id.* at 3:22–25.) These definitions should be applied here.

C. "Buffer," "tonicity agent," "surfactant," and "chelating agent."

The '166 patent defines "buffer" as a "solution that resists changes in pH." (EX1001 at 8:32–40; EX1002 ¶48.) This definition should be applied here. The claims of the '166 patent provide examples of what constitutes a tonicity agent and surfactant. Specifically, Claim 13 states that "sodium chloride" is a "tonicity agent" and Claim 26 indicates that "polysorbate-80" is a "surfactant." Because both of these excipients are disclosed in Relton, defining tonicity agent and surfactant by these examples is sufficient for purposes of this Petition. Finally, the term "chelating agent" is well understood in the art. A "chelating agent" is a substance, such as EDTA, that can form several bonds to a single metal ion. (EX1002 ¶48; EX1029 at 67; EX1052 at 157.)

D. "Light chain variable region and the heavy chain variable region of D2E7" and "D2E7"

The terms "D2E7" and the "light chain variable region and heavy chain variable region of D2E7" are not defined in the '166 patent. However, the construction of these terms is unnecessary here. The van de Putte reference discloses that 20, 40, or 80 mg doses of "D2E7" were administered to patients once

a week over a period of six months. Many other prior art references discussed herein also refer to the administration of "D2E7", which encompasses both D2E7 and the broader claims directed to the light chain variable region and heavy chain variable region of D2E7. (*See, e.g.*, EX1013.)

AbbVie recently took the position that the complete heavy and light chain sequences of D2E7 were publicly available before August 16, 2002. (EX1085 (Grounds of Appeal at 4–5, dated 2/23/16) citing EX1086 (CAS® Registry entry 331731-18-1, dated 4/18/01, at 2–3).) We do not address the merits of that contention here. However, if a definition is required for this proceeding, then Petitioner will, solely for the purposes of this proceeding, accept as true AbbVie's representation that the complete sequence data for the heavy and light chains of D2E7 are as disclosed in CAS® Registry entry 331731-18-1. (EX1086 at 2-3.)

IX. IDENTIFICATION AND RELEVANCE OF THE SUPPORTING EVIDENCE UPON WHICH THE CHALLENGE IS BASED (37 C.F.R. § 42.104(b)(5))

The obviousness challenge is based on a combination of the prior art outlined below, which teaches every element of the claimed invention, a motivation to create it, and a reasonable expectation of success in doing so.

A. van de Putte (EX1007) and other Clinical Trials

In 2000, van de Putte published findings from a clinical study in which D2E7 was delivered to humans weekly by subcutaneous injection over a period of

6 months. (EX1007; EX1002 ¶64.) This study was one of many discussed in a July 2001 review article by Sorbera, which revealed a move from body weight-based doses to a total-body dose (independent of weight). (*See* EX1008 at 641-645 (describing multiple clinical studies, including van de Putte); EX1002 ¶67.) Although key studies are summarized in this Petition, Dr. Manning describes in his declaration these and additional D2E7 clinical studies to provide a complete background of the state of the art. (EX1002 ¶¶57–63, 66.)

The initial D2E7 clinical studies used weight-based dosing. In 1998, van de Putte (EX1037) and Rau (EX1038) reported results from trials using intravenous formulations to deliver between 0.5 and 10 mg of D2E7 per kg of body weight. (EX1002 ¶¶57–58.) Also in 1998, Schattenkirchner reported results from trials using subcutaneous injections to deliver 0.5 mg of D2E7 per kg of body weight, concluding that subcutaneous administration of D2E7 at 0.5 mg/kg was "safe and efficacious." (*Id.* ¶59 *citing* EX1039.)

After these initial studies, the D2E7 clinical trial publications disclosed a shift toward total-body dosing. In 1999, for example, van de Putte reported the results of a Phase II dose-finding study in which patients received weekly doses of 20, 40, or 80 mg of D2E7 (independent of body weight) by "subcutaneous (s.c.) self injection for 3 months." (EX1040.) The study concluded that all three doses (20, 40, and 80 mg/week) were "statistically significantly superior to placebo."

(*Id.*; EX1002 ¶63.) Then in 2000, van de Putte reported the long-term efficacy (up to six months) of those same doses. (EX1007, "van de Putte," stating that the 20, 40, and 80 mg D2E7 doses were administered by "subcutaneous (s.c.) self injection.") This report, like the one in 1999, concludes that all three doses "were statistically equally efficacious when given s.c. in patients with active RA" and indicates that the "treatment benefit was stable for all parameters over time." (*Id.*; EX1002 ¶64.)

Sorbera, a July 2001 review article, includes discussion of those fixed-dose studies by van de Putte, including a table describing this reference. (*See* EX1008 at 642–643.) According to that table (Box 2 on p. 643), the 20, 40, and 80 mg doses were given "s.c. 1x/wk x 6 mo." A POSA would have interpreted this description in Sorbera and van de Putte's disclosure of administration by "subcutaneous (s.c.) self injection" to mean that the 20, 40, and 80 mg doses were delivered subcutaneously in single injection, weekly doses for a period of six months. (EX1002 ¶75.) This interpretation would have been confirmed by Kempeni, which described administering 1 mg/kg D2E7 "as a single subcutaneous or intravenous injection" (EX1017 at I-72) and by Lorenz, which described van de Putte as giving a "weekly sc injection," singular, while describing another study as giving "weekly sc injections," plural. (EX1041 at 189.)

Finally, the Sorbera article also interprets van de Putte to show that "[t]he three adalimumab doses [20, 40, and 80 mg/wk] resulted in stable and comparable efficacy parameters over the treatment period" and further indicates that this study demonstrated the "long-term efficacy of adalimumab." (EX1008 at 642.) Thus, Sorbera demonstrates that van de Putte was understood at the relevant time just as it is now. In sum, van de Putte demonstrates that it was known that D2E7 safely and effectively treated RA when delivered by subcutaneous injection, once per week, in 20, 40, or 80 mg doses.

B. Prior Art Liquid Formulations and Volume Limits

A POSA had a strong motivation to formulate proteins for subcutaneous administration in an injection volume of 0.5 to 1.0 ml. The prior art indicated that liquid formulations were the most convenient form of protein and antibody pharmaceuticals for manufacturers and patients alike, and also that subcutaneous formulations were the most convenient liquid forms. (EX1002 ¶¶69-70.) Finally, the art demonstrated that there was a maximum volume (around 1 ml) that could be administered subcutaneously without causing pain and discomfort to the patient. (*Id.* ¶¶71-73; EX1006 at 4:12–18 (stating that subcutaneous injections "must be low in volume for example approximately 1 ml in volume per dose").) Moreover, POSAs also understood that it was desirable to administer the drug in a single injection so that a patient would be stuck with a needle only once. According to

Dr. Manning, this common understanding "is why Relton and other references refer to 1 ml per dose as opposed to 1 ml per injection." (EX1002 ¶71; EX1006 at 4:16-18.)

Liquid Form. As of August 2002, stable liquid protein formulations were the "preferred therapeutic protein formulations" because of the convenience of manufacturing and clinical use. (EX1002 ¶69.) This was well-known in the art. For example, Carpenter & Manning's RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS states that "[l]iquid formulations have been generally preferred due to the convenience of manufacturing and use." (EX1025 at 10.) The book DEVELOPMENT AND MANUFACTURE OF PROTEIN PHARMACEUTICALS provides further evidence. In a chapter "written to provide the basic approaches and techniques used to design and develop dosage forms of proteins," the authors explicitly omit noninjectables. (EX1029 at 48.) A relevant observation in a third treatise drives the point home. PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS states that an "aqueous liquid formulation is the easiest and most economical to handle during manufacturing and is the most convenient for the end-user." (EX1052 at 179.)

