UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Amgen Inc.
Petitioner

v.

AbbVie Biotechnology Ltd.
Patent Owner

Case IPR: Unassigned
Patent No. 8,916,158

PETITION FOR INTER PARTES REVIEW

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1002	Declaration of Theodore W. Randolph, Ph.D.
1003	U.S. Patent No. 6,171,586 (to Lam).
1004	Barrera et al. (2001) Ann Rheum. Dis. 60:660-69.
1005	U.S. Patent No. 6,090,382 (to Salfeld).
1006	U.S. Patent No. 7,250,165 (to Heavner).
1007	Carpenter et al., Pharmaceutical Research (1997) 14(8):969-975.
1008	File History of U.S. Patent No. 8,916,158.
1009	Bam et al., J Pharm Sci. (1998) 87(12):1554-9.
1010	Johnson et al., Nucleic Acids Research (2000) 28(1):214-218.
1011	Rational Design of Stable Protein Formulations: Theory and Practice (Carpenter and Manning, ed., April 30, 2002).
1012	Manning et al., Pharm. Res. (1989) 6(11):903-918.
1013	Cleland et al., Crit Rev Ther Drug Carrier Syst. (1993) 10(4):307-377.
1014	Pharmaceuticals, The Science of Dosage Form Design, (Michael E. Aulton ed., 2d ed. 2002).
1015	United States Pharmacopeia and National Formulary (USP 24-NF 19) Rockville, MD: United States Pharmacopeia Convention, 2000.
1016	Nail et al. "Development and Manufacture of Protein Pharmaceuticals," (Kluwer Academic/Plenum Publishers, New York, June 30, 2002).
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1019	Exposure Factors Handbook (E.P.A. 1997).
1020	Nema et al., PDA J Pharm Sci and Tech (1997) 51:166-171.
1021	Chiodi et al., Electrophoresis (1985) 6:124-128.
1022	Schein, Nature Biotechnol (1990) 8:308-317.
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1024	Remington: The Science and Practice of Pharmacy (Alfonso Gennaro ed., 20th ed. 2000).
1025	Arakawa et al. Pharmaceutical Research (1991) 8(3):285-291.
1026	Levine, J Parenteral Sci and Tech (1991) 45(3):160-165.
1027	Chang et al., Journal of Pharmaceutical Sciences (1996) 85(12):1325-1330.
1028	ACTIVASE (alteplase) [package insert]. South San Francisco, CA: Genentech, Inc.; 2002.
1029	ARANESP (dargbepoetin alpha) [package insert]. Thousand Oaks, CA: Amgen Inc.; 2002.
1030	KINERET (anakinra) [package insert]. Thousand Oaks, CA: Amgen Inc.; 2001.
1031	NEULASTA (pegfilgrastim) [package insert]. Thousand Oaks, CA: Amgen Inc.; 2002, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/125031_0000_NeulastaTOC.cfm (identifying biologics license approval on Jan. 31, 2002).
1032	NEUPOGEN (filgrastim) [package insert]. Thousand Oaks, CA: Amgen Inc.; 1998.
1033	PEGINTRON (peginterferon alpha-2b) [package insert]. Kenilworth, NJ: Schering Corporation; 2001.
1034	HERCEPTIN (trastuzumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 1998.
1035	REMICADE (infliximab) [package insert]. Malvern, PA: Centocor, Inc.; 1998.
1036	ZENAPAX (daclizumab) [package insert]. Nutley, NJ: Hoffmann-LaRoche, Inc.; 1997.

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1037	U.S. Patent No. 6,281,336 (to Laursen).
1038	U.S. Patent No. 6,238,664.
1039	PCT Publication No. WO 2000/056772.
1040	Kempeni et al., Ann Rheum. Dis. (1999), 58: (Suppl. I) I70-I72.
1041	Lorenz, Current Opinion in Molecular Therapeutics (2002) 4(2):185-190.
1042	U.S. Patent No. 8,802,101.
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1048	Preliminary amendment (filed Feb. 16, 2005) in U.S. patent application No. 10/525,292 (issued as U.S. Patent No. 8,216,583).
1049	U.S. Patent No. 8,932,591.
1050	File History of U.S. Patent No. 8,802,100.
1051	U.S. Patent No. 8,802,100.
1052	EP 1 528 933 (B1).
1053	AbbVie Response to Oppositions Against EP 1 528 933 (B1) (Jan. 17, 2014) (incl. consolidated list of documents filed by all parties (D1 to D49).
1054	Test Report AbbVie submitted to EPO (May 15, 2009) during prosecution of EP 1 528 933 (B1).
1055	Expert Opinion of G. Winter (dated Jan. 13, 2014) AbbVie submitted during opposition of EP 1 528 933 (B1).

Exhibit (Ex.)	Description
1056	Copy of as-filed U.S. patent application No. 13/471,820 (issued as U.S. Patent No. 8,932,591).

I. INTRODUCTION

Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.100 et seq., the undersigned submits this petition for inter partes review of claims 1-4, 9-18, and 20-30 of U.S. Patent No. 8,916,158 (the "'158 patent," Ex. 1001) owned by AbbVie Biotechnology Ltd. ("AbbVie").

The '158 patent claims, directed to a number of liquid pharmaceutical antibody formulations, recite nothing more than a combination of (i) a known antibody and (ii) well-known and commonly used liquid formulation components. The recited antibody, an anti-TNFα antibody called D2E7, was known before the filing of the priority application and had been reported as having shown success in the clinic. The recited formulation components—a polyol, a surfactant, and a buffer system at a pH between 4 and 8—were commonplace, used in the vast majority of commercially available antibody formulations. Given the known D2E7 antibody and the known formulation components, the prior art taught the skilled person to formulate a D2E7 pharmaceutical formulation as recited in the claims.

First, the prior art generally taught persons of skill how to create liquid pharmaceutical formulations for anti-TNFα antibodies that were just like those recited in the '158 patent claims. For example, except for the specific anti-TNFα antibody, D2E7, the Lam patent disclosed every limitation of the '158 patent claims. In light of the Barrera article, which disclosed D2E7's promising clinical

results, the skilled person would have been motivated to select D2E7 as the anti-TNFα antibody to be included in the Lam formulation, or to make the short-term D2E7 formulation taught by Barrera more stable for long-term storage by simply adding a surfactant as taught by Lam.

Second, the prior art showed the effectiveness of pharmaceutical formulations that included D2E7. For example, by teaching D2E7 and how to formulate it for administration to patients, the Salfeld patent expressly or implicitly disclosed every claimed feature of the '158 patent. The features that the Salfeld patent did not expressly disclose—the specific concentration of D2E7 and the specific pH range—were taught by the Heavner patent, which provided guidance on formulating anti-TNFα antibodies.

Any secondary considerations would be insufficient to overcome the strong case of obviousness here. For example, even if AbbVie could show unexpected results for a particular combination of formulation components (which, to date, it has not), those results would not be commensurate with the scope of the challenged claims, which offer not only numerous combinations of formulation components in various amounts, but also a vast breadth of the antibodies and antigen-binding fragments.

II. MANDATORY NOTICES AND PAYMENT OF FEES

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

Amgen Inc. ("Petitioner") is the real party-in-interest.

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

Petitioner is concurrently filing a petition for inter partes review of U.S. Patent No. 8,916,157, which is in the same family as the '158 patent.

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

Petitioner designates Sandip H. Patel (Reg. No. 43,848) as lead counsel and Li-Hsien Rin-Laures (Reg. No. 33,547) as back-up counsel, both with Marshall, Gerstein & Borun LLP, 6300 Willis Tower, 233 South Wacker Drive, Chicago, IL 60606-6357; telephone (312) 474-6300; facsimile (312) 474-0448. A power of attorney is submitted herewith.

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

Service of any documents via hand-delivery may be made at the postal mailing addresses of lead and back-up counsel identified above with courtesy copies to the following email addresses: SPatel@marshallip.com, LRinLaures@marshallip.com, and MGBECF@marshallip.com. Petitioner consents to electronic service at these same email addresses.

E. Fee Payment Authorization (37 C.F.R. § 42.103(a))

Payment of the required fees ($28,000) is submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If payment of any additional fees is due during this proceeding, the Patent Office is authorized to charge such fees to Deposit Account No. 13-2855 under Order No. 01017/10408, and credit any over payment to the same account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that the '158 patent is eligible for inter partes review, and that Petitioner is neither barred nor estopped from requesting such review.

IV. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

A. Effective Filing Date of the '158 patent

The '158 patent issued from U.S. patent application No. 14/453,490 filed on August 6, 2014. The '158 patent claims priority to several continuation applications with the earliest claimed priority application having a filing date of August 16, 2002. The Patent Office never determined that the '490 application is entitled to the priority benefit, under 35 U.S.C. § 120, to any of the earlier-filed applications. For purposes of this petition only the effective filing date of the challenged claims is August 16, 2002.

B. The Prior Art and Statutory Grounds of the Challenge (37 C.F.R. § 42.104(b)(2))

Petitioner requests review of claims 1-4, 9-18, and 20-30 (the "challenged claims") of the '158 patent. The challenged claims are directed to a combination of a known human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody and well-known pharmaceutical formulation components. The challenged claims are unpatentable in view of these publications:

(1) Lam et al. U.S. Patent No. 6,171,586 (the "Lam patent," Ex. 1003), issued January 9, 2001;

(2) Barrera et al. (2001) *Ann Rheum. Dis.* 60:660-69 (the "Barrera article," Ex. 1004), published July 1, 2001;

(3) Salfeld et al. U.S. Patent No. 6,090,382 (the "Salfeld patent," Ex. 1005), issued July 18, 2000; and,

(4) Heavner et al. U.S. Patent No. 7,250,165 (the "Heavner patent," Ex. 1006), July 31, 2007.

Each of publications (1) through (3) is prior art to the '158 patent under 35 U.S.C. § 102(b) because each issued or published more than one year before the effective filing date (August 16, 2002) of the '158 patent (see Section IV.A, above). The Heavner patent (4) is prior art to the '158 patent at least as of its August 1, 2001, filing date under 35 U.S.C. § 102(e).

