Filed on behalf of: AbbVie Biotechnology Ltd.

Filed: August 9, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.
Patent Owner

Case IPR2016-01018
U.S. Patent No. 9,114,166

PATENT OWNER'S PRELIMINARY RESPONSE

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I. Introduction

The Board should deny the Petition of Coherus Biosciences ("Petitioner") seeking *inter partes* review of claims 1–4, 6–10, 13–16, 23–26 and 28 (the "challenged claims") of AbbVie's U.S. Patent No. 9,114,166 ("the '166 patent"). The challenged claims are directed to certain *stable,* liquid, pharmaceutical formulations of the anti-TNFα antibody D2E7 (a/k/a adalimumab) at the high concentration of *50 mg/ml* that are suitable for subcutaneous (s.c.) administration.

The '166 patent covers HUMIRA®, one of the top selling drugs in the world, used by hundreds of thousands of patients to treat rheumatoid arthritis and other inflammatory conditions. (Ex. 2028 at 1.) When HUMIRA launched in 2003, it was a breakthrough in the field of antibody therapeutics, achieving something that no predecessor commercial antibody formulation had before. Specifically, HUMIRA was the first high-concentration, liquid, antibody formulation for subcutaneous administration to be commercialized.

Nonetheless, Petitioner contends that at the time of the August 16, 2002, priority date of the '166 patent, the challenged claims would have been rendered obvious by the combination of van de Putte (Ex. 1007) and Relton (Ex. 1006).[1]

[1] The Petition contains statements regarding the purported overbreadth of the '166 patent. (*See* Pet. at 1.) Patent Owner disagrees with these assertions, but they need

Because Petitioner has failed to meet its burden of establishing that there is a reasonable likelihood that it will prevail in establishing the invalidity of any of the challenged claims based on this combination of references, the Board should deny the Petition in its entirety.

Van de Putte is merely a quarter-page abstract reporting on an early stage clinical trial of D2E7. (*See* Ex. 1007.) Van de Putte makes no reference whatsoever to any formulation. In fact, aside from noting the subcutaneous administration of D2E7, van de Putte makes no mention of any of the limitations of the challenged claims. Significantly, van de Putte does not even disclose whether the clinical trial used a liquid or lyophilized formulation. Further, van de Putte makes no mention of stability or antibody concentration. Moreover, van de Putte does not disclose that there was any problem with the formulation (whatever it may have been) used in the clinical trial. Accordingly, a person of ordinary skill in the art at the time of the '166 patent's priority date in 2002 (a "POSA") would have had no motivation to select van de Putte or to modify the undisclosed D2E7 formulation used in the clinical trial reported therein. In addition, even if such a motivation had existed,

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not be addressed because they are not properly raised in a petition for *inter partes* review.

Petitioner fails to establish any reason why a POSA would turn to Relton to make any such modifications.

Relton does not even mention D2E7 or any formulation thereof. Although Relton discloses certain *low-concentration* subcutaneous formulations (having an antibody concentration of 1.5 mg/ml) for *other, different* monocolonal antibodies (anti-CD4 or anti-CD23 antibodies), Relton does not provide any stability data for those formulations. As such, Petitioner fails to provide any reason to believe that a POSA would turn to Relton to modify the unknown D2E7 formulation of van de Putte, even had there been a reason to modify it.

Even if Petitioner could establish that a motivation existed to combine these two references (which it cannot), Petitioner fails to establish that a POSA could reasonably expect that adding the D2E7 antibody of van de Putte to any particular formulation in Relton would result in a successful stable pharmaceutical formulation of D2E7 at any concentration, much less at the high concentration of 50 mg/ml concentration claimed in the ’166 patent. Rather, Petitioner relies almost entirely on two unsupported (and erroneous) assertions: (i) that the antibody formulation art in 2002 was routine and predictable, and (ii) that once a stable formulation was discovered for one antibody, a skilled artisan would expect the same formulation to stabilize other, different antibodies. Petitioner then attempts to shift the burden of proof to AbbVie to establish that “D2E7 had any unusual

properties that made it more difficult to formulate than any other IgG1 antibody." (Pet. at 35.) Petitioner's attempt to shift its burden of proof is improper. In any event, both of Petitioner's assertions are wrong. As shown below, the scientific literature from the relevant time period—as well as prior admissions by Petitioner and its expert, Dr. Manning—flatly contradict both assertions.

In fact, the positions Petitioner and Dr. Manning advocate here cannot be reconciled with positions they have taken before this Office in prosecuting Petitioner's own patents and applications on which Dr. Manning is a named inventor (the "Coherus-Manning Patents"), some of which purport to cover formulations of D2E7. Nor can they be reconciled with Dr. Manning's contemporaneous publications. For example, in pursuing a Coherus-Manning Patent, Petitioner emphasized that *ten years after* the '166 patent's earliest claimed priority date "protein stabilization is an *extremely unpredictable* art," (Ex. 2022 at 2) and that "slight modifications of excipients may lead to *widely varying* results." (Ex. 2023 at 4.) Likewise, in his own publications, Dr. Manning has repeatedly explained the complexities of preparing stable liquid formulations, and stated that it could be assumed that "most proteins will *not* exhibit sufficient stability in

aqueous solution to allow a liquid formulation to be developed." (Ex. 1025 at 188 (emphasis added[2]).)