Subcutaneous injections. A POSA would have considered subcutaneous injections to be the preferred liquid pharmaceutical form. (EX1002 ¶70.) A subcutaneous injection is superior to intravenous administration because it is

quicker, easier, and less involved (e.g., a subcutaneous dose can be self-administered at home). These advantages were well-known in the art. Relton, for example, states that a "sub-cutaneous preparation has the advantage that it can be self-administered thus avoiding the need for hospitalization for intravenous administration." (EX1006 at 4:21–24.) Requiring trained medical personnel in a clinical environment to administer a dose was expensive and provided an additional reason why self-administered subcutaneous dosing was preferred. Moreover, Aulton's PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN indicates that subcutaneous injections are more "patient friendly" than intravenous injections. (EX1031 at 550.)

Subcutaneous Volume Limitation. A POSA would have known that the volume for a subcutaneous dose should generally be 0.5 to 1.0 ml. (EX1002 ¶¶71–73; *see also* EX1072 at 417 ("Drugs recommended for SC injection include nonirritating aqueous solutions and suspensions contained in 0.5 to 2.0 mL (**target 1 mL or less**) of fluid.") (emphasis added).) The prior art FDA-approved drugs that were administered by subcutaneous injection provide further evidence of this volume limitation. (EX1002 ¶73 (providing a table of more than a dozen 2002 FDA-approved protein products that were subcutaneously administered in a volume between 0.5 and 1.0 ml). This table is reproduced below:

Product	S.C. Injection Volume	Notes
Rebif	0.5 ml	Prefilled syringe intended for s.c. administration
Betaseron	1.0 ml	Lyophilized powder reconstituted in 1.2 ml, and then 1.0 ml is withdrawn for injection.
Actimmune	0.5 ml	Single-dose vial contains 0.5 ml.
Neumega	1.0 ml	Lyophilized powder reconstituted in 1.0 ml of diluent.
Humatrope	0.576 ml	It can be more depending on dosage, but there is a pen which appears to be optional and allows increments of 0.048 ml to be delivered (up to 12).
Neulasta	0.6 ml	Supplied in 0.6 ml prefilled syringes.
Pegasys	1.0 ml	Provided with 1 ml syringes.
PegIntron	0.5 ml	Reconstituted in 0.7 ml; dosing volumes 0.4 or 0.5 ml.
Kineret	1.0 ml	Supplied in 1 ml prefilled syringes.
Aranesp	1.0 ml	Supplied in 1 ml vial.
Epogen	1.0 ml	Single-dose vials are 1 ml.
Procrit	1.0 ml	Single-dose vials are 1 ml.
Enbrel	1.0 ml	Supplied with 1 ml syringe.
Neupogen	0.8 ml	Prefilled syringes of 0.5 ml or 0.8 ml; also available in 1.0 or 1.6 ml vials.
Leukine	1.0 ml	Reconstituted in 1 ml.

(EX1088–90.) These products demonstrate that it was the industry norm to deliver the subcutaneous dose in a single injection. (EX1002 ¶73.)

This is not surprising because the prior art literature consistently pointed to a maximum injection volume of 1.0 ml. (*Id.* ¶72.) Many studies indicated that using a volume below 1.0 ml would reduce discomfort caused by the injection. In 1996, Dr. Jan Jorgensen published findings that the pain of a subcutaneous injection is

related to the solution volume. (EX1026.) The study determined that to optimize patient tolerability the "volume [of a subcutaneous dose] should generally be less than 1.0 ml." (*Id.* at 731.) Relton discloses a similar sentiment, stating that subcutaneous formulations must be "approximately 1 ml per dose." (EX1006 at 4:12–18.) Carpenter & Manning's RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS similarly indicates that "in the case of a subcutaneous injection, there is a maximal volume (~1 mL) that can be given to a patient without discomfort." (EX1025 at 182.)

C. Relton (EX1006)

Relton qualifies as prior art under §102(b) because it issued as a U.S. Patent on June 26, 2001, more than a year prior to the '166 patent's earliest potential priority date of August 16, 2002.

Relton teaches stable subcutaneous IgG_1 formulations at concentrations ranging from ~1 mg/ml to those exceeding 100 mg/ml. (EX1006 at 3:25–28 ("The invention is more preferably applied to a preparation of immunoglobulins of the class IgG_4 and IgG_1, ***most preferably IgG_1")*** (emphasis added); EX1002 ¶¶118-119.) It describes the pH of antibody formulations as generally being from 4 to 9, which, like the challenged claims of the '166 patent, encompasses the pH of essentially all the known protein pharmaceutical products. (EX1006 at 4:24-27; EX1002 ¶131.) Moreover, both its specification and examples indicate a

preference to formulate antibodies under acidic conditions. For example, it describes the optimum pH range as 4.0 to 5.5 (ideally 5.5) for an anti-CD4 antibody and 4 to 6.5 for an anti-CD23 antibody. (EX1006 at 4:30-34; EX1002 ¶¶128-131.) It also states that the desired pH will be different than the isoelectric point (pI) of the antibody. (EX1006 at 4:2–3.) Thus, Relton taught that optimizing the pH was an important initial step in preparing a stable liquid antibody formulation.

Relton also teaches a POSA one way to prepare such formulations, beginning with a low-concentration antibody formulation and increasing the concentration by applying standard ultrafiltration techniques. (EX1002 ¶¶118-119.) More specifically, Relton uses tangential flow filtration to increase the antibody concentration, which had been the formulator's method of choice for performing ultrafiltration since the 1960s. (*Id.*) A POSA would have understood that this technique allowed the antibody concentration to be continuously increased over time, thus allowing access to any concentration simply by stopping the process at the appropriate time interval. (*Id.* ¶127.)

Relton applies this technique in its examples. In Example 1, Relton begins with an IgG_1 antibody (Campath-1H) solution at 16.4 mg/ml and uses ultrafiltration to increase the concentration, collecting samples at 5 hours (34 mg/ml), 6.5 hours (41 mg/ml), 9.5 hours (79 mg/ml), 11.5 hours (106 mg/ml), and

so on. (*Id.* ¶121.) It states that protein recovery "was high up to a concentration of 190 mg/ml, but started to decline markedly above [a concentration of 190 mg/ml] as the viscosity increase led to material sticking to glassware and tubing …." (EX1006 at 6:43–45.) As high as 106 mg/ml, for example, Relton showed 97% protein recovery. (*Id.* at 6:48-55 (Table 1(c)).) The stability of the collected samples was also tested via size-exclusion chromatography and determined to have no more aggregation than the starting formulation. (*Id.* at 7:11–20; EX1002 ¶121.) That means the antibody did not aggregate any more in the 106 mg/ml formulation than it did in the original 16.4 mg/ml formulation; thus indicating to a POSA that the concentrated liquid formulations are stable. (EX1002 ¶123; *see also* EX1020 at 6-7, 10-12(AbbVie stating that Relton teaches "stable liquid formulations").)

Relton repeats the process in Example 2 to demonstrate that another IgG_1 antibody can be concentrated up to about 250 mg/ml, via a process that allows sampling and assessment of intermediate concentrations as described above. (EX1002 ¶122.) This Example begins with an anti-CD4 antibody at a concentration of 13.9 mg/ml and increases the concentration through ultrafiltration while collecting samples like in Example 1. As was the case with Campath-1H, Example 2 showed virtually no increase in protein aggregation at the concentration closest to 50 mg/ml (47.2 mg/ml). (*Id.;* EX1006 at 7:24-9:24.)