The challenged claims are unpatentable based upon the following grounds:

Table 1. Grounds for Inter Partes Review

Ground	Claims	Statutory Basis and Prior Art
1	1-4, 9-18, and 20-30	Obviousness under 35 U.S.C. § 103(a) over the combination of the Lam patent and the Barrera article.
2	1-4, 9-18, and 20-30	Obviousness under 35 U.S.C. § 103(a) over the combination of the Salfeld and Heavner patents.

These grounds are described in detail in Section VI, below, and are supported by the declaration of Theodore W. Randolph, Ph.D. Ex. 1002.

Dr. Randolph is a Professor at the University of Colorado and is an expert in the field of pharmaceutical formulations containing proteins, such as aqueous liquid antibody formulations. *Id*. at ¶s 1-7. By August 16, 2002, he had authored several review articles describing the effect of various ingredients on the stability of proteins in formulations, and had prepared stable protein formulations. *Id*. at ¶ 7; *see e.g*., Carpenter et al., Pharmaceutical Research (1997) 14(8):969-975 (Ex. 1007). As a skilled practitioner in the relevant field since before 2002, Dr. Randolph is qualified to provide an opinion as to what a person having ordinary skill in this art would have understood, known, or concluded as of August 16, 2002. *Id*. at ¶s 8-36. Accordingly, he is competent to testify in this proceeding.

V. SUMMARY OF THE '158 PATENT

A. Summary of the Patent and Prosecution History of the Challenged Claims

The '158 patent describes pharmaceutical formulations of antibodies. The '158 patent broadly claims a pharmaceutical formulation that includes a human IgG1 anti-human TNFα antibody (or an antigen-binding portion thereof) that includes the light and heavy chain variable regions of D2E7, a buffer system having a pH of 4 to 8, a polyol, and a surfactant—ingredients that had been used to prepare many commercially available pharmaceutical formulations, including another anti-TNFα antibody, REMICADE®, other antibodies, and other proteins, all before the '158 patent's effective filing date.

Although the ’158 patent recites broad claims encompassing numerous combinations of formulation components, its specification presents an example of just one of those combinations. That example reports data from freeze/thaw studies of a particular formulation of D2E7 made from at least seven specific excipients. The specification does not report any data regarding whether any formulation, much less that single formulation, is stable over any particular length of time.

Even though it claims a simple combination of a known antibody and known formulation components, the ’158 patent issued from the ’490 application without any prosecution in view of the prior art. Indeed, the ’490 application presenting claims 1-30 issued without modification only about four months after it was filed. *See* ’158 Patent File History, Ex. 1008 at 207 (Dec. 3, 2014, issue notification). The only rejection the Patent Office applied was under the judicially-created doctrine of obviousness-type double patenting (“ODP”) over the ’158 patent’s family members, Ex. 1008 at 107-125 (Oct. 9, 2014, rejection), which AbbVie overcame by filing terminal disclaimers. *Id*. at 150-173 (Oct. 20, 2014, response and disclaimers). The Patent Office then allowed the application. *Id*. at 182-186 (Nov. 14, 2014, notice of allowance).

B. Level of Ordinary Skill in the Art

The subject matter of the ’158 patent relates to pharmaceutical formulations containing a protein, such as a D2E7 antibody. The art relates to the field of

designing pharmaceutical formulations containing proteins. Ex. 1002 at ¶s 27-30. As of the effective filing date, a person having ordinary skill in the art who would be asked to design a pharmaceutical formulation containing an antibody would have a Pharm. D. or Ph.D. and at least two years of experience preparing a stable formulation of a protein suitable for therapeutic use. *Id*. at ¶s 31-34. As a skilled practitioner in the relevant field since before 2002, Dr. Randolph is qualified to provide an opinion as to what a person having ordinary skill in this art would have understood, known, or concluded as of August 16, 2002. *Id*. at ¶s 35-36.

C. Challenged Claims and Claim Construction (37 C.F.R. § 42.104(b)(1) and (b)(3))

The '158 patent issued with one independent claim (claim 1):

> 1. A stable liquid aqueous pharmaceutical formulation comprising
>
> (a) a human IgG_1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, at a concentration of 20 to 150 mg/ml,
>
> (b) a polyol
>
> (c) a surfactant, and
>
> (d) a buffer system having a pH of 4 to 8,
>
> wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.

Ex. 1001 at 39:11-20. Claims 2-30 depend from claim 1. *See* Ex. 1002 at ¶s 37-38.

A claim term is presumed to have its "ordinary and customary meaning," which is the "meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.,* 504 F.3d 1249, 1257 (Fed. Cir. 2007). That presumption is rebutted, however, where the patentee acts as his/her own lexicographer, giving the term a particular meaning in the specification with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Some claim terms are not expressly defined, but have a well-known meaning to the skilled person (e.g., "concentration" or "subcutaneous injection") and, accordingly, may be defined with a commonly-referenced dictionary. Other claim terms are expressly defined in the specification (Ex. 1001), such as, for example, "pharmaceutical formulation," "polyol," "nonreducing sugar," and "buffer." Ex. 1001 at 7:4 to 8:39; Ex. 1002 at ¶s 39-40. Still other terms should be construed as set out below.

Table 2. Claim Interpretation

Claim Term	Proposed Construction
stable	"that retains its physical stability and/or chemical stability and/or biological stability upon storage"
IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody	"immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds"
antigen-binding portion	"one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα)"

Claim Term	Proposed Construction
wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7	any antibody that includes one heavy and one light chain variable region that retain the CDR3 sequences of a D2E7 antibody disclosed in the Salfeld patent (Ex. 1005)

1. "stable"

The '158 patent expressly defines a "stable" formulation as one "in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." Ex. 1001 at 7:23-25. Although the specification discloses various preferred storage conditions (time and temperature)—such as "stable at room temperature (about 30° C.) or at 40° C. for at least 1 month and/or stable at about 2-8° C. for at least 1 year for [*sic*, or] at least 2 years," *id*. at 7:30-37—"stable" cannot be limited to one of these preferred embodiments. Not one example in the specification shows that the claimed formulations are stable at those storage conditions.

The term "stable" is recited only in the preamble of the challenged independent claims. Neither the body of these claims nor any of the dependent claims relies on, or derives antecedent basis, from the term "stable" in the preamble. Thus, despite the express definition, the term should be accorded no patentable weight. *See*, *e.g.*, *DeGeorge v. Bernier*, 768 F.3d 1318, 1322n.3 (Fed. Cir. 1985).

If patentable weight is accorded to the term "stable," then it means a formulation that "retains its physical stability and/or chemical stability and/or biological stability upon storage" for any period of time, no matter how short. Ex. 1002 at ¶ 41. The term "stable" does not *require* storage at a specific temperature or for a specific time, for three reasons.

First, the '158 patent merely expresses a *preference* for various possible time and temperature conditions as emphasized in the text quoted above. The mere fact of a particular embodiment being taught or preferred is insufficient to justify limiting otherwise broad claim scope to that particular embodiment. *See, e.g., Agfa Corp. v. Creo Prods., Inc.*, 451 F.3d 1366, 1376-77 (Fed. Cir. 2006) (find that a claimed "stack" of printing plates was not limited to the particular horizontal stack shown as a preferred embodiment in the specification). Second, the '158 patent offers no evidence that the broadly disclosed and claimed formulations (or even the single exemplified formulation) are stable for any particular time under any particular conditions, such as 2-8°C. for at least 1 year. Thus, the Board should avoid an interpretation that implicates issues—written description and enablement—not addressable in inter partes review. Third, established case law counsels against importing into broad claim language limitations from the specification. *See e.g., In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1371-72 (Fed. Cir. 2007) (rejecting proposed construction that claimed method of

formulating omeprazole be performed at a specific temperature where the specification disclosed variable temperatures).

2. "IgG_1 … antibody"

The term "IgG1 … antibody" is recited in independent claim 1. According to the '158 patent, "antibody" refers to "immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds." Ex. 1001 at 9:37-40; Ex. 1002 at ¶ 42. This term encompasses any number of variations within the variable regions and/or constant regions.

3. "antigen-binding portion"

The '158 patent defines "antigen binding portion" of an antibody as "one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα)." Ex. 1001 at 9:58-61. The '158 patent further identifies examples of such fragments, such as an isolated CDR. *Id*. at 9:61-10:7; Ex. 1002 at ¶ 43. Thus, the term "an antigen-binding portion" encompasses an antibody fragment that can be as small as one CDR (5 to 17 amino acids). Ex. 1002 at ¶ 43.

4. "wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7"

Instead of specifying sequences by SEQ ID NOs, AbbVie chose to use the broad phrase "the light chain variable region and the heavy chain variable region of D2E7." This phrase is recited in independent claim 1. D2E7 is not expressly defined in the '158 patent, but it is described in the Salfeld patent (Ex. 1005),

which the ’158 patent incorporates by reference for its disclosure of antibodies and antigen-binding portions. Ex. 1001 at 9:54-57 and 10:25-28. The Salfeld patent states that D2E7 has a light chain CDR3 domain that includes the amino acid sequence of SEQ ID NO:3, and a heavy chain CDR3 domain that includes the amino acid sequence of SEQ ID NO:4. Ex. 1005 at 2:59-63. Thus, this phrase encompasses any antibody that includes one heavy and one light chain variable region that retain these CDR3 sequences. These regions can include any number of mutations outside of the CDR3 sequences. Ex. 1002 at ¶ 44.

VI. DETAILED EXPLANATION (37 C.F.R. § 42.104(b)(4) and (b)(5))

The Supreme Court recently reaffirmed that the four factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), “continue to define the inquiry that controls” an obviousness analysis, and further emphasized that the patentee’s particular motivation or avowed purpose do not control a determination that the claimed invention is obvious; instead “[w]hat matters is the objective reach of the claim.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 407, 419 (2007).