Dr. Manning's IPR-inspired assertions here should not be credited, particularly given the close business relationship that he and Petitioner have with regard to Petitioner's planned commercial launch of a biosimilar version of AbbVie's HUMIRA product, to which the Petitioner admits the '166 patent is an "IP risk." (Ex. 2036 at 3, 5.) Not only is Dr. Manning the named inventor of numerous Coherus-Manning Patents covering various aspects of Petitioner's planned biosimilar version of AbbVie's HUMIRA product, he is also a founder, owner, and officer of Legacy BioDesign, LLC, a contract service organization that was engaged by, and invested in, Coherus. (Exs. 2019, 2041, 2042, 2043.) Because Dr. Manning is necessarily influenced by his strong personal and business interest in the outcome of this proceeding, the Board should give little or no weight to the many conclusory assertions in his Declaration, particularly those that are contradicted by his prior statements.

Finally, a review of the then-existing commercial antibody formulations, including those cited by Dr. Manning, further demonstrates that a POSA would not have had a reasonable expectation of success in developing a stable, liquid,

[2] In this paper, all emphases are added unless otherwise indicated.

pharmaceutical formulation of D2E7 at a high concentration of 50 mg/ml. All of the commercially available liquid antibody formulations at the time had concentrations between 1 and 10 mg/ml, that is between 1/5 and 1/50 of the claimed concentrations. Simply put, the art did not teach that one could quintuple (or more) these commercial antibody concentrations to 50 mg/ml and expect to get a stable liquid pharmaceutical formulation for any antibody, much less for D2E7. Rather, due to the unpredictability and difficulties associated with creating stable liquid antibody pharmaceutical formulations—particularly at high concentrations—publications by Dr. Manning and others in the field *taught away* from the preparation of liquid antibody formulations and instead toward lyophilized (freeze-dried) formulations.

The Petition entirely ignores these teachings, and instead repackages the same meritless arguments that were thoroughly considered and rejected by this Board in two prior IPR proceedings.[3] In the *Amgen* IPRs, the Board denied institution of Amgen's petitions challenging claims directed to stable, liquid,

[3] *See Amgen, Inc. v. AbbVie Biotechnology, Ltd.*, No. IPR2015-01514, (P.T.A.B. Jan. 14, 2016) ("*Amgen* '514 IPR"), Paper 9 (Decision Denying Institution); *Amgen, Inc. v. AbbVie Biotechnology, Ltd.*, No. IPR2015-01517, (P.T.A.B. Jan. 14, 2016) ("*Amgen* '517 IPR"), Paper 9 (same) (collectively, the "*Amgen* IPRs").

pharmaceutical formulations of the anti-TNFα antibody D2E7 (a/k/a adalimumab) at the high concentration of 20 to 150 mg/ml in two patents in the same patent family, having the same specification, and the same effective filing date as the '166 patent. There, Amgen made essentially the same line of arguments about the Barrera and Lam references underlying the *Amgen* IPR petitions that Petitioner makes here with respect to van de Putte and Relton. According to Amgen (and now Petitioner), a person of ordinary skill would have been motivated to combine a reference that purportedly teaches the use of D2E7 in an early stage clinical trial with a second reference that purportedly teaches stable, liquid formulations of different antibodies at high concentrations. But the Board soundly rejected those arguments, finding that the prior art in 2002 did not "provide[] sufficient guidance such that a skilled artisan would have had a reasonable expectation of success in arriving at the formulation of stable, liquid pharmaceutical compositions comprising antibodies at a concentration of 20 to 150 mg/ml." *Amgen* '514 IPR, Paper 9 at 14; *Amgen* '517 IPR, Paper 9 at 15.

Petitioner entirely ignores the Board's findings in the *Amgen* IPRs, and fails to identify (nor can it) anything different about the prior art it relies on here that would warrant a different result. In short, the Petition simply fails to address and overcome the unpredictability and complexities that existed in the antibody formulation art at the relevant priority date, and fails to establish the core aspects

necessary to support an obviousness challenge. Accordingly, the Board should also deny this Petition in its entirety.

II. Level of Ordinary Skill in the Art and Claim Construction

A. Level of Ordinary Skill in the Art

For the limited purpose of this Preliminary Response, Patent Owner does not contest the level of ordinary skill in the art. (Pet. at 16.)

B. Claim Construction

1. "stable"

Consistent with the specification and the Board's decisions in the *Amgen* IPRs, the term "stable" should be construed as requiring stability for storage and use as a liquid aqueous pharmaceutical product.

"[S]table" appears in the preamble of claim 1 and modifies "liquid aqueous pharmaceutical formulation." The specification of the '166 patent expressly states that "[a] 'stable' formulation is one in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." (Ex. 1001 ('166 patent) at 7:24–26.)

"Stable" is properly read in the context of the "liquid aqueous pharmaceutical formulation" to which it applies. Given the practical realities of therapeutic antibodies, a POSA would have understood that a liquid aqueous pharmaceutical formulation would need to be stable for storage and use as an

approved pharmaceutical product. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1352 (Fed. Cir. 2013) (construing term "storage stable" in the context of a claim to a pharmaceutical composition to mean "a composition that maintains its stability during its shelf life for its intended use as an approved pharmaceutical product for sale and home use by ordinary customers."). For example, the '166 patent describes the "invention" as "a liquid aqueous pharmaceutical formulation … having a shelf life of at least 18 months" (Ex. 1001 at 3:22–26) or "with an extended shelf life." (*Id*. at 3:14–15; *see also id*. at Abstract.).