In Example 4, Relton focuses on antibody preparations intended for subcutaneous administration. (EX1002 ¶125.) It describes four distinct subcutaneous antibody formulations, including one formulation that contains an acetate buffer, sodium chloride, polysorbate-80, and optionally a chelating agent (EDTA). (EX1006 at Example 4 (formula b in table).) By applying the teachings in the previous examples, the antibody concentrations "could have been increased from 1.5 mg/ml to 50 mg/ml, or even concentrations exceeding 100 mg/ml, while recovering almost all of the protein and without causing aggregation or instability." (Ex 1002 ¶127.) Significantly, the ***only*** difference between the formulation components in Example 4 (formula b) and the challenged claims is the presence of a different IgG_1 antibody, as opposed to the IgG_1 antibody D2E7. (*Id.* ¶128.)

In addition, Relton offers guidance on the desirability of subcutaneous injections and their proper volume requirements. It teaches that formulating an antibody for subcutaneous delivery was desirable because the formulation could be "self-administered thus avoiding the need for hospitalisation for intravenous administration." (EX1006 at 4:21–23.) Given the relatively small volume available for a subcutaneous dose, Relton taught that "a concentrated preparation will invariably be necessary." (*Id.* at 4:16–18; *see also supra* pp. 25-27 (discussing the 1 ml maximum volume for subcutaneous injections).) As detailed herein,

Relton teaches one way of preparing stable and concentrated subcutaneous formulations, though other methods were known in the art.

Additionally, Relton teaches that its disclosed formulations will work for any antibody class, but "most preferably" the IgG_1 subclass to which D2E7 belongs, and provides specific examples of stable, liquid, high concentration formulations. (*Id.* 3:25–27.) The antibody formulations include sodium chloride as a tonicity agent, polysorbate-80 as a surfactant, a chelating agent, and numerous buffers resulting in a pH between 4 and 9. (*Id.* at 3:49–60, 3:67–4:10, 4:24–42, 11:50–12:23; EX1002 ¶¶130-131.) Relton further teaches that the resulting formulations are isotonic, (*id.* at 4:24–25; EX1002 ¶132), and stresses the importance of pH in developing subcutaneous injections (*id.* at 3:64–4:3). It teaches that the pH, and hence the buffer, is selected within a range of pH 4 to 9. (*Id*. at 4:26-27) The exemplary formulations in Relton contain a high concentration of an IgG_1 antibody, ranging up to 100 mg/ml or greater. (*Id.* at 5:40-11:50.)

To be clear, Relton discloses that a subcutaneous volume of injection should not exceed 1 ml and thus the formulation must be concentrated to deliver the necessary therapeutic dose. Although it focuses on stable IgG_1 formulations that exceed 100 mg/ml, Relton also teaches that a range of antibody concentrations (~1 mg/ml to those exceeding 100 mg/ml) are stable. (EX1002 ¶¶118, 120, 127.) A

POSA would have considered Relton to teach this full concentration range of stable IgG_1 antibodies (*Id.* ¶127; *accord* EX1020 at 6-7, 10-12 (AbbVie arguing that Relton's examples anticipate claims to a stable 80 mg/ml antibody formulation in a patent that defined "stable" in essentially the same way as the '166 patent).) Making stable concentrated antibody formulations was not surprising or new; after all, the background section of Relton discloses a 50 mg/ml IgG intravenous formulation that was stable for at least 2.5 years at 5 °C. (EX1006 at 1:26–30).

X. THE CHALLENGED CLAIMS ARE OBVIOUS OVER VAN DE PUTTE IN VIEW OF RELTON

The question of obviousness requires analyzing: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Here, these factors favor a finding of obviousness because the difference between the claimed subject matter and prior art is small, the level of skill in the art was high enough to provide an expectation of success, and the objective evidence of nonobviousness (to the extent it exists) does not overcome the strong *prima facie* case of obviousness.

As the Supreme Court stated in *KSR* "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007). Here, combining familiar elements according to known methods, i.e.,

exchanging one IgG_1 antibody for another in known stable formulations, provided a POSA with a reasonable expectation of success in preparing the formulations of the challenged claims. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). Thus, as discussed herein, the challenged claims are obvious over van de Putte in view of Relton.

A. The prior art provided strong motivation to make the formulations in the challenged claims.

It was well-known that D2E7 effectively treated RA when administered as a weekly fixed-dose of 20, 40, or 80 mg D2E7 by "subcutaneous (s.c.) self injection." (*See supra* pp. 20-23; EX1007; EX1008 at 643.) Thus, a POSA wanting to produce a drug product to treat RA would have been motivated to have that finished drug product deliver 20, 40, or 80 mg D2E7 in a single liquid volume suitable for weekly subcutaneous delivery. (EX1002 ¶¶68, 152.)

A POSA would have been motivated to prepare a stable liquid formulation of D2E7 with a buffer system because liquid formulations were the preferred form of delivering proteins due to the convenience of manufacturing and clinical use. (*See supra* pp. 23-24 (citing three sources); EX1002 ¶69; EX1025 at 10.) A POSA would have further targeted single, subcutaneous injections because they improved patient experience and obviated the need for weekly visits to a medical center.

(*See supra* pp. 24-26 (citing three sources); EX1002 ¶70; EX1006 at 4:21–23 ("A sub-cutaneous preparation has the advantage that it can be self-administered thus avoiding the need for hospitalization for intravenous administration.").) The prior art also taught that it was preferable to deliver that dose of D2E7 in a single subcutaneous injection having a volume between 0.5 ml and 1.0 ml. (*See supra* pp. 25-27 (citing five sources); EX1002 ¶¶71–73.)

In sum, the prior art provided significant motivation to deliver 20, 40, or 80 mg total-body doses of D2E7 to treat RA, and to do so in a single, subcutaneous injection having a volume between 0.5 and 1.0 ml. The prior art also taught that such formulations would be stable. (EX1002 ¶¶ 45, 64.) Put another way, the prior art revealed a motivation to produce subcutaneous formulations having concentrations of D2E7 between 20 mg/ml and 160 mg/ml. (*See supra* Table at p.7; EX1002 ¶¶74, 151–157.) The 50 mg/ml D2E7 concentration of the challenged claims was merely a design choice within the disclosed range, and thus AbbVie "must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *accord In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). There is no evidence of criticality here, nor would a POSA expect there to be any such evidence. (EX1002 ¶¶174-182.)

B. Any difference between the challenged claims and prior art is the predictable result of combining familiar excipients according to known methods.

The formulations in Relton are nearly identical to those recited in the challenged claims. (*Id.* ¶158 ("Relton describes a clear path to producing the claimed formulations.").) For example, the only difference between Claim 1 and Relton is that the IgG_1 antibody recited in the claim has the light and heavy chain variable regions of D2E7, whereas Relton recites the formulation for the entire IgG_1 subclass. (EX1006 at 3:26-27, Example, 4; EX1002 ¶118.) That difference is irrelevant because the IgG_1 subclass disclosed in Relton includes D2E7 and nothing in the prior art or the '166 patent indicates that D2E7 had any unusual properties that made it more difficult to formulate than any other IgG_1 antibody. (EX1002 ¶¶162-163.) Thus, a POSA would not have thought formulating D2E7 with a buffer system *as the only specified requirement* posed any special challenges compared to other IgG_1 antibodies. (*Id.* ¶¶128–29.) This is particularly true because, upon reading van de Putte or Sorbera, a POSA would have thought that D2E7 had already been formulated for subcutaneous injection at a concentration of 80 mg/ml (80 mg fixed-dose in 1 ml), if not higher. (*Id.* ¶163; *see also* ¶¶75, 79 ("A POSA would have believed that D2E7 had already been formulated at concentrations up to and above 50 mg/ml.")