The Court stated that one way in which a claimed invention can be proved obvious is by showing that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent’s claims. *Id*. at 419-20. That statement is pertinent because this petition will show that more than one year before the ’158 patent’s effective filing date, combinations

of prior art—not applied by the Patent Office, but described herein—taught formulations encompassed by the challenged claims that addressed AbbVie's asserted need in the art: a stable aqueous pharmaceutical formulation with extended shelf-life that includes a therapeutically suitable anti-TNFα antibody, including a high protein (antibody) concentration. Ex. 1001 at 3:10-17. When there is such a need and "there is a finite number of identified predictable solutions," the skilled person "has good reason to pursue known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *See KSR*, 550 U.S. at 421.

A. General State of the Art

By August 16, 2002, the anti-TNFα antibody D2E7 had been formulated for administration to patients in clinical trials. D2E7 showed promising clinical results. Ex. 1002 at ¶s 78-79. By the same time, the science of designing parenteral protein formulations was well established. It taught a limited number of formulation components that the skilled person would have tried when designing a new formulation of D2E7. *Id.* at ¶s 45, 72-73. It also taught how to formulate antibodies, including anti-TNFα antibodies, such as D2E7. Although the skilled person would have first looked at formulations of anti-TNFα antibodies and other antibodies that are structurally similar to D2E7, the skilled person would also have been motivated to try excipients used in formulations of other antibodies and

proteins. *Id.* at ¶s 53-58, 74-76 (citing product information (Exs. 1028-1035 and Ex. 1016 at p. 54-56 (Table IV)). The skilled person would have known how to prepare a stable, isotonic formulation of D2E7 and would have had a reasonable expectation of success in doing so. Ex. at ¶ 77.

First, the prior art taught the skilled person how to meet the two goals of any parenteral pharmaceutical formulation, including a parenteral formulation of an anti-TNFα antibody, such as D2E7: (1) that the formulation is stable for its intended use, and (2) that the formulation has essentially the same osmotic pressure as human blood to minimize pain when the formulation is injected into a patient. *See id.* at ¶s 46-47 (discussing stability and Exs. 1011-1013) and ¶s 48-49 (discussing osmotic pressure and Ex. 1014); *see also*, Ex. 1003 (Lam patent) at 6:32-37. To accomplish those goals, the skilled person would have sought a buffer providing an appropriate pH range (Ex. 1002 at ¶s 59-62 (discussing Exs. 1011 and 1016)), an appropriate polyol (Ex. 1002 at ¶s 63-65 (discussing Exs. 1014, 1015, 1020, 1025, and 1017 (the "Wang article"))), and optionally, an appropriate surfactant (Ex. 1002 at ¶s 66-71 (discussing Exs. 1026, 1011, 1015, 1016, 1020, and 1027))—the three formulation components recited in the challenged claims.

Second, protein and antibody formulations commercially available as of August 16, 2002, taught the skilled person to formulate D2E7 using the formulation components recited in the challenged claims. The FDA had approved

many protein formulations that included a buffer system at a pH between 4 and 7.3, a polyol, and a surfactant, such as polysorbate 80. *See* Ex. 1002. at ¶ 74 (Table 1 lists eight such commercial protein formulations). The FDA had also approved many parenteral antibody formulations that included a buffer system at a pH between 6 and 7.5, a polyol, and polysorbate 80. *See id.* at ¶ 74 (Table 2 lists eight such commercially-available antibody formulations). Additionally, the FDA had approved formulations of antibodies in the IgG class of antibodies that encompasses the claimed IgG D2E7 antibody that included a pH between 4 and 8, a polyol, and a surfactant. *See id.* at ¶ 78. And the FDA had approved an IgG anti-TNFα antibody, REMICADE®, formulated at pH 7.2 with sucrose (a polyol) and polysorbate 80 (a surfactant). *See id.* at ¶ 74; Ex. 1035; *see also id.* at ¶ 75 (describing other formulated antibodies known in the patent literature (Exs. 1018, 1023, 1037-1039)).

Third, numerous anti-TNFα antibody formulations were known in the literature as of August 16, 2002, many of which included a buffer system at a pH between 4 and 8, a polyol, a surfactant, and an antibody concentration ranging from 20 to 150 mg/ml. *See* Ex. 1002 at ¶ 76 (generally describing the prior art (Exs. 1003, 1004, 1005, and 1006) underlying the petitioned grounds).

The skilled person would have had a reasonable expectation of success in applying the formulations commercially available and taught in the literature to

D2E7. The skilled person would have understood that the formulation components of an antibody formulation could be applied to a new formulation of a structurally similar antibody. *See* Ex. 1002. at ¶s 74-77. For example, antibodies of the same IgG class are structurally similar and will exhibit similar properties in formulations. *See id.* at ¶s 55-56. Thus, a skilled person tasked with designing a formulation of D2E7, which is an IgG antibody, would have first considered using formulation components that had been successful in other IgG formulations. *See id.* at ¶s 56-58.

B. GROUND 1: Claims 1-4, 9-18, and 20-30 Are Rendered Obvious by the Combination of the Lam Patent and the Barrera Article

1. Claims 1 and 17 Would Have Been Obvious

Claim 1 of the '158 patent recites (i) an anti-TNFα antibody having particular sequences of D2E7, and (ii) specific formulation components. In particular, claim 1 recites a stable liquid aqueous pharmaceutical formulation that comprises a buffer system having a pH of 4 to 8, a polyol, a surfactant, and 20 to 150 mg/ml of a human IgG1 anti-TNFα antibody (or an antigen-binding portion thereof) that includes the light and heavy chain variable regions of D2E7. Ex. 1002 at ¶ 81. That formulation of D2E7 would have been obvious. The Barrera article reported positive clinical results with a D2E7 formulation, and the Lam patent (assigned to Genentech, Inc.) taught all the formulation components recited in

claim 1. Moreover, as shown in Table 3 below, the Lam patent had already solved what the ’158 patent seeks to solve: a stable aqueous formulation of an antibody.

Table 3. The Prior Art Lam Patent and the ’158 Patent Seek to Solve the Same Problem.

The Lam Patent (Ex. 1003)	**The ’158 Patent (Ex. 1001)**
“There is a need in the art for a stable aqueous pharmaceutical formulation comprising an antibody, such as an anti-CD18 or anti-CD20 antibody, which is suitable for therapeutic use. SUMMARY OF THE INVENTION Accordingly, the invention provides a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol.” Ex. 1003 at 2:19-29.	“There is a need for a stable aqueous pharmaceutical formulation with an extended shelf life, comprising an antibody which is suitable for therapeutic use to inhibit or counteract detrimental hTNFα activity. There is also a need for a stable aqueous pharmaceutical formulation with an extended shelf life, comprising an antibody suitable for therapeutic use which is easily administered and contains a high protein concentration. This invention provides a liquid aqueous pharmaceutical formulation consisting of a therapeutically effective amount of an antibody in a buffered solution forming a formulation having a pH between about 4 and about 8 and having a shelf life of at least 18 months.” Ex. 1001 at 3:10-22.

Further, the Lam patent also claimed an invention similar to the one the ’158 patent claims as its own. Specifically, the Lam patent claims a stable aqueous pharmaceutical formulation that includes an antibody, an acetate buffer having a pH of about 4.8 to 5.5, a surfactant, and a polyol. Ex. 1003 at 57:2-7 (claim 1).

The Lam patent (Ex. 1003) and the Barrera article (Ex. 1004) would have offered the skilled person two routes for achieving the claimed invention. Ex. 1002 at ¶ 82.

First, in disclosing how to prepare stable formulations of antibodies, including anti-TNFα antibodies, the Lam patent discloses every feature recited in the '158 patent claims except the particular anti-TNFα antibody, D2E7. Ex. 1002 at ¶ 83.The Barrera article reports positive results with a clinical formulation containing D2E7. *Id*. at ¶ 84.The skilled person would have been motivated to add D2E7 to the Lam formulation, leading to the claimed formulation. *Id*. at ¶ 85.

The Lam patent discloses a stable aqueous pharmaceutical formulation that includes a therapeutically effective amount of an antibody, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant, and a polyol. Ex. 1003 at 2:25-30. Although "stable" in the preamble should not be accorded patentable weight, even if it were, the definition of "stable" in the Lam patent (*id.* at 5:59 to 6:31) is word-for-word identical to the definition of "stable" in the '158 patent. The formulated antibody of the Lam patent is directed against antigens of interest, including tumor necrosis factor-alpha (TNFα) (*id*. at 10:7 and 10:19). An exemplary antibody concentration in the formulation is from about 0.1 mg/mL to about 50 mg/ml. *Id*. at 22:10-17. According to the Lam patent, the polyol acts as a tonicifier (i.e., a tonicity agent) and may stabilize the antibody. *Id*. at 22:31-32.

Thus, the Lam patent discloses every feature recited in the '158 patent claims except the particular anti-TNFα antibody, D2E7. Ex. 1002 at ¶ 83.

The D2E7 antibody was disclosed, however, in the Barrera article (Ex. 1004). The Barrera article reported phase I clinical trial results, explaining that D2E7 is "safe and results in rapid clinical improvement in patients with active RA [rheumatoid arthritis]." Ex. 1004 at 661. The article also explained that D2E7 has a significant advantage over other known anti-TNFα antibodies (such as REMICADE®), since D2E7 is a fully human antibody and thus less likely to generate adverse immune reactions. *Id.* at 661-662; Ex. 1002 at ¶ 84. In addition to promising clinical results, the Barrera article disclosed a short-term formulation appropriate for phase I clinical trials: 25 mg/mL D2E7, 1.2% mannitol, 0.12% citric acid, and 0.02% sodium citrate. *Id*. at 661; Ex. 1002 at ¶ 84.

Given the successful clinical results of D2E7, the skilled person would have been motivated to select D2E7 as the anti-TNFα antibody included in the Lam formulation, resulting in the same formulation recited in the challenged claims. Ex. 1002 at ¶ 85. The skilled person would have had a reasonable expectation of success in doing so because the Lam patent taught formulations for anti-TNFα antibodies and D2E7 was an anti-TNFα antibody, and because the art provided guidance on formulating antibodies. Ex. 1002 at ¶s 85-86.