In the *Amgen* IPRs, the Board adopted this construction of the term "stable" in the context of the same claim phrase in two patents in the same family as the '166 patent:

> [W]e do not consider "stable" as stating merely an intended use or purpose of the claimed invention; rather, it describes a mandatory characteristic thereof. Accordingly, based on our review of the '157 patent as a whole..., we conclude that "stable," as used in the [preamble of claim 1], breathes life and meaning into [claim 1] and, therefore, limits it scope. … Thus, AbbVie contends, and we agree, that *one of skill in the art "would have understood that a formulation would need to be stable for storage and use."*

Amgen '514 IPR, Paper 9 at 6–7; *Amgen* '517 IPR, Paper 9 at 7-8. The same construction should apply here. *See, e.g.*, *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005) (When "patents all derive from the same

parent application and share many common terms, we must interpret the claims consistently across all asserted patents."); *Mallinckrodt, Inc. v. Masimo Corp.*, 147 Fed. Appx. 158, 169 (Fed. Cir. 2005) ("[T]he same terms in related patents are presumed to carry the same meaning"); *Abtox, Inc. v. Exitron Corp.*, 131 F.3d 1009, 1010 (Fed. Cir. 1997), modifying 122 F.3d 1019 (Fed. Cir. 1997) (improper to construe the same term in related patents differently).[4]

[4] Petitioner's assertion that its proposed construction is supported by an alleged admission by AbbVie regarding Relton made in a foreign opposition proceeding involving a different patent (Pet. at 17-18) is factually and legally misguided. Nowhere in the opposition paper on which Petitioner relies did AbbVie purport to define stability, or even discuss the stability, or lack thereof, of any particular formulation in Relton. (*See* Ex. 1020.) Moreover, arguments allegedly made in connection with a European opposition proceeding of an unrelated patent are not relevant to the proper construction of any term in the '166 patent under U.S. law. *See, e.g.*, *Pfizer, Inc. v. Ranbaxy Labs., Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006); *Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1167-68 (Fed. Cir. 2004); *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1318 (Fed. Cir. 2005).

2. "a human anti-human Tumor Necrosis Factor alpha (TNFα) IgG1 antibody . . . , wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7"

The individual words of this phrase are interrelated and should be construed together to convey their proper meaning—not in isolation as Petitioner has done. *See, e.g.*, *Cadence Pharm., Inc. v. Paddock Labs. Inc.*, 886 F. Supp. 2d 445, 455 (D. Del. 2012). The correct construction is: A human anti-human TNFα antibody of the IgG1 subclass that retains binding activity against human TNFα and includes the complete light chain variable (V_L) region and the heavy chain variable (V_H) region of the antibody D2E7.

As acknowledged by Petitioner, IgG1 is a particular antibody subclass distinct in sequence, physical, and chemical properties from other IgG subclasses and other immunoglobulin classes. (Pet. at 18–19; *see also* Ex. 2031 at 7–9.) And as acknowledged by this Board in the *Amgen* IPRs in the context of the claims of two related patent family members:

> "D2E7" refers to an antibody disclosed in Salfeld [(Ex. 1013)], incorporated by reference in the [parent '158 Patent]. … Salfeld provides amino acid sequences for the light chain variable region (SEQ ID NO:1), light chain CDR3 domain (SEQ ID NO:3), heavy chain variable region (SEQ ID NO:2), and heavy chain CDR3 domain (SEQ ID NO:4) for the D2E7 antibody. (*See* [Salfeld, Ex. 1013 at 2:59–67].

Amgen '514 IPR, Paper 9 at 8 (footnotes omitted); *Amgen* '517 IPR, Paper 9 at 8-9 (footnotes omitted). The same construction should apply here.

3. Other terms

For the limited purpose of this Preliminary Response, Patent Owner does not contest the constructions of the terms "buffer," "tonicity agent," "surfactant," and "chelating agent." (Pet. at 19.)

III. The Petition Fails to Demonstrate a Reasonable Likelihood That Any Challenged Claim is Unpatentable

The Board should deny the Petition and refuse to institute trial because Petitioner has failed to provide sufficient evidence to establish "that there is a reasonable likelihood that [it] would prevail with respect to at least 1 of the claims challenged in the petition." *See* 35 U.S.C. § 314(a).

A. Background and State of the Art

1. Before HUMIRA, no commercial stable, liquid, high-concentration antibody formulations had been successfully developed

Prior to AbbVie's invention of the formulations claimed in the '166 patent in 2002, only two types of antibody formulations were commercially available: (i) low-concentration, liquid formulations, and (ii) lyophilized formulations. The table below identifies the therapeutic antibody products available in 2002 and their concentrations.