Relton teaches the desirability of subcutaneous IgG_1 antibody formulations (D2E7 is an IgG_1 antibody) and provides detailed information on how to make stable, liquid formulations with IgG_1 antibody concentrations up to and exceeding 100 mg/ml. (*Id*. ¶¶130, 158-159.) This information includes which excipients and pH range to select for stabilizing an IgG_1 antibody. (See *infra* pp. 39-47 for excipient-by-excipient discussion.) Moreover, as AbbVie argued in its opposition to EP1324776 (EX1020 at 6-7, 10-12), Relton's Examples 1 and 2 show that the formulations are stable over a range of antibody concentrations. Importantly, the reference teaches that the liquid IgG_1 formulations would be stable at 50 mg/ml. (*See* EX1002 ¶¶120, 127; EX1006 at 5:42-9:24 (Table 1(b), 1(d), 2(a), 2(c)); *see also id.* 1:26–30 (disclosing that a 50 mg/ml IgG solution was stable for at least 2.5 years).) Thus, there is a *prima facie* case of obviousness because the '166 patent's 50 mg/ml concentration of an IgG_1 antibody falls within the range of Relton. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that any overlap between a claimed range and one in the prior art establishes a *prima facie* case of obviousness); *see also* M.P.E.P. § 2144.05.

Moreover, Relton is presumed to be enabled for both "claimed and unclaimed" disclosures. *See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354–56 (Fed. Cir. 2003) ("[W]e hold a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.").

AbbVie itself claimed in the August 16, 2002, priority application that its liquid formulation applied to *all* antibodies, not just D2E7. (*See* EX1004 at 37 (claim 1 stating "[a] liquid pharmaceutical formulation comprising a therapeutically effective amount of *an antibody* in a buffered solution …" regardless of the antibody subclass and whether or not it was directed to anti-TNFα) (emphasis added).) Thus, a POSA would not have expected D2E7 to present any particular problems in a formulation that included a buffer system or any of the other claimed components. (EX1002 ¶¶162-163). A POSA reading the van de Putte study, or the Sorbera review article, would have believed that subcutaneous formulations of D2E7 had already been made having a concentration of at least 50 mg/ml. (*See supra* p. 35.)

A POSA also would have known that the volume of a subcutaneous injection should be below 1.0 ml. (*See supra* pp. 25-27; EX1002 ¶71–73.) Accordingly, he or she would have believed that one dose of the self-injected formulation used in van de Putte contained 80 mg D2E7 in no more than 1.0 ml, which would make the concentration at least 80 mg/ml.[3] If the POSA was not

[3] After the date of invention, on 12/19/02, the results of a biweekly dosing study were published indicating that each biweekly dose of 20, 40, or 80 mg D2E7 (total-body dose) was "administered as two s.c. injections of 1.6 ml each." (EX1087 at 34; EX1002 ¶78.) This, and other post-invention date disclosures, are irrelevant

certain that the concentration was as high as 80 mg/ml, he or she would be certain that it reached at least 50 mg/ml. Even a self-injected volume of 1.6 ml would yield the claimed 50 mg/ml dose. (EX1002 ¶76 (noting that the injection volume could exceed the desirable volume limit by 60% and still meet the 50 mg/ml D2E7 concentration required by the challenged claims (80 mg in 1.6 ml is 50 mg/ml).)

Thus when read with van de Putte, Relton provided a reasonable expectation of success in making the challenged claims' D2E7 formulations. Relton teaches which pH ranges, tonicity agents, surfactants, buffers, and chelating agents should be used to produce stable, subcutaneous formulations containing high concentrations of an IgG_1 antibody. Importantly, other than pH ranges and the antibody concentration, ***the challenged claims do not require any particular concentrations or amount of any ingredient.*** The challenged claims merely recite and repeat the common excipients that any POSA would have routinely selected to make any IgG_1 antibody formulation. Claiming the presence of these common excipients does not make the formulation patentable. *See In re Brimonidine Patent Litigation*, 643 F.3d 1366, 1371–72 (Fed. Cir. 2011) (holding that a formulation is obvious where the "only distinction between [a prior art formulation] and the

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for the obviousness analysis of the '166 patent, which claims a priority date of August 16, 2002. *See In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (stating that a pre-AIA obviousness analysis is determined from the date of invention).

claimed invention is the presence of tonicity and buffering components and an explicit pH limitation").

pH Ranges. The challenged claims limit the formulation's pH range. Independent claim 1 requires a range of 4.0–8.0. Dependent claims 6, 7, and 8 recite a pH range of 4.5–6.0, 4.8–5.5, and 5.0–5.2, respectively. Dependent claim 4 recites one of five possible buffers and a pH range of 4.8–5.5. These ranges are merely design choices within the physiologically-acceptable pH range for a subcutaneous dosage form.

A POSA would have known that pH is critical in controlling the solubility and stability of a protein formulation. (EX1002 ¶¶91, 161; EX1029 at 60 ("The effect of solution pH on stability is probably the most important factor to study in early protein dosage form development.").) Therefore, a POSA would have conducted a pH-stability study as a first step in developing a new antibody formulation. (EX1002 ¶¶93, 161.) These studies were routinely done well before the 2002 priority date. FORMULATION AND DELIVERY OF PROTEINS AND PEPTIDES (1994) stated that formulators often conducted pH studies on formulation candidates early in the process because solution pH was known to impact all the major degradation pathways. (EX1023 at 5.) Carpenter & Manning also taught that pH is the "most powerful" formulation variable and the "[p]roblems associated with the physical properties of a protein, e.g., precipitation due to solubility and/or

stability, are generally very difficult to manage by other formulation means. Optimization of pH is a *simple* but very useful solution for such problems." (EX1025 at 13 (emphasis added).)

pH Range of 4.0 to 8.0: "Very early" in the formulation process, a POSA would have performed "pH-stability studies … to understand relative protein stability over a pH range, typically from about pH 3 to pH 10." (EX1029 at 61.) The two primary issues for a POSA to monitor would have been the solubility and stability, e.g., deamidation, of the protein. (*Id.*; *see also* EX1002 ¶102.) "In dosage form development, the scientist must first determine what pH range provides acceptable solubility of the protein for proper dosage, then determine whether this pH range also provides acceptable stability." (EX1029 at 61.) By conducting this study, a POSA would "usually" be able to find a pH that was "optimal for both [solubility and stability]." (*Id.*; EX1002 ¶¶102, 108.) In this case, a POSA would have been able to determine the claimed pH ranges by routine optimization. (EX1002 ¶94.)

In addition, the literature identified specific reasons why a POSA would have selected the claimed pH. For instance, a POSA would not have selected an extreme pH—less than 4 or greater than 9—in a subcutaneous formulation to minimize patient discomfort. (*Id.* ¶92; EX1006 at 4:26–28 ("The preferred pH range for a sub-cutaneous formulation will in general range from pH 4 to pH 9");

EX1025 at 186 ("[M]ost protein formulations will exist at pH values between 4 and 9.").) Instead, a POSA would have selected a pH within the physiologically-acceptable pH range that would have also been expected to solubilize the D2E7 protein. This would have directed a POSA to select a pH below 8. (EX1002 ¶¶93, 101.)

It was well-known that a protein's isoelectric point[4] ("pI") is an important factor in determining solubility because "[p]rotein solubility is usually at a minimum at its isoelectric point." (EX1029 at 61; EX1033 at 309 ("Proteins precipitate around their pI and resolubilize as the pH is adjusted upward or downward"; EX1006 at 3:67-4:9.) From examples such as insulin, a POSA would have known that moving further away from the protein's pI would increase solubility. (EX1029 at 61) (stating that insulin, which has a pI of 5.4, "is quite insoluble in water (<0.1 mg/ml)" but far more soluble (>30 mg/ml) when the pH is adjusted to less than 4 or more than 7).)