Second, the Barrera article reports positive results with a clinical formulation of D2E7 but does not disclose the pH of that formulation or whether that formulation had a surfactant. Ex. 1002 at ¶s 87-89. The Barrera article thus discloses everything recited in claim 1 of the '158 patent except the pH range and surfactant. *Id*. The skilled person would have been motivated to apply the teachings of the Lam patent to modify the Barrera formulation to have the claimed pH range and surfactant. *Id*.

Because the Barrera article taught a formulation of D2E7 that did not need to be stored (since it was used for short-term phase I clinical studies), the skilled person would have been motivated to build off of that success by designing a stable formulation for long-term storage for commercial purposes. *Id*. at ¶ 88. The Lam patent taught how to design such a formulation. *Id*. First, the Lam patent taught that a stable anti-TNFα antibody formulation should have a pH between about 4.5 to about 6.0. Ex. 1003 at 2:25-30. That teaching is consistent with the fact that as of August 16, 2002, nearly all commercially available protein formulations, including antibody formulations, had a pH within that range. Ex. 1002 at ¶s 59-62. Second, the Lam patent taught that a stable anti-TNFα antibody formulation should include a surfactant, such as polysorbate 80. Ex. 1003 at 22:49-51. That teaching is consistent with the fact that surfactants were known to prevent antibodies from aggregating and thus increase the stability of an antibody

formulation. Ex. 1002 at ¶s 66-69. For example, the skilled person would have known to add a surfactant to a protein formulation if the formulation was not sufficiently stable for its intended purpose (e.g., short term storage, shipping stress, and/or long term storage). *Id*. As of August 16, 2002, the most common excipient used to improve stability of parenteral formulations was a nonionic surfactant, and the most commonly used nonionic surfactant was polysorbate (e.g., polysorbate 80 and polysorbate 20), and in particular, polysorbate 80. *Id*. at ¶s 68-69 (discussing Exs. 1016 and 1022 (Table II)). Further, many commercially available protein formulations, including antibody formulations, included a surfactant such as polysorbate 80. Ex. 1002 at ¶ 74.

Accordingly, the combination of the Lam patent and Barrera article, in view of the state of the art, renders obvious claim 1 of the '158 patent. *Id*. at ¶s 91-93.

Claim 17 depends from claim 1. Claim 17 recites that the antibody is D2E7, which, as noted above, is expressly disclosed in the Barrera article as the subject of the formulation that Barrera prepared and administered to patients. Consequently, the skilled person would have considered the subject matter recited in claim 17 obvious for the same reasons as those presented for claim 1. *Id*. at ¶ 94.

2. Claims 2-4, 9-16, 18, and 20-30 Would Have Been Obvious

Each feature recited in dependent claims 2-4, 9-16, 18, and 20-30 is disclosed in the Lam patent. Each of these claims is therefore obvious for at least

the same reasons that the independent claims are obvious. *See generally*, Ex. 1002 at ¶s 95-105. Set forth below is a table showing where in the Lam patent can be found an express disclosure of the features recited in these claims:

Table 4. Disclosure in the Lam Patent

'158 Patent Claim	**Disclosure in Lam Patent (Ex. 1003)**
2. The formulation of claim 1, wherein the concentration of the antibody or antigen-binding portion is 45 to 105 mg/ml.. **3**. The formulation of claim 2, wherein the concentration of the antibody or antigen-binding portion is 50 mg/ml. **26**. The formulation of claim 17, wherein the concentration of the antibody or antigen-binding portion is 50 mg/ml.	"The therapeutically effective amount of antibody present in the formulation is determined by taking into account the desired dose volumes and mode(s) of administration, for example. From about 0.1 mg/mL to about 50 mg/mL … is an exemplary antibody concentration of the formulation." Ex. 1003 at 22:10-17.
27. The formulation of claim 1, wherein the buffer system comprises histidine. **28**. The formulation of claim 1, wherein the buffer system comprises succinate. **29**. The formulation of claim 1, wherein the buffer system comprises acetate. **30**. The formulation of claim 1, wherein the buffer system comprises phosphate or gluconate.	"Examples of buffers that will control the pH in this range include acetate (e.g. sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers." Ex. 1003 at 6:66 to 7:2. "Examples of buffers that will control the pH within this range include acetate (e.g. sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers." Ex. 1003 at 22:22-25.
4. The formulation of claim 1,	"A 'polyol' is a substance with multiple

’158 Patent Claim	Disclosure in Lam Patent (Ex. 1003)
wherein the polyol is a sugar alcohol. **18**. The formulation of claim 17, wherein the polyol is a sugar alcohol.	hydroxyl groups, and includes sugars (reducing and nonreducing sugars), sugar alcohols and sugar acids.” Ex. 1003 at 6:38-40.
9. The formulation of claim 1, wherein the surfactant is a polysorbate. **10.** The formulation of claim 9, wherein the polysorbate is polysorbate 80. **20**. The formulation of claim 17, wherein the surfactant is a polysorbate. **21**. The formulation of claim 20, wherein the polysorbate is polysorbate 80.	“A surfactant is also added to the antibody formulation. Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbates 20, 80 etc) ….” Ex. 1003 at 22:49-51.
11. The formulation of claim 10, wherein the polysorbate 80 concentration is between 0.1 to 10 mg/ml. **12**. The formulation of claim 11, wherein the polysorbate 80 concentration is between 0.5 to 5 mg/ml. **13**. The formulation of claim 12, wherein the polysorbate 80 concentration is 1 mg/ml. **22**. The formulation of claim 21, wherein the polysorbate 80 concentration is 1 mg/ml.	“The amount of surfactant added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. For example, the surfactant may be present in the formulation in an amount … most preferably from about 0.01% to about 0.1%.” Ex. 1003 at 22:52-59.
14. The formulation of claim 1, wherein the pH is from 4.5 to 6.0.	“The buffer of this invention has a pH in the range from about 4.5 to about 6.0;

’158 Patent Claim	Disclosure in Lam Patent (Ex. 1003)
15. The formulation of claim 14, wherein the pH is from 4.8 to 5.5. **23**. The formulation of claim 17, wherein the pH is from 4.5 to 6.0. **24**. The formulation of claim 23, wherein the pH is from 4.8 to 5.5.	preferably from about 4.8 to about 5.5; and most preferably about 5.0.” Ex. 1003 at 6:61 to 7:3; *id*. at 22:18-25 (same).
16. The formulation of claim 1, which is suitable for single use subcutaneous injection. **25**. The formulation of claim 17, which is suitable for single use subcutaneous injection.	“The formulation is administered to a mammal in need of treatment with the antibody, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, … subcutaneous … routes.” Ex. 1003 at 23:32-38.

The express disclosure in the Lam patent corresponding to claims 2, 3, and 26 renders those claims obvious because skilled persons understood that antibodies often had to be formulated at higher concentrations due to their high molecular weight, low potency, and volume limitations of subcutaneous administration. Ex. 1002 at ¶s 95-96.

The express disclosure in the Lam patent corresponding to claims 27-30 renders those claims obvious because skilled persons understood that common buffers in pharmaceutical formulations included histidine, succinate, acetate, and gluconate, *id*. at ¶ 62, and the Lam patent taught to use these excipients in

combination with the same formulation components recited in claim 1. *Id*. at ¶s 97-98.

The express disclosure in the Lam patent corresponding to claims 4 and 18 renders those claims obvious because skilled persons understood that sugar alcohols (such as mannitol) are a type of polyol that were commonly used in pharmaceutical formulations to stabilize proteins. *Id*. at ¶s 63-64, 74-76, and 99-100.

The express disclosure in the Lam patent corresponding to claims 9-13 and 20-22 renders those claims obvious because skilled persons understood that polysorbate 80 was the most common surfactant used in parenteral pharmaceutical formulations as of August 16, 2002, and skilled persons would have reasonably expected it to stabilize formulations. *Id*. at ¶s 101-102.

Claims 11-13 and 22, specify amounts of polysorbate 80 in units of mg/ml. The Lam patent specifies amounts of the same surfactant in different units. Dr. Randolph explains how to convert between these different units, and that polysorbate concentration of 0.01% to 0.1% v/v disclosed in the Lam patent (see Table 1, above) is about 0.1 mg/ml to 1 mg/ml. *See* Ex. 1002 at ¶ 80.

The subject matter recited in each of claims 11-13 and 20 would have been obvious because the claimed ranges encompass (claim 11) and overlap (claim 12) the concentration range (0.1 to 1 mg/ml) taught by the Lam patent, *see Ormco*

Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) (stating that a claimed range is presumptively obvious when it overlaps with a prior art range), and the concentration specified in claims 13 and 22 is identical to the end-point of the range disclosed in the Lam patent. The skilled person would reasonably expect success with these concentrations given the state of the art. *See* Ex. 1002 at ¶ 102.

The express disclosure in the Lam patent corresponding to claims 14, 15, 23 and 24 renders those claims obvious because skilled persons understood that the state of the art generally guided the skilled person to avoid extremes in pH, and taught that although the pH of a particular formulation depends on the particular antibody, pH optimization was routine. Ex. 1002 at ¶s 59-62. Further, skilled persons understood that subcutaneous dosage forms of claims 16 and 25 were desirable because such forms were convenient and associated with fewer risks than intravenous dosage forms. Ex. 1002 at ¶s 103-104.

3. AbbVie's Criticisms of the Lam Patent Lack Merit

Despite copying various definitions for claim terms right out of the Lam patent's specification, and despite undeniable similarities between the '158 patent and the Lam patent in descriptions of various formulation excipients, AbbVie has criticized the teachings in the Lam patent (during prosecution of another member of the '158 patent family) as offering skilled persons no reasonable expectation that any antibody formulations disclosed therein would stabilize an antibody

having sequences (including CDRs) differing from the ones exemplified. *See* Ex. 1043 at 140-172 (Amend., Apr. 16, 2014); Ex. 1002 at ¶s 106-108. AbbVie's criticisms, advanced though attorney argument, lack merit.