Table 1. Commercially Available Antibody Formulations (08/16/2002)[5]

Name	Reference	Concentration	Delivery
Liquid Antibody Formulations			
ORTHOCLONE OKT3 (muromonab-CD3) *(anti-CD23)*	Ex. 2009	**1 mg/ml**	i.v.
RITUXAN (rituximab) *(anti-CD20)*	Ex. 2010	**10 mg/ml**	i.v.
REOPRO (abciximab) *(anti-GPIIb/IIIa receptor)*	Ex. 2011	**2 mg/ml**	i.v.
CAMPATH (alemtuzumab) *(anti-CD52)*	Ex. 2012	**10 mg/ml**	i.v.
ZENAPAX (dacilizumab) *(anti-IL2)*	Ex. 2013	**5 mg/ml**	i.v.
Lyophilized Formulations			
REMICADE (infliximab) *(anti-TNFα)*	Ex. 2014	100 mg/vial (powder) **10 mg/ml reconstituted**	i.v.
HERCEPTIN (trastuzumab) *(anti-HER2)*	Ex. 2015	440 mg/vial (powder) **21 mg/ml reconstituted**	i.v.
WINRHO SDF *(gamma globulin)*	Ex. 2016	0.120–1 mg/vial (powder) **0.048–0.240 mg/ml reconstituted**	i.v. or intra-muscular
SYNAGIS (palivizumab) *(anti-RSV protein F)*	Ex. 2039	50 or 100 mg/vial (powder) **100 mg/ml reconstituted**	intra-muscular
SIMULECT (basiliximab) *(anti-IL-2Rα)*	Ex. 2040	20 mg/vial (powder) **4 mg/ml reconstituted**	i.v.

[5] This table includes antibodies identified by Dr. Manning (Ex. 1002 at ¶¶ 54 and 144) and certain additional lyophilized products.

As this table shows, all commercially available liquid[6] antibody formulations at the time were provided at a concentration of 10 mg/ml or less. (*See* Exs. 2009–2013.)[7]

No one had succeeded in commercializing a formulation like those claimed by AbbVie. The reality was that it was extremely difficult, and often impossible, to make *any* stable, liquid, pharmaceutical formulations of antibodies, much less at the high concentrations that permit HUMIRA to be delivered in the small injection volumes that support single dose subcutaneous administration. (*See, e.g.*, Ex. 2033 at 271 ("[A] considerable proportion of human monoclonal antibody candidates *fail formulation studies*"); Ex. 2005 at 1905; Ex. 2029 at 237; Ex. 2030 at 612; Ex. 2006 at 82.)

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[6] Antibody concentration in the lyophilized formulations is not relevant because those formulations are not intended to be stable *following reconstitution*.

[7] Even the non-antibody proteins Petitioner cites illustrate this point. (Pet. at 26.) Of the fifteen protein formulations listed, five were lyophilized, one was provided as both lyophilized or a liquid formulation having a concentration less than 10 mg/ml, and eight of the remaining nine had a concentration of 10 mg/ml or less. (Exs. 1088–1090.)

2. The art taught away from liquid formulations and toward lyophilized formulations

Recognizing the difficulties in making stable liquid antibody formulations, the prior art actually taught away from making liquid formulations and instead pointed toward lyophilization. (*See, e.g.,* Ex. 1031 at 545 ("Most proteins degrade too fast when formulated as aqueous solutions, … [T]hey have to be stored in a dry form [(*i.e.,* lyophilized)] and be reconstituted before administration."); Ex. 2017 at 167 ("The practical solution to the protein stability dilemma is to remove the water."); Ex. 2007 at 18 ("Like most proteins, some antibodies are not stable enough in a liquid form, and lyophilized dosage forms will have to be considered.").)

Indeed, a 2002 book, edited by Dr. Manning, directed away from liquid formulations and toward the development of *lyophilized* formulations:

> [W]ith many proteins*, it is not possible ... to develop sufficiently stable aqueous formulations*. … In contrast, a properly lyophilized formulation can maintain adequate physical and chemical stability of the protein during shipping and long-term storage, even at ambient temperatures. … *Considering these issues plus the fact that formulation scientists now have to deal with numerous proteins and/or variants of a given protein, lyophilization should be considered as a primary mode for product development.*

(Ex. 1025 at 109–10 (citations omitted); *see also id.* at 10, 99–100 ("Due to the

fact that many proteins do not possess adequate stability in solution in order to provide a reasonable shelf life, many protein pharmaceuticals are prepared as lyophilized products.").) Dr. Manning also authored a chapter in that book, in which he likewise directed those in the formulation art away from the claimed invention and toward lyophilization:

> It can be assumed that *most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed*. Our understanding of the basic requirements for obtaining a *stable lyophilized protein formulation is relatively well developed*.

(Ex. 1025 at 188; *see also* Ex. 1060 at 365 ("[A] comprehensive strategy to achieve stable liquid formulations has not yet emerged. In contrast, the ability to design a stable lyophilized protein formulation rationally is more highly developed.").)

3. Formulating proteins, particularly antibodies, was complicated and unpredictable

In reality—and as previously admitted by Dr. Manning outside of the context of this proceeding—at the time of the August 16, 2002 priority date of the '166 patent, development of stable liquid antibody formulations, especially those at a concentration high enough to be suitable for subcutaneous administration, was complicated and unpredictable. (*See, e.g.*, Ex. 1025 at 188; *see also* Ex. 2005 at 1906.) The antibody formulation process typically required a large amount of

scientific judgment with little guidance or predictability about what might work in a particular circumstance, or whether formulation would work *at all* given that "many proteins" were "not possible" to formulate as a liquid formulation, much less at a high concentration like 50 mg/ml. (Ex. 1025 at 109–10.)