At the time of invention, the pI of D2E7 had been reported to be in the range of 8.6 to 8.8. (EX1002 ¶101 *citing* EX1049 at 107.) Thus, a POSA would have known to adjust the solution pH away from this range in order to solubilize D2E7. A POSA would have ruled out an upward pH adjustment because doing so would

4 The isoelectric point (pI) is the pH in which the net charge of the protein is zero. (EX1002 ¶100.)

result in a formulation outside the physiological pH range. (EX1002 ¶26.) Instead a pH lower than D2E7's isoelectric point would have been chosen to increase the antibody's solubility and because a POSA would have known that proteins are more stable at low pH. (EX1025 at 186.) A POSA would not select too low a pH, however, because "[t]he more a pH deviates from physiological conditions … the more likely the product will contribute to tissue damage or injection pain." (EX1072 at 415; EX1002 ¶92.)

With that balance in mind, even before 1993, "the pH of many protein formulations [was] approximately 5 to 7" in order to "reduce chemical degradation." (EX1027 at 314.) The formulations disclosed in Relton's Example 4, which would have a pH around 6, are but one example of protein formulations within that pH range. (Ex 1002 ¶125.) A POSA interested in developing a stable liquid formulation of a human antibody at high concentration also likely would have looked to the many plasma-derived immunoglobulin products that were on the market as of August 2002. (*Id*. ¶147.) These products, sometimes referred to as gamma-globulin or IVIG, were formulated at a pH range between 4.0 and 7.2 and displayed extended stability at concentrations up to and exceeding 50 mg/ml as aqueous solutions. (*Id*., *citing* EX1056; *see also* EX1006 at 1:26–30 (discussing a 50 mg/ml IgG intravenous formulation that was stable for at least 2.5 years at 5 °C.)

pH Range of 4.5–6.0: The biggest stability concerns for a protein formulator would have been aggregation, deamidation, and oxidation. (EX1027 at 307; EX1025 at 85; EX1002 ¶87.) The prior art taught that acidic conditions, specifically a pH range of 5–6, would provide the maximal reduction of deamidation. (EX1002 ¶98 *citing* EX1023 at 5 (noting that the pH range of 5–6 is optimal for minimizing deamidation) and EX1025 at 13 (same).) Studies on antibodies also demonstrated that pH was optimal for stability between 5 and 6. (*E.g.*, EX1002 ¶¶ 95, 99 *citing* EX1078 at 771.) Thus, a POSA would have selected a pH within the physiologically-acceptable range and would have further limited the range to an acidic pH to minimize deamidation, which was the most common cause of chemical protein instability. (EX1002 ¶¶87, 95.)

pH Ranges of 4.8–5.5 and 5.0–5.2: The prior art taught that certain amino acid sequences were especially susceptible to degradation. These sequences are often referred to as "hot spots." For example, a POSA would have known that asparagine (N) and glutamine (Q) residues followed by glycine (G) or serine (S) residues were sites likely to undergo deamidation. (EX1002 ¶¶96–97; EX1053 at 262–263; EX1050 at 5–6; EX1075.) Since AbbVie has represented that the amino acid sequence of D2E7 was known prior to August 2002, (*see* EX1086), a POSA would have been able to determine the antibody had sixteen "hot spots," as shown below (EX1002 ¶97):

	Number of Hot Spots				
D2E7 Antibody Sequence	Asn-Ser (NS)	Gln-Gly (QG)	Asn-Gly (NG)	Gln-Ser (QS)	**Total**
Heavy Chain Variable Region	3	1	-	-	**4**
Heavy Chain Constant Region	2	1	2	1	**6**
Light Chain Variable Region	-	2	-	1	**3**
Light Chain Constant Region	1	1		1	**3**

This unusually large number of hot spots in D2E7's amino acid sequence would have indicated to a POSA the likelihood of deamidation and thus would have directed him or her to formulate D2E7 at an acidic pH. (*Id.* ¶¶97–99.)

To address the potential deamidation the prior art taught a POSA to use a pH from around 5 to 6. (*Id.* ¶100.) Three protein studies disclosed that a pH of around 5 was optimal for minimizing deamidation. (EX1071at 2288-89, EX1073 at 380; EX1074 at 1685.) Antibody studies also reported that stability was optimal with a pH between 5 and 6. (*E.g.*, EX1078 at 771.) This is consistent with Carpenter & Manning's statement in RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS that protein deamidation is minimized at a pH between 5.0 and 6.0. (EX1025 at 13 (Table 6).) Thus, a POSA would have had a reasonable expectation of success in preparing a stable liquid formulation of D2E7 at a pH range of 4 to 6, and would have perceived a safe range for minimizing deamidation in a pH range of 5 to 6.

(EX1002 ¶161; *see also* EX1006 at 4:29–34 (indicating pH is preferably between 4 to 5.5 and 4 to 6.5 for subcutaneous formulations of anti-CD4 antibodies and anti-CD23 antibodies, respectively); EX1012 at 6:63–65 (indicating the buffer for the antibody formulations of the invention preferably had a pH from 4.5 to 6.0 and most preferably of about 5.0).)

"It is up to the scientist to identify what pH is optimal" for the balance of solubility and stability. (EX1029 at 61.) But this could have easily been achieved based on the routine "pH-stability studies [that] are conducted very early" in the formulation development process. (*Id.* at 60–61; *accord* EX1002 ¶¶93, 102, 108.) Moreover, a POSA would have been motivated to prepare a liquid formulation of D2E7 in the acidic range for both solubility and stability reasons. (EX1002 ¶¶102, 161; EX1025 at 13 ("Optimization of pH is a simple but very useful solution for such problems.").) With the foregoing points in mind, a POSA would have conducted the pH-stability study and, through routine experimentation, determined that D2E7 was stable around pH 5.2. (EX1002 ¶102.) Thus, there is nothing inventive about the pH ranges of the challenged claims.

Tonicity Agents. Only four of the challenged claims require a tonicity agent. Claims 10 and 16 require generally a "tonicity agent." Claims 13 and 23 require, more specifically, "sodium chloride." It was widely-known that tonicity agents should be added to make a subcutaneous formulation isotonic, which is standard

for subcutaneous injections. (*Id.* ¶¶110–111; EX1006 at 4:39-42; EX1025 at 182; EX1031 at 317.) Relton disclosed using sodium chloride in all of its subcutaneous formulations. (EX1006 at 11:50-12:23 (Example 4).) This is not surprising since sodium chloride was one of the most common tonicity agents added to subcutaneous formulations. (EX1002 ¶112; EX1031 at 317 ("The most widely used isotonicity modifiers are dextrose and sodium chloride."); EX1006 at 4:39–42 (indicating that sodium chloride may be used to adjust the solution's tonicity).)

Surfactants. Only three of the challenged claims require a surfactant. Claim 24 requires generally a "surfactant." Claim 25 requires, more specifically, "polysorbate." Claim 26 requires, most specifically, "polysorbate-80." As with tonicity agents, the challenged claims are not limited to certain concentrations of surfactants. It was widely-known that surfactants contributed to protein stability, and it would have been common for a POSA to add a surfactant to a subcutaneous formulation. (EX1002 ¶¶113–116; EX1036 at 160; EX1025 at 160.) In fact, Relton includes polysorbate-80 in all of its subcutaneous formulations. (EX1006 11:50-12:23 (Example 4).) That would have been expected since, by August 2002, "polysorbate-80 was the most commonly used surfactant in pharmaceutical formulations." (EX1002 ¶115.) According to a 1997 article by Nema, polysorbate-80 appeared in thirty-one injectable formulations, whereas the second most common surfactant appeared in only nine injectable formulations. (EX1032

at 167 (Table II).) Thus, just as with tonicity agents, there is nothing inventive or surprising about including a surfactant or, more specifically, polysorbate-80 in the challenged claims.