First, contrary to AbbVie's argument, the development of a new protein formulation was not a complex process as of August 16, 2002. As explained by Dr. Randolph, skilled persons understood how to achieve a stable, isotonic protein formulation. *See, e.g.*, Ex. 1002 at ¶s 49-50. The Wang article (Ex. 1017), which AbbVie relied on to argue that "formulating pharmaceutical compositions of proteins was a complex process," actually provides guidance on how to formulate such compositions. It teaches *all* of the excipient components recited in the challenged claims of the '158 patent, and *how* to optimize those features to develop a stable formulation. Just because each new formulation must be optimized on a case-by-case basis does not mean that the formulation development is complex or not routine. Ex. 1002 at ¶ 74. Further, numerous commercial protein formulations, which included an optimized combination of the same excipients that the Wang article teaches, also provided the skilled person with sufficient guidance. *Id.* at ¶s 109-110.

AbbVie's second argument fares no better. AbbVie relied on three other articles (Exs. 1044-1046) to assert that because the hydrophobicity of antibody CDRs is a key determinant of the propensity of antibodies to aggregate, success

with one antibody is not predictive of success with another antibody having different CDRs. Ex. 1002 at ¶s 108, 111. But those articles are not relevant to the design of new protein formulations because all three involve altering the antibody *itself* to observe the effect of mutations on stability, rather than altering the *excipients* with which it interacts. The antibody mutants were not intended for therapeutic use (or pharmaceutical formulations) but rather were tested for altered susceptibility to denaturants. *Id*. at ¶ 111(a), (f), and (g).

Further, although hydrophobicity is a factor in determining whether a protein will aggregate, understanding the hydrophobicity of a particular protein merely enables the skilled person to determine whether to start the routine experimentation using a higher amount of surfactant (if the protein has a higher degree of hydrophobicity), or a lower amount of surfactant (if the protein has a lower degree of hydrophobicity). *Id.* at ¶ 111(b), (e). While CDRs of two antibodies may have a low degree of sequence identity, the antibodies may still have similar hydrophobicities, and therefore, similar aggregation properties. *Id*.

Different monoclonal antibodies typically have different CDR sequences. Even though the CDRs of the D2E7 antibody do not have 100% sequence identity with the CDR sequences of the Lam antibody, the skilled person would not have been deterred from applying the teachings of Lam to D2E7. Although differences in CDR sequences could result in different hydrophobicities, the hydrophobicity of

D2E7 is not significantly different from the hydrophobicity of the other antibodies disclosed in the art. Even if there were some significant difference in hydrophobicity (which there is not), as described above, knowledge of that difference would merely enable the skilled person to determine whether to start the routine experimentation. *See* ¶ 111(b). Indeed, the skilled person would have used routine experimentation to determine the optimal amount of a formulation component taught by Lam—such as the amount of surfactant—so that it would work with D2E7, regardless of differences between the CDR sequences. *See, e.g.*, *id*. at ¶s 49, 53, 59, 63, 70, 150-151. While some antibodies may require more experimentation to arrive at the optimal formulation, the process of designing the formulation was still the same, and optimizing the formulation for a particular antibody was still routine as of August 16, 2002. *Id*. at ¶ 111(b). Additionally, the WINRHO® FDA-approved immune globulin formulation shows that numerous antibodies that vary in sequence can be stabilized in the same formulation using the claimed components. *Id.* at ¶ 111(d).

AbbVie's arguments are also inconsistent with the antibody formulation claims it has sought. For example, in the PCT application for the '158 patent and in family members of the '158 patent (U.S. Patents 8,216,583 and 8,932,591), AbbVie sought to claim formulations that applied to *any* antibody, regardless of its CDRs. *Id.* at ¶ 111(h).

In sum, contrary to AbbVie's arguments, skilled persons would not have concluded that success with another antibody would be unpredictable simply because each new antibody has different CDRs. Indeed, the skilled person would have looked to the formulations of other antibodies for guidance when designing a formulation for D2E7. While some antibodies may require more experimentation than others to arrive at the optimal formulation, the process of designing the formulation was still the same: the skilled person would have used the formulation components that were known and would have optimized for D2E7. *Id*. at ¶ 112. Indeed, the Lam patent states that "[i]n designing antibody formulations, it may be useful to analyze the structural properties of the antibody to be formulated, *but this is not necessary*." Ex. 1003 at 26:64-65 (emphasis supplied). Further, the Lam patent teaches the skilled person how to design stable aqueous formulations of antibodies beyond the ones it tested, and specifically states that its formulation design will apply to antibodies that bind TNFα, *id*. at 10:7 and 10:19, such as D2E7. Consequently, AbbVie's criticism of the Lam patent and the state of the art lacks merit, and is not a basis on which to deny inter partes review on Ground 1.

C. GROUND 2: Claims 1-4, 9-18, and 20- 30 Are Rendered Obvious by the Combination of the Salfeld and Heavner Patents

1. Claims 1 and 17 Would Have Been Obvious

Claim 1 recites a stable liquid aqueous pharmaceutical formulation that comprises a buffer system having a pH of 4 to 8, a polyol, a surfactant, and 20 to

150 mg/ml of a human IgG1 anti-human TNFα antibody (or an antigen-binding portion thereof) that includes the light and heavy chain variable regions of D2E7. Ex. 1002 at ¶ 113. The Salfeld patent discloses or teaches all of these claimed features: it expressly discloses every feature except the antibody concentration of 20 to 150 mg/ml and the pH of 4 to 8, and implicitly teaches those two features. Even if those two features are not considered implicitly taught by the Salfeld patent, they are expressly taught by the Heavner patent.

The Salfeld patent is directed to pharmaceutical compositions of anti-TNFα antibodies, and claims a pharmaceutical composition of the specific antibody D2E7 or an antigen binding portion thereof. Ex. 1005 at 58:29-31 (claim 29). The Salfeld patent also discloses how to formulate such antibodies. It teaches that a pharmaceutical composition of D2E7 can be in a liquid dosage form (*id*. at 21:12-16) and includes a surfactant (*id*. at 21:45-49), a buffer (*id*. at 21:9-10), and a "polyol, which acts as a tonicifier and may stabilize the antibody." Ex. 1002 at ¶s 116-117. Although "stable" in the preamble should not be accorded patentable weight, even if it were, the compositions of the Salfeld patent are disclosed to be stable under the conditions of manufacture and storage. Ex. 1005 at 21:28-29; Ex. 1002 at ¶ 117. Thus, the Salfeld patent expressly discloses every claimed feature except for the antibody concentration and pH; it implicitly teaches those two features, as explained below.

Like the Salfeld patent, the Heavner patent is directed to pharmaceutical compositions of anti-TNFα antibodies and teaches how to formulate them. It teaches that anti-TNF antibodies can be highly concentrated (Ex. 1006 at 44:42-51) in formulations that may include a surfactant (*id*. at 4:45-55), a buffer (*id*. at 30:54-62) with a preferred pH range of about 6.0 to about 8.0 (*id*. at 32:28-33), and a polyol (*id*. at 32:23-25 and 42:38-41). Ex. 1002 at ¶ 120.

The two claimed features that are not expressly disclosed by the Salfeld patent are taught by Salfeld. The Salfeld patent teaches an antibody concentration that falls with the claimed range of 20 to 150 mg/ml. This teaching comes from the Salfeld patent's disclosure that the antibody concentration is preferably 1-10 mg/kg. Ex. 1005 at 23:12-15; Ex. 1002 at ¶ 119. The effective dose of 1 mg/kg disclosed in the Salfeld patent, in light of the average patient weight (70 kg) and the practical injection volume for a subcutaneous administration (about 0.3 ml to about 1.5 mL), translates to an antibody concentration of about 50-90 g/ml. *See* Ex. 1002 at ¶s 52, 119.

The Salfeld patent also teaches a pH that falls within the claimed range of 4 to 8, for two reasons. First, the Salfeld patent discloses a phosphate buffered saline, which buffers at a pH that falls within the claimed range. Second, the Salfeld patent discloses a "physiologically compatible" carrier; the skilled person would

have understood that term to mean that the formulation has a pH between 4-8, the pH range that is physiologically compatible with human patients. *Id.* at ¶ 118.

Even if the Salfeld patent did not teach the claimed antibody concentration and pH range, the Heavner patent taught that anti-TNFα antibody formulations should have these values. First, the Heavner patent taught that anti-TNFα antibody formulations should have a pH between about 6.0 and about 8.0. Ex. 1006 at 32:28-33; Ex. 1002 at ¶ 120. This is consistent with the fact that as of August 16, 2002, nearly all commercially available protein formulations, including antibody formulations, had a pH within that range. Ex. 1002 at ¶s 59-62. Second, the Heavner patent taught an antibody concentration of up to 100 mg/ml. Ex. 1006 at 44:42-51; Ex. 1002 at ¶ 120. This is consistent with the fact that art at the time taught concentrated formulations of IgG antibodies, from concentrations above 50 mg/ml to concentrations above 100 mg/ml. Ex. 1002 at ¶ 75 (discussing Ex. 1018 and Ex. 1037).

The skilled person would have been motivated to combine the disclosures of the Salfeld and Heavner patents because both focus on anti-TNFα antibodies, both focus on IgG antibodies, and both teach how to formulate these antibodies. *Id.* at ¶s 115, 121. The skilled person would reasonably have expected the Salfeld composition to be effective at the pH and antibody concentrations disclosed in the

Heavner patent because antibodies of the same class (e.g., IgG_1) share similar three dimensional structure and behave similarly. *Id*. at ¶s 56, 121.

Accordingly, the combination of the Salfeld and Heavner patents would render obvious claim 1 of the ’158 patent. *Id*. at ¶ 122.

Claim 17 depends from claim 1. Claim 17 recites that the antibody is D2E7, which, as noted above, is expressly disclosed in the Salfeld patent. Consequently, the skilled person would have considered the subject matter recited in claim 17 obvious for the same reasons as those presented for claim 1. *Id*. at ¶ 123.