As such, in its decisions denying institution in the *Amgen* IPRs, this Board explicitly recognized that the high unpredictability in the art foreclosed a POSA in 2002 from having a reasonable expectation of success in developing stable, high-concentration, liquid formulations of D2E7. (*Amgen* '514 IPR, Paper 9 at 14; *Amgen* '517 IPR, Paper 9 at 15 ("We are not persuaded that the prior art provided sufficient guidance such that a skilled artisan would have had a reasonable expectation of success in arriving at" the claimed formulations); *see also Amgen* '514 IPR, Paper 9 at 15; *Amgen* '517 IPR, Paper 9 at 16 ("We agree with AbbVie that, on the whole, Wang suggests a high degree of *un*predictability in the antibody formulation art.") (emphasis in original).) Petitioner's arguments here do not, and cannot, overcome this fundamental obstacle that a POSA would have faced.

a. Many possible components and combinations existed with no direction as to which would be successful

Among the many complexities of protein formulation was the large number of potential problems and even larger number of potential avenues to address them. (*See, e.g.*, Ex. 1027 at 307; Ex. 1030 at 164–168, 178.) Dr. Manning himself

recognized that there were many "potential stability problems in protein formulations, potential causes, and possible solutions." (Ex. 1002 at ¶ 88.) As Dr. Manning (and others) have explained, typical stability problems observed in protein pharmaceuticals include (i) non-covalent aggregation, (ii) covalent aggregation, (iii) deamidation, (iv) cyclic imides, (v) cleavages, (vi) oxidation, and (vii) surface denaturation/adsorption. (*Id.* (citing Ex. 1025 at 13 (Table 6)); *see also* Ex. 1030 at 177–178.) And potential causes of these respective stability problems include (i) "[s]olubility, structural changes, heat, shear, surface, denaturants, impurities," (ii) "[d]isulfide scrambling, other unknown mechanisms," (iii) "pH < 5.0 or > 6.0," (iv) "pH around 5," (v) "[p]rotease impurities, other unknown mechanisms," (vi) "[a]ctive oxygen species, free radicals, metals, light, impurity," and (vii) "[l]ow protein concentration, specific affinity, protein hydrophobicity." (Ex. 1002 at ¶ 88 (citing Ex. 1025 at 13 (Table 6)); *see also* Ex. 1030 at 145–153.)

Moreover, there were numerous alternative ways that a POSA might attempt to address these various stability problems, including pH optimization, ionic additives, amino acids, surfactants, protein concentration, raw material purity, inhibitors, free radical scavengers, and active oxygen scavengers, among others. (Ex. 1002 at ¶ 88 (citing Ex. 1025 at 13 (Table 6)); *see also* Ex. 1030 at 163–172.)

Further, different antibodies have different degradation profiles (s*ee, e.g.*, Ex. 2008 at 386; Ex. 2033 at 270; Ex. 1025 at 185–186), and there was no way to predict which, if any, approach or formulation components might work for a particular protein or antibody. (*See, e.g.*, Ex. 1030 at 164–168, 178 ("In the development of a protein formulation, the most challenging task is the stabilization of a protein to achieve an acceptable shelf life. . . . [T]here is no single pathway to follow in selection of a suitable stabilizer(s), partly due to the lack of a clear and definitive understanding of protein-cosolute interactions and proteins' multiple inactivation mechanisms."); Ex. 1027 at 307 ("Predicting *a priori* the alteration of pharmaceutical properties caused by the three degradation pathways [(*i.e.,* protein aggregation, deamidation, and oxidation)] is difficult and must be determined on a case-by-case basis).)

Moreover, it was well known that adjusting a formulation in an attempt to address one instability mechanism was very likely to cause instability via other mechanisms. (*See, e.g.*, Ex. 1025 at 110 ("[S]ometimes there are conflicting conditions (*e.g.*, pH) needed to slow sufficiently multiple degradation pathways in aqueous solution."); Ex. 2032 at 969 ("[T]here are cases where conditions that minimize chemical degradation foster physical damage and *vice versa*. Then, conditions that provide a compromise affording the requisite long-term stability

cannot be found."); Ex. 1025 at 67 ([Salts] must be used with care, since they can also dramatically affect protein solubility").)

Indeed, in pursuit of Coherus-Manning Patents, Petitioner repeatedly and correctly told the Examiner that there were too many potential stabilization agents, each with unpredictable effects, for a purely empirical screening approach to protein formulation to be predictable or successful. For example, in 2011, during prosecution of a Coherus-Manning Patent, Petitioner explained:

> [Q]uite simply, *there are too many possible stabilization agents* and there would be no credible reason to select a polyol, as opposed to some other stabilization agent. … In summary, stabilization of proteins is *a very uncertain matter* and *in no way predictable* from one stabilizer to the other even within specific categories of sugars or polyols or amino acids ... . The prior art…*clearly states the unpredictable nature of stabilizing proteins* and further supports the basis for patentability of the claimed invention.

(Ex. 2025 at 6–7; *see also* Ex. 1063 at 1554 (explaining that a wide variety of excipients in FDA approved formulations "provid[ed] the formulation developer with a huge number of possible excipient combinations"); Ex. 2005 at 1902 (In 2007, the plethora of available formulation components yielded "far too many possible sets of formulations to allow a purely empirical screening approach to be successful."); Ex. 2027 at 2720–21 (In 2012, "exploring" various solvent

conditions for protein formulations is a "tedious and time-consuming process," requiring "large and cumbersome studies"); Ex. 1030 at 178 (In 2013, "there is no single pathway to follow in selection of suitable stabilizers…[, and] research activities directed toward a general solution to protein instability will continue for at least a few decades").)