Buffers. Independent Claim 1 requires a "buffer system," which is simply used to maintain the pH at the desired level. Claims 2 and 14 require, more specifically, that the buffer system comprises an organic acid, and Claims 3 and 15 require, most specifically, that the organic acid be selected from the group consisting of gluconate, citrate, succinate, acetate, and histidine. Many of these same organic acids were commonly used as buffers in protein and antibody formulations. (EX1002 ¶108 ("Commercially available protein and antibody formulations as of August 16, 2002 illustrate that citrate and acetate were two of the most commonly used buffers, both of which buffer well in the acidic pH range"); EX1029 at 63; EX1035 at 785–786.) Relton teaches acetate and succinate as preferred buffers. (EX1006 at 4:34–37.) Another antibody formulation patent described gluconate as an option, along with acetate, succinate, histidine, and citrate. (*See* EX1012 at 6:66–7:3.) Thus, recitations of "buffer system" "organic acid" and the naming of conventional buffers reflect nothing unexpected or surprising in the challenged claims. Patentability of these claims cannot be alleged to reside in any inventive use of buffers. (EX1002 ¶¶107–109.)

Chelating Agents. Only one challenged claim requires a chelating agent. Claim 28 requires generally a "chelating agent." The use of a chelating agent in protein formulations was very common. (*Id.* ¶117; EX1029 at 68 ("Chelating agents … are used in protein formulations to aid in inhibiting free radical formation and resultant oxidation of proteins ….").) Unsurprisingly, Relton teaches the use of EDTA as a chelating agent. (EX1006 at 3:12–17, Example 4.)

Therefore, van de Putte in view of Relton establishes a *prima facie* case of obviousness for the challenged claims. The van de Putte reference established a motivation to create a stable subcutaneous formulation having a D2E7 concentration between 20 and 160 mg/ml and taught that single subcutaneous dosage forms of D2E7 likely were made having a concentration of at least 50 mg/ml of D2E7. Relton teaches that a 50 mg/ml subcutaneous formulation of an IgG_1 antibody, a class that includes D2E7, would not have any aggregation and thus would be stable. Moreover, the Relton formulations include all the excipients recited in the challenged claims. A POSA would have expected they were included for their established functions (*e.g.*, adding a surfactant to increase stability and a tonicity agent to make the formulation isotonic). (EX1002 ¶126.) The challenged claims' use of these same common excipients according to their established functions is a strong indication of obviousness. *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (stating that "a court must ask whether the

improvement is ***more than*** the predictable use of prior art elements according to their established functions") (emphasis added).

Through another lens, the combination of van de Putte and Relton reflects an "obvious solution to a known problem," because, as discussed above, a POSA would have appreciated that subcutaneous fixed-dose formulations (as described in van de Putte) were desirable and must be delivered to a patient in a limited volume (ideally less than 1 ml). Relton taught how to formulate them accordingly. That Relton addresses the same problem of stabilizing antibodies in a subcutaneous formulation discussed and claimed in the '166 patent "goes a long way towards demonstrating a reason to combine the two references." *See* M.P.E.P. § 2143 (quoting *ICON Health & Fitness, Inc.*, 496 F.3d 1374 (Fed. Cir. 2007)). This is additional proof of obviousness. *KSR*, 550 U.S. at 420 ("One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.").

As supported by Dr. Manning, a POSA "would have been motivated to apply the teachings of Relton to formulate the D2E7 antibody." (EX1002 ¶118.) The POSA would have had a reasonable expectation of success based on the teaching of van de Putte that stable, liquid formulations of D2E7 for single-use subcutaneous dosing had already been made and used in patients. Again, this

combination is nothing more than "the predictable use of prior art elements according to their established functions" and is therefore obvious. *See KSR*, 550 U.S. at 417.

The following claim chart shows on a limitation-by-limitation basis that each of the challenged claims are rendered obvious under § 103(a) by van de Putte in view of Relton.

'166 Patent Claim	van de Putte (EX1007) and Relton (EX1006)
Claim 1. A stable liquid aqueous pharmaceutical formulation comprising:	Stable aqueous adalimumab (D2E7) pharmaceutical formulations for subcutaneous self-injection were provided to patients weekly over a period of six months. (EX1007; EX1008 (Sorbera) at 643 stating that van de Putte discloses ("1/wk x 6 mo").) "The present invention relates to a concentrated antibody preparation, pharmaceutical formulations containing such a preparation, its use in human therapy and processes for its preparation." (EX1006 at 1:6–9.) "During the production of purified antibodies whether for therapeutic or diagnostic use, it is important that the antibody is sufficiently stable on storage . . . ." (*Id.* at 3:8–10.) *See* EX1006 at Table 1(b), 1(d), 2(a), 2(c) (stability data); Example 4 (exemplary aqueous subcutaneous formulations). *See also supra* p. 18 (noting AbbVie's statement that Relton teaches liquid formulations for subcutaneous administration that "have a low aggregate formation capability," and thus Relton anticipates claims directed to "[a] stable liquid formulation comprising an immunoglobulin . . . ." (EX1020 at 6-7, 10-12).)
a human anti-human Tumor Necrosis Factor alpha	A single 20, 40, or 80 mg dose of "D2E7, a fully human anti-TNF antibody" was given to patients

(TNFα) IgG_1 antibody at a concentration of 50 mg/ml,	weekly by "subcutaneous (s.c.) self-injection" over a period of up to six months. (EX1007.) To convert these doses into a concentration, a POSA would have used the typical volume for subcutaneous injection (0.5 to 1.0 ml). Therefore, a POSA would have been motivated to produce a formulation with a concentration between 20 and 160 mg/ml. *See supra* pp. 33-34. Moreover, van de Putte discloses a range of D2E7 concentrations – and for the 80 mg dose, a concentration of at least 80 mg/ml. *Id* p. 35. It was known that D2E7 was a human anti-human Tumor Necrosis Factor alpha (TNFα) IgG_1 antibody. (EX1086 at 2.) Relton teaches that it is preferably applied "to a preparation of immunoglobulins of the class IgG_4 and IgG_1, most preferably IgG_1." (EX1006 at 3:25–27.) Relton teaches a range of stable IgG_1 antibody concentrations that includes 50 mg/ml. (*Id.* at Table 1(b), 1(d), 2(a), 2(c) (stability data).) *See supra* pp. 31-32.
wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7, and a buffer system;	A single 20, 40, or 80 mg dose of D2E7 was provided to patients weekly for "subcutaneous (s.c.) self injection." (EX1007.) "[S]ub-cutaneous formulations according to the invention…will be buffered to a particular pH." (EX1006 at 4:24–25; s*ee also* Example 4 (using various buffers in the formulations).)
wherein the formulation is isotonic, suitable for single-use subcutaneous injection, and has a pH of 4.0 to 8.0.	"Preferably, sub-cutaneous formulations according to the invention are isotonic and will be buffered to a particular pH. The preferred pH range for a sub-cutaneous formulation will be in general range from pH 4 to pH 9. The preferred pH and hence buffer will depend on the isoelectric point of the antibody concerned." (EX1006 at 4:24–30; *see supra* pp. 39-40.)