2. Claims 2-4, 9-16, 18, and 20-30 Would Have Been Obvious

Each feature recited in dependent claims 2-4, 9-16, 18, and 20-30 is disclosed in one of the Salfeld and Heavner patents. Each of these claims is obvious, therefore, for at least the same reasons that the independent claims are obvious. *See generally*, *id.* at ¶s 124-141. The following table shows where in these patents can be found an express disclosure of the features recited in these claims:

Table 5. Disclosures in the Salfeld and Heavner Patents

’158 Patent Claim	Disclosure in Salfeld/Heavner Patents
2. The formulation of claim 1, wherein the concentration of the antibody or antigen-binding portion is 45 to 105 mg/ml. **3**. The formulation of claim 2, wherein the concentration of the antibody or antigen-binding portion is 50 mg/ml.	“Formulations of at least one anti-TNF antibody composition protein … typically include antibody composition protein in an aqueous solution at a concentration of … 45, 50, 60, 70, 80, 90 or 100… mg/ml or mg/gm.” Ex. 1006 at 44:42-51.

’158 Patent Claim	Disclosure in Salfeld/Heavner Patents
26. The formulation of claim 17, wherein the concentration of the antibody or antigen-binding portion is 50 mg/ml.	
27. The formulation of claim 1, wherein the buffer system comprises histidine. **28**. The formulation of claim 1, wherein the buffer system comprises succinate. **29**. The formulation of claim 1, wherein the buffer system comprises acetate. **30**. The formulation of claim 1, wherein the buffer system comprises phosphate or gluconate.	“Representative amino acid/antibody components, which can also function in a buffering capacity, include … histidine, … and the like.” Ex. 1006 at 30:38-42. “Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Ex. 1006 at 30:56-60. “Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof.” Ex. 1005 at 21:1-4.
4. The formulation of claim 1, wherein the polyol is a sugar alcohol. **18**. The formulation of claim 17, wherein the polyol is a sugar alcohol.	“In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition.” Ex. 1005 at 21:4-7. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). Ex. 1006 at 42:39-41.
9. The formulation of claim 1, wherein the surfactant is a polysorbate.	“[A]nti-TNF antibody compositions of the invention can include … surfactants (e.g., polysorbates such as “TWEEN 20”

’158 Patent Claim	Disclosure in Salfeld/Heavner Patents
10. The formulation of claim 9, wherein the polysorbate is polysorbate 80. **20**. The formulation of claim 17, wherein the surfactant is a polysorbate. **21**. The formulation of claim 20, wherein the polysorbate is polysorbate 80.	and “TWEEN 80”).” Ex. 1006 at 30:63-64 and 31:1-3.
14. The formulation of claim 1, wherein the pH is from 4.5 to 6.0. **15**. The formulation of claim 14, wherein the pH is from 4.8 to 5.5. **23**. The formulation of claim 17, wherein the pH is from 4.5 to 6.0. **24**. The formulation of claim 23, wherein the pH is from 4.8 to 5.5.	“The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9 ….” Ex. 1006 at 32:28-30.
16. The formulation of claim 1, which is suitable for single use subcutaneous injection. **25**. The formulation of claim 17, which is suitable for single use subcutaneous injection.	“The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). … In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.” Ex. 1005 at 21:21-27. “The invention further relates to the administration of at least one anti-TNF antibody by . . . subcutaneous, means.” Ex. 1006 at 43:15-16.

The express disclosure in the Salfeld patent corresponding to claims 2, 3, and 26 renders those claims obvious because skilled persons understood that a preferred dose specified in the Salfeld patent is 1 mg/kg and that a subcutaneous formulation delivering that dose would require an antibody concentration close to 50 mg/ml. Ex. 1002 at ¶s 125-126. Further, the Heavner patent expressly discloses a formulation having an anti-TNFα antibody concentration of 50 mg/ml, and the skilled person would have been motivated to use that concentration for the composition of Salfeld. And because both patents focus on formulating anti-TNFα antibodies, the skilled person would reasonably have expected the composition disclosed in the Salfeld patent to be effective at the antibody concentration disclosed in the Heavner patent. *Id*. at ¶ 127.

The Heavner patent identifies as representative buffers salts of succinic acid, acetic acid, and gluconic acid, which the skilled person understood as succinate, acetate, and gluconate. This express disclosure in the Heavner patent (as well as that identified in the Table above) corresponding to claims 27-30 renders those claims obvious because skilled persons understood that common buffers in pharmaceutical formulations included histidine, succinate, acetate, phosphate, and gluconate, *id*. at ¶ 62, and the Heavner patent taught to use these excipients in combination with the same formulation components recited in claim 1. *Id*. at ¶s 128-130. Further, the Salfeld patent includes an express disclosure of a

phosphate-based buffer, in combination with the same formulation components recited in claim 1 further rendering claim 30 obvious. *Id*. at ¶ 130.

The express disclosure in the Salfeld patent corresponding to claims 4 and 18 renders those claims obvious because skilled persons understood that common polyols in pharmaceutical formulations included mannitol, which is a sugar alcohol. *Id*. at ¶s 131-132. Further, the express disclosure in the Heavner patent corresponding to these claims also renders each obvious because skilled persons would have been motivated to use the sugar alcohol (mannitol) of the Heavner patent as the polyol in the Salfeld patent because both patents relate to the formulation of anti-TNFα antibodies. Accordingly, skilled persons would reasonably expect the composition disclosed in the Salfeld patent to be effective using the sugar alcohol disclosed in the Heavner patent. *Id*. at ¶ 133.

The express disclosure in the Heavner patent corresponding to claims 9, 10, 20, and 21 renders those claims obvious because skilled persons would have been motivated to use polysorbate disclosed in the Heavner patent as the surfactant the Salfeld patent discloses because both patents relate to the formulation of anti-TNFα antibodies. *Id*. at ¶s 134-135. In addition to the disclosure in the Heavner patent, polysorbates 20 and 80 were two of the most commonly used surfactants in parenteral pharmaceutical formulations as of August 16, 2002. These surfactants would have been the first surfactants the skilled person would have used and the

skilled person would had a reasonable expectation of success in modifying the Salfeld formulation to include one of these surfactants. *Id*. at ¶ 135.

Claims 11-13 and 22 specify that the polysorbate 80 is present in a concentration of 0.1 to 10 mg/ml (claim 11), 0.5 to 5 mg/ml (claim 12), and 1 mg/ml (claims 13 and 22). *Id.* at ¶ 136. Skilled persons understood that polysorbate 80 was the most commonly used surfactant in commercial parenteral protein formulations (Ex. 1020 at p. 167, Table II; Ex. 1002 at ¶ 66), that 1 mg/ml polysorbate 80 had been reportedly required to stabilize an antibody formulation subjected to simulated shipping stress (Ex. 1002 at ¶ 67), and that determining the amount to include was routine. Accordingly, the concentrations of surfactants recited in claims 11-13 and 22 would have been obvious. *Id*. at ¶ 136.

The express disclosure in the Heavner patent of formulations having pH 5 falls within the ranges recited in claims 14, 15, 23, and 24, thus, rendering those claims obvious. Additionally, the Salfeld patent teaches that the pharmaceutical composition includes a carrier that is "physiologically compatible," which the skilled person would have understood to mean appropriate for administration to a patient, i.e., pH of 4 to 8. The skilled person would have reasonably expected the composition disclosed in the Salfeld patent to be effective at the pH values recited in claims 14, 15, 23, and 24. *Id*. at ¶s 138-139.

The express disclosure in the Salfeld and Heavner patents corresponding to claims 16 and 25 renders those claims obvious because skilled persons understood that subcutaneous dosage forms were convenient and associated with fewer risks than intravenous dosage forms. *Id*. at ¶ 140.

3. AbbVie's Criticism of the Salfeld and Heavner Patents Is Not Applicable or Relevant

During prosecution of a related patent (U.S. Patent No. 8,802,100) in the same family as the '158 patent claiming an obvious variation of the formulations recited in the challenged claims, AbbVie argued that the Heavner patent in view of the Salfeld patent does not render obvious its formulation. File History of U.S. Patent No. 8,802,100 (Ex. 1050) at 149-186 (Amend. April 16, 2014). Specifically, AbbVie argued that the Heavner patent relates to an anti-TNF antibody having specific heavy and light chain sequences, but does not teach how to stabilize the antibody in an aqueous pharmaceutical solution, describing only lists of preservatives, administration routes, and doses. *Id*. at 163-164. According to AbbVie, the skilled person "would have seriously doubted that all these hundreds of thousands of combinations would provide a stable formulation for an anti-TNF antibody." *Id*. Consequently, according to AbbVie, there would have been no motivation to combine the D2E7 antibody disclosed in the Salfeld patent with the formulation the Heavner patent teaches with a reasonable expectation of success. *Id*; Ex. 1002 at ¶s 142-143. Those arguments lack merit.

When formulating D2E7, the skilled person would not have been faced with a random choice of "hundreds of thousands of potential combinations of formulation ingredients." Rather, the skilled person would have rationally selected from a standard, limited set of buffers, tonicity agents (e.g., polyols), and surfactants—excipients that were known to be safe and effective in pharmaceutical formulations—and optimized to find the best combinations and amounts through routine experimentation. The skilled person was further guided by the commercial formulations of antibodies and proteins available as of August 16, 2002, which also illustrated the use of a limited list of each type of excipient. *Id*. at ¶s 144-147.

AbbVie's argument that the skilled person would not have expected the Heavner patent's teachings to apply to D2E7 because of sequence differences (72.7% and 69.2% identity) between Heavner's antibody and D2E7 also lacks merit. *Id*. at ¶s 148-149. First, many commercial antibodies have different sequences but are formulated using the same components. *Id*. at ¶ 149. Second, a sequence difference between two antibodies does not imply that one antibody is so structurally different from the other antibody that formulation components that work for one antibody would not work for the other. *Id*. Third, AbbVie's argument is contradicted by the fact that it sought claims in the PCT application for the '158 patent and related patents for a formulation that works for all antibodies, even ones having different sequences. Ex. 1002 at ¶ 111(h).