Accordingly, in view of the large number of potential problems and even larger number of potential avenues to address them, each with unpredictable and potentially deleterious effects, mere routine experimentation would not have been a predictable avenue for successfully achieving a stable, liquid, high-concentration pharmaceutical formulation of the D2E7 antibody of the type claimed in the '166 patent.

b. A formulation designed for one antibody could not reasonably be expected to result in a stable formulation for a different antibody

Numerous scientific publications at the relevant time, including those of Petitioner's expert, Dr. Manning, acknowledged that a major problem in the field was determining which of the many potential excipients (if any) might yield a stable liquid protein formulation, much less a stable, liquid, high-concentration formulation. This could only be assessed by extensive trial-and-error experimentation requiring the exercise of scientific judgment. This problem would not have existed if, as Petitioner now suggests, new proteins, such as novel

antibodies, could simply have been added to existing formulations with a reasonable probability of success.

A 1999 Wang review article explained that achieving acceptable stability is "the most formidable challenge in formulating a liquid protein pharmaceutical." (Ex. 1030 ("Wang") at 178.) Wang further explained that there is not a one-size-fits all approach, as Petitioner would have this Board believe:

> [T]he structural differences among different proteins are so significant that *generalization of universal stabilization strategies has not been successful*.

Id. at 130. Rather, Wang taught that proteins needed to be evaluated on a case-by-case basis:

> Unfortunately, *there is no single pathway* to follow in formulating such a product. Usually, *proteins have to be evaluated on a case-by-case basis*. Much more effort is still needed to understand the basic behavior of proteins, their instability factors and mechanisms, and their stabilization mechanisms in a broader and clearer perspective.

(*Id.* at 178; *see also id.* at 130 ("Very often, proteins need to be evaluated individually and *stabilized on a trial-and-error basis*."); Ex. 1027 at 307; Ex. 1060 at 365.)

And as late as 2012, the literature acknowledged that protein folding and physical instability remain "complex phenomena," such that "*[e]ven minor*

differences in amino acid sequence or posttranslational modification may result in significantly different physical instability." (Ex. 2004 at 125; *see also* Ex. 2018 at 1326 ("Each protein is unique both chemically and physically and therefore *will exhibit unique stability behavior*."); Ex. 2029 at 244; Ex. 2030 at 613.)

In his publications, Dr. Manning likewise consistently acknowledged that there was not a one-size-fits-all approach to protein formulation. For example, Dr. Manning provided "[a] summary of the additives that have been used to inhibit aggregation in some protein of pharmaceutical interest" as of 2002, but for the ten exemplary proteins provided, there were ten completely different strategies implemented to reduce aggregation (Ex. 1060 at 367), which is only one of many types of possible "stability problems" identified in the Manning Declaration. (Ex. 1002 at ¶ 88.) According to Dr. Manning, these problems extended even to "closely related proteins":

> The exquisite sensitivity of protein structure, function, and stability to the primary sequence does not readily lend itself to a generic approach for protein formulation. … *Even for closely related proteins, the relative stability and major pathways for degradation might be quite different*.

(Ex. 1025 at 185–186.)

c. Even antibodies with similar sequences often have different instability issues

That there is no one-size-fits-all approach to formulation is especially true with regard to antibody formulations because even small changes in antibody amino acid sequence can have a large impact on instability in a given formulation. In the *Amgen* IPRs, this Board expressly recognized that the literature at the time suggested a "high degree of *un*predictability in the antibody formulation art." *Amgen* '514 IPR, Paper 9 at 15; *Amgen* '517 IPR, Paper 9 at 16 (emphasis in original). In fact, "antibodies with identical constant domains, but different variable domains, *can vary widely in their stability profiles*." (Ex. 2033 at 270; *see also* Ex. 2051 at 2079; Ex. 2052 at 532; Ex. 2053 at 280.)

Even as late as 2007, the scientific literature made clear that teachings relating to one antibody cannot be transferred to another with a reasonable expectation of success:

> It should be stressed that one formulation excipient stabilizing a specific antibody may not be suitable for another *because of the differences in their sequence*.

(Ex. 2007 at 14; *see also id*. at 1 ("[D]evelopment of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior."); *id*. at 21 ("Due to the *significant difference in the primary sequence among different antibodies*, the relative severity

of [] degradation pathways can be significantly different."); *id*. at 14 ("[Antibodies'] tendency to generate such degradants *depends very much on their individual sequence, pI, hydrophobicity, and carbohydrate content.*").)

Due to structural differences between different antibodies, the literature also stressed that "[a]ll the formulation excipients and buffering agents used in commercial antibody products . . . should be evaluated individually for each antibody drug candidate through stability studies before they are chosen as part of the product . . ." (*Id.* at 21; *see also* Ex. 2008 at 386 ("Exposed surface residues of each antibody are unique and require specific formulation excipients to provide maximal stability"); Ex. 2035 at 690 ("[T]he interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity").)

Thus, the literature before, during, and after the relevant time makes clear that a formulation designed for one antibody could not reasonably be expected to result in a stable formulation for a different antibody. Rather, formulation components must be selected and evaluated for each particular antibody so as to account for its unique sequence, structure, and stability characteristics.

4. Petitioner and Dr. Manning's conclusory and contradictory assertions should be accorded no weight

Although in connection with this Petition, Petitioner and Dr. Manning assert

in a conclusory manner that "[t]he science of rationally designing stable, liquid protein formulations was well-established by August 2002" (Pet. at 12 (citing Ex. 1002 at ¶¶ 85–86 and Ex. 1025)), as shown above, outside of the context of this proceeding, they tell a different story.