	"Sub-cutaneous formulation according to the invention may also optionally contain sodium chloride to adjust the tonicity of the solution." (*Id.* at 4:40–42.) The D2E7 formulation was provided to patients weekly for "subcutaneous (s.c.) self injection." (EX1007; EX1008 (Sorbera) at 643 stating that van de Putte discloses ("1/wk x 6 mo").) *See supra* p. 22.)
Claim 2. The formulation of claim 1, wherein the buffer system comprises an organic acid.	Relton's Example 4 discloses organic acids as the buffer in the exemplary subcutaneous formulations (b–d) of the invention (acetic acid, maleic acid, and succinic acid). (EX1006 at 12:7–23.) Succinate is the conjugate base of succinic acid and acetic acid is the conjugate base of acetate. (EX1002 ¶125.)
Claim 3. The formulation of claim 2, wherein the organic acid is selected from the group consisting of gluconate, citrate, succinate, acetate, and histidine.	
Claim 4. The formulation of claim 3, wherein the pH is 4.8 to 5.5.	"[S]ub-cutaneous formulations according to the invention…will be buffered to a particular pH. The preferred pH range for a sub-cutaneous formulation will in general range from pH 4 to pH 9. The preferred pH and hence buffer will depend on the isoelectric point of the antibody concerned as discussed above." (EX1006 at 4:24–30; *see also supra* pp. 39-45 (describing the routine strategy of pH selection for an antibody formulation.) "[I]n the case of sub-cutaneous preparations containing anti-CD4 antibodies the pH will preferably be in the range of pH 4 to pH 5.5, for example pH 5.0 to pH 5.5 e.g. pH 5.5, and in the case of anti-CD23 antibodies in the range of pH 4 to pH 6.5." (EX1006 at 4:30–34.)
Claim 6. The formulation of claim 1, wherein the pH is 4.5 to 6.0.	
Claim 7. The formulation of claim 1, wherein the pH is 4.8 to 5.5.	
Claim 8. The formulation of claim 1, wherein the pH is 5.0 to 5.2.	

<table>
<tr><td>Claim 9. The formulation of claim 1, where the antibody is D2E7.</td><td>A formulation containing a 20, 40, or 80 mg dose of D2E7 was provided to patients weekly. (EX1007)</td></tr>
<tr><td>Claim 10. The formulation of claim 9, where the formulation further comprises a tonicity agent.</td><td rowspan="2">“Sub-cutaneous formulations according to the invention may also optionally contain sodium chloride to adjust the tonicity of the solution.” (EX1006 at 4:40–42.)

Example 4 discloses using sodium chloride in all of the exemplary subcutaneous formulations (a–d). (Id. at 11:50–12:23.)</td></tr>
<tr><td>Claim 13. The formulation of claim 10, wherein the tonicity agent is sodium chloride.</td></tr>
<tr><td>Claim 14. The formulation of claim 9, wherein the buffer system comprises an organic acid.</td><td rowspan="2">Relton’s Example 4 discloses organic acids as the buffer in the exemplary subcutaneous formulations (b–d) of the invention (acetic acid, maleic acid, and succinic acid). (Id. at 12:7–23.) Succinate is the conjugate base of succinic acid and acetic acid is the conjugate base of acetate. (EX1002 ¶125.)</td></tr>
<tr><td>Claim 15. The formulation of claim 14, wherein the organic acid is selected from the group consisting of gluconate, citrate, succinate, acetate, and histidine.</td></tr>
<tr><td>Claim 16. The formulation of claim 1, where the formulation comprises a tonicity agent.</td><td rowspan="2">“Sub-cutaneous formulations according to the invention may also optionally contain sodium chloride to adjust the tonicity of the solution.” (EX1006 at 4:40–42.)

Example 4 discloses using sodium chloride in all of the exemplary subcutaneous formulations (a–d). (Id. at 11:50–12:23)</td></tr>
<tr><td>Claim 23. The formulation of claim 16, wherein the tonicity agent is sodium chloride.</td></tr>
<tr><td>Claim 24. The formulation of claim 1, wherein the formulation comprises a surfactant.</td><td rowspan="3">“Optionally the formulation contains Polysorbate for stabilization of the antibody.” (Id. at 3:59–60.) Polysorbate is a well-known surfactant. See supra pp. 46-47.

Example 4 discloses using polysorbate-80 in all of the exemplary subcutaneous formulations (a–d).</td></tr>
<tr><td>Claim 25. The formulation of claim 24, wherein the surfactant is a polysorbate.</td></tr>
<tr><td>Claim 26. The formulation</td></tr>
</table>

of claim 25, wherein the polysorbate is polysorbate 80.	(EX1006. at 11:50–12:23)
Claim 28. The formulation of claim 1, wherein the formulation comprises a chelating agent.	Relton teaches adding EDTA as a chelating agent to improve stability. (*Id.* at 3:15–17). Example 4 discloses the optional use of EDTA in all of the exemplary subcutaneous formulations (a–d). (*Id.* at 11:50–12:23).

C. Any Secondary Considerations Patentee May Raise Do Not Overcome the *Prima Facie* Case of Obviousness

Objective evidence of nonobviousness, even when available, cannot defeat a strong case of obviousness based on the prior art references themselves. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA* LLC, 683 F.3d 1356, 1364–65 (Fed. Cir. 2012). To rely on secondary considerations, the patentee must establish that the evidence is due to the claimed invention, and not from something already known in the art, such as the antibody itself or the syringe design. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (stating that the evidence must be due to the claimed invention rather than prior art or other extrinsic factors). When the "difference between the claimed invention and the prior art is some range or other variable within the claim …, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *accord In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003.)

That is the situation here. Relton's range of IgG_1 antibody concentrations encompass 50 mg/ml, and a POSA would have interpreted van de Putte as disclosing a stable subcutaneous D2E7 formulation having a concentration of at least 50 mg/ml, if not 80 mg/ml. Challenged independent claim 1 does not specify any other excipients that must be included in the subcutaneous formulation. Relton discloses using the same excipients recited in the challenged dependant claims to stabilize the IgG_1 antibodies, which are often the most common excipients used in protein formulations. In other words, the challenged claims achieve an expected result by combining familiar excipients according to known methods.

1. Unexpected Results

AbbVie relied on unexpected results during prosecution of applications related to the '166 patent. That evidence was submitted in response to rejections of claims having much narrower scope than those of the '166 patent. But, "evidence of secondary considerations must be reasonably commensurate with the scope of the claims." *Huai-Hung Kao*, 639 F.3d at 1068. Any such evidence should not be afforded substantial weight unless AbbVie "establish[es] a nexus between the evidence and the merits of the *claimed invention.*" *Id.* (emphasis in original).

a. The Data Presented in the '166 Patent Are Not Unexpected and Are Not Commensurate in Scope with the Challenged Claims.

The '166 patent includes three examples. Example 1 describes a protocol for preparing a formulation that contains a single antibody sequence (presumably

D2E7) at a concentration range of 55–80 mg/ml, a combination of buffer components (citrate-phosphate), two tonicity agents (mannitol and NaCl), and a surfactant (polysorbate-80). Example 2 describes freeze-thaw studies at a D2E7 concentration of 63 mg/ml, and Example 3 describes a microbial growth study. However, the challenged independent claim is not limited to any particular buffer or to a formulation having specific buffers, tonicity agents, and surfactants. While various excipients are recited in challenged dependent claims, AbbVie's testing does not link the stability data to any specific claimed excipient. Even for the challenged claims directed to an organic buffer, the Examples only include a citrate-phosphate buffer system.

By August 16, 2002, the use of surfactants, tonicity agents, chelating agents, and buffers to stabilize IgG_1 antibodies was well-known. (EX1002 ¶170; EX1025 at 14 (listing "important" components of protein formulations); *see also supra* pp. 45-48 (discussing each excipient).) The data in the '166 patent merely demonstrates that commonly known excipients do not yield any unexpected properties, and instead behave consistent with their commonly understood uses. (EX1002 ¶170.)