Finally, different monoclonal antibodies typically have different CDR sequences. Even though the CDRs of the D2E7 antibody do not have 100% sequence identity with the CDR sequences of the Heavner antibody, the skilled person would not have been deterred from applying the teachings of Heavner to D2E7. Although differences in CDR sequences could result in different hydrophobicities, the hydrophobicity of D2E7 is not significantly different from the hydrophobicity of the other antibodies disclosed in the art (such as the antibody of Heavner). Even if there were some significant difference in hydrophobicity (which there is not), knowledge of that difference would merely enable the skilled person to determine whether to start the routine experimentation using a higher amount of surfactant (if the antibody has a higher degree of hydrophobicity), or a lower amount of surfactant (if the antibody has a lower degree of hydrophobicity). *See* ¶s 150-151. Indeed, the skilled person would have used routine experimentation to determine the optimal amount of a formulation component taught by Heavner—such as the amount of surfactant—so that it would work with D2E7, regardless of differences between the CDR sequences. *See, e.g.*, *id*. at ¶s 49, 53, 59, 63, 70, 150-151. While some antibodies may require more experimentation to arrive at the optimal formulation, the process of designing the formulation was still the same, and optimizing the formulation for a particular antibody was still routine as of August 16, 2002. *Id*. at ¶s 152-153.

Consequently, AbbVie's criticism of the Heavner and Salfeld patents and the state of the art lack merit, and is not a basis on which to deny inter partes review on Ground 2.

D. Any Secondary Considerations of Nonobviousness Fail to Overcome the Strong Prima Facie Showing of Obviousness

To counter the overwhelming evidence that the challenged claims are obvious, AbbVie may try to rely on secondary considerations of nonobviousness. Any such evidence would be "insufficient" to "overcome the strong [case] of obviousness" here. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Petitioner nonetheless preliminarily addresses some considerations that AbbVie may allege, and requests that consideration of such evidence not be undertaken until Petitioner has had an opportunity to respond. *See Amneal Pharms., LLC v. Supernus Pharms., Inc.*, IPR2013-00368, Paper 8 at 12-13 (P.T.A.B. 2013).

1. No Unexpected Results

There is no evidence that the broad formulations recited in the claims, which are devoid of concentration amounts for the recited, standard pharmaceutical excipient classes (e.g., buffer, tonicity agent, and surfactant)—yield *any* result unexpected relative to the prior art underlying the grounds presented herein. Even if there were objective evidence of unexpected results (and there is not), such

results would not be commensurate in scope with the claimed invention as required by case law. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

(a) The Data Presented in the ’158 Patent Are Not Unexpected and Are Not Commensurate in Scope with the Challenged Claims

As explained below, the data presented in the ’158 patent are neither unexpected nor commensurate in scope with the challenged claims. Specifically, these data (and also data AbbVie presented during a pending, foreign opposition) are limited to testing of a single antibody sequence, a specific combination of four buffer components, a specific combination of two tonicity agents (only one of which is a polyol), and a specific surfactant. In contrast, the challenged independent claim is not so limited and broadly specifies these classes of excipients. Thus, it is impossible for such results to be commensurate in scope with the breadth of all of the ’158 patent claims, which read on antibody-binding portions as small as one CDR, because analogous results would need to be shown for such fragments which are only 5 to 17 amino acids in length. *See* Section V.C.3. Similarly, it is impossible for such results to be commensurate in scope with the breadth of a claim reciting “antibodies” that reads on any number of variations within the constant regions, on any number of variations within the variable regions provided CDR3 is retained. *Id.*

The ’158 patent includes two examples. Example 1 describes a protocol for preparing a formulation containing D2E7, mannitol and NaCl tonicity agents, polysorbate 80, and a citrate-phosphate buffer, and Example 2 describes freeze/thaw studies. Ex. 1001 at 21:39 to 22:40 and 23:1-32; Ex. 1002 at ¶s 154-156. No information is offered as to the particular D2E7 sequence tested. The ’158 patent asserts that the data reported in Table 2 show that “the inclusion of polysorbate 80 improved the physiochemical properties of D2E7 antibody drug substance as evidenced by the lower number of subvisible particles.” Ex. 1001 at 22:62-67; Ex. 1002 at ¶ 157.

The skilled person would have expected that result. As of August 16, 2002, the most common way to stabilize and prevent aggregation of protein formulations was to add a nonionic surfactant to the formulation, and the most common surfactant used commercially for this purpose was polysorbate 80. *See* Ex. 1002 at ¶s 68-69. Therefore, even if the subvisible particle data presented in Table 2 indicate that the presence of 0.1% w/v polysorbate 80 decreased the number of subvisible particles, that data would have been expected and unsurprising. Ex. 1002 at ¶ 158.

Further, the ’158 patent only tests the effect of 0.1% w/v (i.e., 1 mg/ml) polysorbate 80 on the formulation described in Example 2, and offers no comparative data using a different concentration of polysorbate. Thus, the ’158

patent contains no evidence that the selection of a concentration of polysorbate 80 yields unexpected or surprising results. Moreover, even if AbbVie showed that 1 mg/ml polysorbate 80 was superior to other concentrations of polysorbate 80 (which it has not shown), the skilled person would have reached that conclusion through routine experimentation. Accordingly, there is no scenario in which the presence of 0.1% w/v (0.1 mg/ml) of polysorbate 80 in an antibody formulation would be unexpected or surprising. *Id*. at ¶s 157-161.

The other data reported in Table 2 are not evidence of unexpected results. Instead, these data indicate that the presence of polysorbate 80 had no effect on color, formulation pH, size exclusion chromatography, or cation exchange chromatography. Further, although the data regarding clarity and in vitro TNF neutralization appear to show small differences in the values reported, depending on whether 0.1% polysorbate 80 is present, the ’158 patent does not explain what the values mean or whether the differences are significant. Even if the data were to have indicated that the presence of polysorbate 80 results in an improvement in clarity and biological activity, such results would not have been surprising due to the surfactant’s known function in stabilizing proteins and preventing protein aggregation. *Id*. at ¶ 162.

The ’158 patent is also silent about how the data in Table 2 were obtained, what experimental protocols were used, whether control tests were conducted (and

results thereof), units of the measured data, and degree of experimental error. The skilled person cannot, therefore, evaluate or reproduce the data, and would have no confidence that the reported values are accurate or precise. *Id*. at ¶ 163.

(b) The Data Presented in the European Counterpart to the '158 Patent Are Not Unexpected and Are Not Commensurate in Scope with the Challenged Claims

As explained below, the data AbbVie presented in Europe ("EP") to support much narrower claims do not show unexpected results commensurate in scope with the broad claims challenged here. *Id*. at ¶s 164-165. AbbVie presented data and arguments (Ex. 1053) that its narrowly claimed EP formulation is, under the European patent laws, patentable over the prior art (including the Barrera article and the Salfeld patent). Specifically, AbbVie argued that its claimed EP formulation yields results unexpected or surprising relative to what the prior art disclosed. *Id*. at ¶s 166-168. As explained below, those arguments lack merit, and the data supporting those arguments do not demonstrate anything surprising or unexpected. Moreover, AbbVie's arguments and data are irrelevant to the challenged grounds presented herein because the challenged claims do not recite the specific features on which AbbVie relied for the patentability arguments it presented in Europe. Thus, those arguments should not be considered as a basis to deny inter partes review.

Specifically, the European Patent Office ("EPO") granted AbbVie patent No. 1 528 933 on an application that is a counterpart to the '158 patent and, accordingly, shares the same specification disclosure. Importantly, the claims in the '933 EP patent are substantially more narrow than the challenged claims of the '158 patent. Specifically, the EP claimed 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 each of citric acid monohydrate, sodium citrate, disodium phosphate dehydrate, sodium dihydrogen phosphate dehydrate, and sodium chloride. Test Report AbbVie submitted to EPO (May 15, 2009) during prosecution of EP 1 528 933 (B1) (Ex. 1054) at 25; Ex. 1002 at ¶ 165. The '933 EP patent has been opposed in Europe and that opposition is pending before the Opposition Division ("OD") at the EPO. Ex. 1002 at ¶s 169-171.

For the reasons discussed below, the data submitted to the OD are not surprising and relate to only a few specific embodiments of the broad challenged U.S. claims. *See id.* at ¶ 172. The data presented on buffers that fall outside of the EP claims but within the U.S. claims indicate that these buffers lack unexpected results. Additionally, data on other antibodies (to targets other than TNF) indicate the general applicability of the claimed formulations to stabilize antibodies with various CDR sequences, thus contradicting the argument AbbVie made during U.S. prosecution about the unpredictability of formulating antibodies with different

CDR sequences. Other data merely demonstrate the known ability of these formulation components to stabilize various antibody concentrations, and the known stabilization effect of mannitol and polysorbate 80. These data do not demonstrate any unexpected results compared to the Salfeld and Barrera references raised during EP prosecution. Even if these data were somehow unexpected, AbbVie seems to attribute them to the specific combination of phosphate and citrate that is not required by the U.S. claims.

(i) Buffers Within the Scope of the Challenged Claims Lacked Unexpected Results

AbbVie's own data in Example B of the test report (EP 1 528 933 (B1), Ex. 1052) indicate that formulations within the scope of the challenged U.S. claims lacked unexpected results. In particular, an acetate/phosphate buffer was not as good at stabilizing D2E7 as a citrate/phosphate buffer (when combined with the NaCl, polysorbate 80, and mannitol components of the formulation claimed in Europe). Table 10 indicates that the acetate/phosphate formulation which is encompassed by the challenged U.S. claims produced a much higher clarity score (e.g., 530 compared to 77.3, indicating lower physical stability).

Even if AbbVie were to argue that the data for these inferior acetate/phosphate formulations were unexpected, these data do not support a position that *all* buffer systems within the recited pH range unexpectedly stabilize the protein. *Id*. at ¶s 176-177. In contrast, the skilled person would consider a

narrow pH range (e.g., pH 4 to 8) as likely suitable to stabilize a large protein, such as an antibody.

(ii) Stabilization of Antibodies to Other Targets Demonstrates the Ability to Stabilize Antibodies of Various Sequences

AbbVie's results also demonstrate that there is nothing unexpected about the formulation of the challenged claims being able to stabilize particular IgG1 antibodies. The data indicated that its claimed EP formulation (containing a citrate-phosphate buffer system) within a pH range of 3 to 8 could stabilize *other* IgG_1 antibodies (anti-IL12 and anti-IL13), which have different antigen specificity and different CDRs. *Id*. at ¶ 178. AbbVie's reported results suggest that there is nothing particularly difficult in stabilizing different IgG_1 antibodies (having different CDRs)—results that contradict AbbVie's arguments presented in prosecution of its U.S. applications within the '158 patent family and that instead are consistent with AbbVie's original attempt in in family members of the '158 patent to claim formulations of any antibody. *See* Section VI.C.3, above. Further, AbbVie's reported results lead to a conclusion that the stability purportedly achieved is attributable to the citrate-phosphate buffer system at pH 3 to 8 in combination with the other specific ingredients of the claimed EP formulation, which is not commensurate in scope with the challenged U.S. claims. Ex. 1002 at ¶ 178.