In particular, before filing this IPR, both Petitioner and Dr. Manning consistently acknowledged the complex and unpredictable nature of protein formulation that thwarted efforts to commercialize protein and antibody therapeutics. For example, a book published in 2002, edited by Dr. Manning, and cited by Petitioner (Ex. 1025), explains that the antibody formulation process typically required a large amount of scientific judgment with little guidance or predictability about what might work *at all* given that "many proteins" were "not possible" to formulate as a liquid formulation. (*Id.* at 109–10.) In that book, Dr. Manning further explained that "[i]t can be *assumed* that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." (*Id.* at 188 (emphasis added); *see also id.* at 184 ("[F]or most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is extremely difficult."); Ex. 1027 at 310 ("Many proteins are only marginally stable in solution; therefore they are easily denatured and this results in aggregation.").)

Similarly, in pursuit of its own formulation patents, Petitioner repeatedly

stressed the unpredictability of the art of protein formulation. For example, during prosecution of EP Serial No. 12841765.6—a Coherus-Manning Patent application directed to formulations of another anti-TNFα biologic that claimed a priority date of October 18, 2012, over *ten years after* the '166 patent's August 16, 2002, priority date—Petitioner argued that protein stabilization was "an extremely unpredictable art," and that the teachings from one protein could not be applied to another protein with a reasonable expectation of success. (Ex. 2022 at 2 ("[P]rotein stabilization is an extremely unpredictable art, and therefore, agents that stabilize some proteins will not stabilize others.").) During prosecution of another Coherus-Manning Patent application filed in 2013, Petitioner further argued that it was "surprising" that adalimumab, in combination with what Petitioner now asserts were "well-known" excipients, resulted in a stable adalimumab formulation:

> [T]he claimed invention is directed to *a surprising finding* that a combination of adalimumab, histidine buffer, salt, polysorbate 80, and glycine and/or mannitol or sorbitol, results in a stable adalimumab formulation.

(Ex. 2024 at 9.) These assertions made by Petitioner in pursuit of its own protein formulation patents, including adalimumab formulation patents, directly contradict Petitioner's assertions in the present Petition, such as, that "[b]y August 16, 2002, the use of surfactants, tonicity agents, chelating agents, and buffers to stabilize IgG1 antibodies was well-known" (Pet. at 56.)

Because Petitioner and Dr. Manning's assertions in connection with the present position are conclusory and directly contradict their prior representations to this Office and the scientific community, the Board should accord their IPR-inspired assertions no weight. *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, No. IPR2014-00654 (P.T.A.B. Sept. 21, 2015), Paper 69 at 25 (discrediting Petitioner's assertions in view of contradictory statements by its expert that formulating a reliable dosage form was "very difficult"); *Zany Toys, LLC v. Pearl Enters., LLC*, No. CIV.A. 13-5262 JAP, 2014 WL 2168415, at *6 (D.N.J. May 23, 2014) (finding it would be "manifestly unjust" to permit defendant to take position in litigation that was contrary to position it previously took to the USPTO); *Freedom Card, Inc. v. JPMorgan Chase & Co.*, 432 F.3d 463, 476 (3d Cir. 2005) (holding district court correctly ruled that plaintiff was bound by its prior representations to the USPTO, whether viewed "as judicial estoppel, an admission, waiver, or simply hoisting [the party] by its own petard."); *TRW Automotive US LLC, v. Magna Elecs, Inc.*, No. IPR2014-00258 (P.T.A.B. Aug. 27, 2014), Paper 18 at 11 (recognizing "the Board's well-established discretion to give little weight to conclusory, unsupported expert testimony").

B. The Challenged Claims Would Not Have Been Obvious In View of Van De Putte and Relton

A patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "To establish a prima facie case of obviousness based on a combination of elements disclosed in the prior art requires that one 'explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious.'" *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (citations omitted). Further, the obviousness inquiry requires that a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, *and…would have had a reasonable expectation of success in doing so*." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (citations omitted). For example, the Federal Circuit previously determined that certain stable pharmaceutical formulations were nonobvious because:

> There is no indication in the prior art which of these possible formulations would be the most promising to try. And, [testing of] the storage stability of these formulations . . . would likely take one to three months per formulation. Without a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent years experimenting without success.

Leo Pharm., 726 F.3d at 1357.

Here, especially in view of the known difficulty and unpredictability of developing stable liquid formulations, and the corresponding teachings towards lyophilized formulations, it is evident that Petitioner's alleged ground for obviousness is based on hindsight using the '166 patent as a roadmap. *First*, Petitioner fails to establish that a POSA would have been motivated to select and combine van de Putte and Relton to address any known problem. *Second*, because van de Putte and Relton, even in combination, do not disclose or suggest the claimed subject matter, Petitioner fails to establish that the claimed invention would have been achieved even *if* a motivation to combine the two references had existed. *Third*, Petitioner offers no specific evidence to show *why* a POSA would reasonably expect that adding the D2E7 antibody of van de Putte to the formulations in Relton would result in successful stable formulations of D2E7 at any concentration, much less at the claimed 50 mg/ml concentration. *Fourth*, Petitioner's recourse to routine experimentation is unavailing and is belied by the teachings in the art at the time.