Moreover, all the challenged claims require a protein concentration of 50 mg/ml, yet none of the Examples in the '166 patent disclose this concentration or test an antibody formulation within the scope of the challenged claims. There is

also no evidence indicating that a formulation containing 50 mg/ml D2E7 demonstrates unexpected results. Therefore, the data presented in the '166 patent are not commensurate in scope with the challenged claims and thus cannot be used to demonstrate unexpected results. *Huai-Hong Kao*, 639 F.3d at 1068.

b. The Data Presented in the European Counterpart to the '166 Patent Are Not Unexpected and Are Not Commensurate in Scope to the Challenged Claims.

AbbVie's EP1528933 patent is a related application to the '166 patent, and hence these two patents have the same specification. (Compare EX1010 with EX1001.)[5] However, the claims in EP1528933 contain additional limitations not present in the challenged claims of the '166 patent. Specifically, that formulation has a pH of 4 to 8 and includes: 20–130 mg/ml of a D2E7 antibody; 10–14 mg/ml mannitol; 0.1–5 mg/ml polysorbate-80; and specific amounts of citric acid monohydrate, sodium citrate, disodium phosphate dehydrate, sodium dihydrogen phosphate dehydrate, and sodium chloride. (EX1010 at 25; EX1002 ¶¶173.)

During prosecution of this patent, AbbVie presented test reports and arguments that purportedly demonstrated that its claimed formulation exhibited unexpected results compared to the cited prior art. (EX1002 ¶171-175.) However, most of the recited features in the test data are not commensurate in scope to the

5 EP1528933 was revoked by the European Patent Office in October 2015. (EX1015 at 5.)

challenged claims here. The "Test Report" (EX1047) contains only one composition (formulation "C") that is relevant to the '166 patent. (EX1002 ¶176.) Nevertheless, Dr. Manning has reviewed all the Test Report data and concluded that, counter to AbbVie's position of unexpected results, the Report supports the argument that it ***was expected*** that a 50 mg/ml formulation of D2E7 would be stable. (*Id.* ¶176 (conclusion), ¶¶177–89 (analysis).) For example, Example A of the Report demonstrates that a formulation capable of stabilization at 12.5 mg/ml or 25 mg/ml will also be stable at 50 mg/ml. (*Id.* ¶178.) Its remaining test series are irrelevant because they have insufficient stability data. (*Id.* ¶¶179-181.)

2. Long Felt Need, Failure of Others or Skepticism of Experts

There was a not a long-felt need for a stable 50 mg/ml D2E7 subcutaneous formulation. There is no evidence suggesting that experts or POSAs were skeptical that a subcutaneous formulation of 50 mg/ml D2E7 could be made or that anyone failed in attempting to do so. In fact, Relton demonstrated one method of preparing stable high concentration subcutaneous formulations (including at 50 mg/ml) for the IgG_1 subclass. Moreover, by August 2002, there were already safe and effective pharmaceutical products on the market for the treatment of RA. (*Id.* ¶54.) Regardless, any such evidence is only relevant if it shows that the prior attempts failed because they lacked the limitations claimed in the '166 patent. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312–13 (Fed. Cir. 2006)

(rejecting "failures of others" argument where evidence did not suggest that the prior attempts failed because the "devices lacked the claimed features").

3. Commercial Success

While the sales volume of HUMIRA® has been high, sales volume alone is not sufficient to prove commercial success. Rather, "for commercial success to be probative of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success." *Wm. Wrigley*, 683 F.3d at 1363. AbbVie cannot demonstrate a nexus here. As supported by the Declaration of Dr. Reisetter, who has co-authorized numerous book chapters regarding the strategic pricing of pharmaceuticals, the commercial success of HUMIRA® is driven by the antibody itself, not the specific claimed formulations, and AbbVie's marketing and sales strategies. (EX1066 ¶¶10–11.)

AbbVie had other patents covering HUMIRA® that existed prior to August 2002, including the '382 Salfeld patent (EX1013) for which AbbVie obtained a Patent Term Extension. AbbVie stated in its PTE application that "U.S. Patent 6,090,382 claims the approved product, HUMIRA™ (Adalimumab)." (EX1064.) The '382 patent was granted 326 days of PTE, which extended its expiration date to December 31, 2016. (EX1065.) "Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the claims], from

evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013).

Much of the commercial success of HUMIRA® derives from AbbVie's marketing and sales strategies rather than its formulation. (EX1066 ¶10.) Upon FDA approval in 2003, Abbott Labs (the predecessor to AbbVie) engaged in a "massive marketing campaign … to sell Humira." (EX1054 at 1.) A 2003 IMS Health Assessment stated that "Abbott is so determined to make Humira a success that it warned investors in January 2003 that earnings would be affected by the heavy promotion planned for product – and froze salaries for six months in order to focus on Humira's launch, the company's biggest ever." (*Id* at 2.) This marketing blitz has continued to present day. (EX1066 ¶¶13–15 (noting that AbbVie spent $132.4 million on direct-to-consumer advertising for HUMIRA® in 2013 and that the HUMIRA® marketing team was named 2014 Marketing Team of the Year).)

AbbVie's contracting strategies have also significantly contributed to HUMIRA®'s commercial success. (*Id.* ¶¶16-17.) HUMIRA® is frequently on prescription benefit preferred drug lists. (*Id.*) As drugs are given preferred status by contracting with insurance companies, HUMIRA®'s consistently preferred status relative to other TNFα inhibitors reflects AbbVie's greater ability to contract with payers. (*Id.* ¶17.)

AbbVie has also touted its syringe design as relevant to its commercial success. (*Id.* ¶18.) But the syringe design is not claimed in the '166 patent. AbbVie recently stated that HUMIRA® is successful because it is protected by numerous patents, but did not mention the '166 patent or subcutaneous dosing as elements to that success. (EX1069 at 19 ("Biosimilar intellectual property and litigation protect Humira from biosimilar entry until 2022.").)

Thus, AbbVie cannot show that the commercial success of HUMIRA® is due to the claimed subject matter in the '166 patent. Doing so would contradict AbbVie's prior statements and would discount the tremendous success of autoimmune treatments generally.

XI. CONCLUSION

Claims 1–4, 6–10, 13–16, 23–26, and 28 of the '166 patent are obvious and unpatentable over van de Putte in view of Relton. Petitioner respectfully requests that the Board institute *inter partes* review of these claims. Recitations concerning pH, protein concentration and tonicity, and routine excipients do not impart patentability to a formulation exercise that was entirely within the grasp of the skilled artisan; namely, the preparation of a stable, pH-appropriate, isotonic formulation of D2E7 at a conventional concentration suitable for a subcutaneous injection volume. van de Putte's clinical study, delivering 20, 40 and 80 mg

subcutaneous doses of D2E7, indicates such a formulation had been achieved as of August 16, 2002; and Relton provides a teaching on how it could be done.

Respectfully submitted,

Dated: May 9, 2016

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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 May 6, 2016, a complete and entire copy of this Petitioner Coherus BioSciences Inc.'s Petition for Inter Partes Review of U.S. Patent No. 9,114,166 with supporting exhibits were provided via Federal Express, costs prepaid, to the Patent Owner by serving the correspondence address of record as follows

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CERTIFICATE OF COMPLIANCE

In accordance with 37 CFR 42.24, as amended, the undersigned certifies that this Petition complies with the applicable type-volume limitations of 37 CFR 42.24(a)(i). Exclusive of the portions exempted by 37 CFR 42.24(a), this Petition contains 13,930 words as counted by the word processing program used for its preparation (Microsoft Word 2007).

Dated: May 9, 2016

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