(iii) Stabilization of Various Antibody Concentrations Was Known

In contrast to AbbVie's argument that it was surprising that various concentrations of antibody (e.g., 1 to 158 mg/ml) were stabilized by the same formulation in Example A (Ex. 1054), the skilled person would not have considered these data surprising as these types of components frequently stabilize different concentrations of antibody. Ex. 1002 at ¶s 173-175 (discussing prior art formulations (Exs. 1018, 1037, and 1023) containing high antibody concentrations). Further, as each of the tested formulations contained exactly the same phosphate-citrate buffer system, polyol, and surfactant, these data do not demonstrate unexpected results relative to the broad scope of the challenged claims of the '158 patent, which do not specify this phosphate/citrate buffer system or the tested concentrations of polyol and surfactant. *Id*. at ¶ 176.

(iv) Stabilization by Mannitol Was Known

The data in Example C on various concentrations of mannitol (polyol) are not surprising given the known ability of mannitol to stabilize antibodies, and are not commensurate in scope to the challenged claims of the '158 patent, which are neither limited to mannitol nor a particular concentration of mannitol. *Id*. at ¶ 179.

(v) Stabilization by Polysorbate 80 Was Known

Data in Example C on one concentration of polysorbate 80 merely shows the well-known effect of polysorbate 80 on reducing the number of subvisible particles. AbbVie concludes the presence of 1 mg/ml polysorbate 80 effectively

stabilized the formulation compared to the same formulation without polysorbate 80, and characterizes this as "very surprising, as polysorbate 80 has repeatedly been reported to increase protein stability upon air-liquid interface or ice-water interface stress, but not during quiescent storage (where polysorbate 80 is known to be prone to autoxidation, eventually causing protein oxidation resulting in aggregation)." Ex. 1052 at 19; Ex. 1002 at ¶s 180-185. As explained above, *see* Section VI.A, there is nothing surprising in the ability of polysorbate 80 to stabilize a protein formulation. The skilled person understood that the presence of polysorbate 80 would reduce protein aggregation and would not have expected properly purified polysorbate to cause or contribute to protein oxidation resulting in aggregation. Ex. 1002 at ¶ 71.

AbbVie's test report also includes other data and commentary that the presence of polysorbate 80 is not necessary to stabilize the D2E7 protein and thus indicates that there was nothing surprising about the effect of polysorbate 80 on D2E7 formulations. *Id*. at ¶s 186-187. Indeed, a separate report (Ex. 1055) authored by AbbVie's expert witness ("Gerhard Winter") and submitted to the EPO with its January 2014 submission, states that "Polysorbate 80 contributes to stability but it is not the Polysorbate 80 alone that is responsible for the high stability regarding preservation of the monomeric antibody but to a large extent the phosphate/citrate combination." Ex. 1055 at 8; Ex. 1002 at ¶s 186-188. Thus, the

alleged surprising stability is attributed to the specific combination of phosphate and citrate as the buffer system, which is not commensurate in scope with the challenged claims, which encompass *any* buffer system or buffer systems other than a phosphate and citrate buffer system. Ex. 1002 at ¶ 184.

(vi) Data Fail to Show Unexpected Results in View of Salfeld or Barrera

AbbVie's test report (Ex. 1054) and submission (Ex. 1053) to the OD do not show that the claimed EP formulation is patentably distinguishable from what Salfeld or Barrera discloses. The Salfeld patent discloses pharmaceutical ("physiologically compatible") compositions for subcutaneous injection that contain adalimumab (D2E7), a polyalcohol (e.g., mannitol), and a surfactant. The data presented in AbbVie's test report do not compare or distinguish different polyalcohols or different surfactants that were then known to comprise these excipient classes and thus do not demonstrate any unexpected results compared to these known formulations. More importantly, the data do not rebut a conclusion that the formulation recited in the challenged claims of the '158 patent is obvious over the Salfeld patent when considered in view of the Heavner patent. Ex. 1002 at ¶ 188.

The data in AbbVie's January 2014 submission to the OD for the formulation in the Barrera article (designated as "D11" in that submission) is also not surprising because it was known that polysorbate 80 reduces aggregation,

resulting in fewer subvisible particles and less monomer loss. Specifically, AbbVie's submission states that the Barrera formulation differs from the claimed formulation in that it lacks a combined phosphate-citrate buffer, polysorbate, and sodium chloride, and has a pH of 3.8. Ex. 1053 at 35; Ex. 1002 at ¶ 186. AbbVie argues that its claimed EP formulation "exhibits significantly higher stability than the Citrate formulation of D11 [the Barrera article]." Ex. 1053 at 35 (¶ 167); Ex. 1002 at ¶s 189-190.

Contrary to AbbVie's arguments, there is nothing unexpected or surprising in the comparative data. Ex. 1002 at ¶s 191-194. The Barrera article describes a formulation for a phase I clinical trial—a formulation that does not need to be shelf stable for any extended time period. It is not, therefore, surprising that the Barrera formulation did not achieve the same stability as the comparative formulation AbbVie is attempting to patent in Europe. The skilled person motivated to prepare a storage stable version of the Barrera formulation knew the steps to take to modify that formulation to achieve increased stability. Thus, the comparative data are neither surprising nor unexpected. *Id*. at ¶ 191. The challenged claims of the '158 patent are not limited to the specific combination or concentrations of the phosphate-citrate buffer, polysorbate 80, and sodium chloride that they argued is more stable than the Barrera formulation, and thus the comparative data are not commensurate in scope with the challenged claims. Ex. 1002 at ¶s 192-195.

2. No Other Objective Evidence of Non-obviousness

AbbVie cannot establish that the challenged claims describe a formulation that satisfied any long-felt, but unmet, need. Pharmaceutical formulations containing a D2E7 anti-TNFα antibody existed before any AbbVie commercial product embodied in the challenged claims. *See* Ex. 1002 at ¶s 74-77. Further, long-felt, but unmet need should be a need created by a technical challenge to the skilled person once market forces had created a purported need for a shelf-stable pharmaceutical formulation containing a D2E7 antibody—not by non-technical considerations. *Friskit, Inc. v. Real Networks, Inc.*, 306 F. App'x 610, 617-18 (Fed. Cir. 2009). If there was any need for the formulations recited in the challenged claims, it was anything but long-felt or unmet in view of the state of the art, the disclosures in the prior art, and combinations thereof comprising the grounds presented herein, each demonstrating the claimed formulations would have been obvious.

AbbVie cannot demonstrate that the claimed formulations were met with skepticism or that other skilled persons tried but failed to prepare stable pharmaceutical formulations, having a pH of 4 to 8, and containing, for example, 50 mg/ml antibody, as the '158 patent states is its invention (*see* Ex. 1001 at 6:54-58). *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983). Any evidence of failure of others must suggest that the prior attempts failed because

they lacked the claimed features. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006). AbbVie also cannot demonstrate that the *claimed formulation* was met with any praise in the industry. Because pharmaceutical formulations containing a D2E7 anti-TNFα antibody (and shown to be safe and effective in clinical trials) existed as of the '158 patent's effective filing date, there can be no genuine skepticism or praise for the broad formulation claimed. Any success of AbbVie's specific commercial formulation would be due solely to the D2E7 antibody itself.

E. The Presented Grounds Are Not Redundant

The proposed grounds for unpatentability of the challenged claims are not redundant because important differences exist between the grounds. In Ground 1, the Lam patent and the Barrera article complement each other in different ways to support independent conclusions that the challenged claims would have been obvious no matter which publication is considered the primary reference. The skilled person was motivated to combine the teachings of anti-TNFα antibody formulations in Lam with the disclosure of the particular D2E7 anti-TNFα antibody in Barrera. Alternatively, that person also was motivated to combine the teachings of a clinical D2E7 formulation in Barrera with the disclosure of a surfactant in Lam for improving stability. In Ground 2, the Salfeld patent, lacks only an *express* disclosure of the concentration of the antibody and buffer solution

pH. Thus, the two grounds rely on different combinations of prior art to supplement disclosure of different features (e.g., particular antibody, surfactant, concentration of antibody, and pH) and, accordingly, to demonstrate that the challenged claims are obvious for many reasons.

As only two grounds are presented against a common state of the art as of August 16, 2002, there is no basis to conclude that instituting inter partes review on the both of the presented grounds would be contrary to the administration of the proceeding in a just, speedy, and inexpensive manner. To the contrary, if one of the grounds is denied in view of the Board's discretion, then AbbVie could be burdened with addressing the denied ground in another inter partes proceeding. Further, as the challenged claims may encompass AbbVie's commercial biologic drug product, HUMIRA®, competitive entities known to be pursuing a biosimilar of this product could be burdened with addressing the denied ground in another inter partes proceeding. Accordingly, institution of inter partes review on *both* grounds is appropriate.

F. Supporting Evidence

The exhibit numbers marking the evidence supporting this petition are identified on the pages immediately following the table of contents, and copies of the evidence (exhibits) are submitted herewith.

VII. CONCLUSION

There is a reasonable likelihood that at least one of the challenged claims is unpatentable and, therefore, the petition should be granted.

Respectfully submitted,

June 26, 2015 / Sandip H. Patel, Reg.# 43848 /

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), copies of this petition (including the listed exhibits) and the other papers transmitting and accompanying this petition to the Patent Office are being deposited on June 26, 2015, with FedEx Express, utilizing its "FedEx Standard Overnight" service under Tracking No. 863841777101 in a box addressed to the attention of:

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which is the correspondence address of record (37 C.F.R. § 1.33(c)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,916,158.

June 26, 2015

/ Lidia Cortez /

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