1. A POSA would not have had a motivation to select and combine van de Putte and Relton

a. Van de Putte does not identify a problem to be solved

Van de Putte (Ex. 1007) is an abstract for an early stage (phase II) clinical trial of D2E7. Medical professionals—and not formulation scientists—were the abstract's intended audience. In fact, the word "formulation" is not used, and no

guidance on the development of any pharmaceutical formulations is provided. Indeed, with the exception of noting the subcutaneous administration of D2E7, van de Putte is completely silent as to the limitations of the claims of the '166 patent. Van de Putte provides no details as to (i) whether the formulation was stable or unstable, (ii) the concentration of antibody in the formulation, (iii) the ingredients of the formulation, or (iv) whether it was administered as a single dose or a multi-dose delivery.

Furthermore, Petitioner fails to provide any evidence that a POSA would have been motivated to modify the formulation used in the van de Putte clinical trial (whatever the formulation might have been). Nowhere does van de Putte suggest that there was any problem with the undisclosed formulation used in the clinical trial or any need to improve it. Thus, van de Putte does not identify the problem that the '166 patent solves: creating a stable, liquid, high-concentration formulation of D2E7. Absent any teaching of a problem to be solved, Petitioner's assertion that a POSA would look to modify van de Putte is necessarily based on impermissible hindsight. *See, e.g.*, *Novartis Pharms. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015); *Leo Pharm.*, 726 F.3d at 1354 ("[B]ecause neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi.").

Significantly, nothing in van de Putte mentions, or even suggests, whether the antibody used in the clinical trial was prepared in an liquid formulation versus a reconstituted lyophilized formulation. And as discussed above, based on the teachings in the field in 2002 and an understanding of the then-existing commercially available antibody products, a POSA would have more likely believed that the formulation used in the van de Putte clinical trial was a lyophilized formulation. Thus, were a POSA to have contemplated developing a formulation in 2002 comprising the D2E7 antibody used in the van de Putte clinical trial, the art at the time would have directed the POSA towards the development of a lyophilized formulation, not a liquid formulation.

b. Even had van de Putte identified a problem to be solved, a POSA would not have been motivated to turn to Relton to solve it

There would be no reason that a POSA contemplating the development of a stable pharmaceutical formulation (of any kind) of the D2E7 antibody would turn to Relton. Relton is not directed to teaching a POSA how to create lyophilized formulations, or even stable liquid formulations. Rather, Relton is a patent directed to using ultrafiltration methods for concentrating antibodies. Relton's only discussion of stability is in the background section, discussing previously existing polyclonal antibody formulations. (*See, e.g.*, Ex. 1006 at 1:22–29; 2:15–19.) Relton

does not provide any assessment of, or even mention, the stability for storage and use of any monoclonal antibody formulations.

Moreover, nowhere does Relton even mention D2E7, much less disclose any pharmaceutical formulations thereof. The only purported subcutaneous pharmaceutical formulations exemplified in Relton, which are set forth in Example 4, are *low*-concentration formulations for other, different antibodies.[8] In particular, in Example 4 of Relton—which are the reference formulations that Petitioner relies on its claim chart (*see* Pet. at 50–51)—the antibodies are only present at a concentration of *1.5 mg/ml* (0.15 g antibody/100 g water). (Ex. 1006 at 11:52–12:21.) Thus, the antibody concentrations in the only purported subcutaneous pharmaceutical formulations disclosed in Relton are more than *30-fold lower* than the 50 mg/ml D2E7 antibody concentration recited in the claims of the '166 patent.

Furthermore, Example 4 of Relton specifies that the identified formulations are "[s]ub-cutaneous formulations *for anti-CD4 and anti-CD23 antibodies*." (Ex. 1006 at 11:52–58). Those are completely different antibodies from D2E7. They

[8] Petitioner concedes that Relton discloses only four subcutaneous antibody formulations, which are set forth in Example 4. (*See* Pet. at 30 ("[Relton] describes four distinct subcutaneous antibody formulations . . ." (citing Ex. 1006 at Example 4)).)

bind to different antigens, have different amino acid sequences, e.g., in their VL and VH regions, and have different structures than the fully human D2E7 antibody. Relton would have provided no basis for a POSA to believe that a formulation for use with either an "anti-CD4 antibody" or an "anti-CD23 antibody"—both antibodies of unknown sequence, species or isotype—could be used to stably formulate any other particular antibody, and certainly not D2E7.

Although Petitioner asserts that Relton "provided the answer" because it "indicated that its teachings were 'most preferably' applied to IgG1 antibodies, the subclass to which D2E7 belongs" (Pet. at 3), this assertion is directly contradicted, not only by the many references discussed above in Sections III.A.3.b–c, which show that that teachings relating to one antibody cannot be transferred to another with a reasonable expectation of success, but by Petitioner's own prior representations to this Office. In fact, to address an obviousness rejection in one of the Coherus-Manning adalimumab formulation applications, Petitioner argued that a reference generally related to immunoglobulins was not applicable:

> Zolton does not teach compositions containing adalimumab. Instead Zolton teaches immunoglobulins in general … *There are nearly infinite possible immunoglobulins and Zolton does not give direction as for which immunoglobulins its compositions would be useful*.

(Ex. 2026 at 6.)

As discussed in Sections III.A.3.b–c, and as both Petitioner and Dr. Manning have recognized, the sequence of the antibody to be formulated matters. Indeed, "antibodies with identical constant domains, but different variable domains, can vary widely in their stability profiles." (Ex. 2033 at 270; *see also* Ex. 2051 at 2079; Ex. 2052 at 532; Ex. 2053 at 280.) That is, even similar antibodies can have different instability issues; and there is no one-size-fits-all generic approach for antibody formulation.

In fact, in the *Amgen* IPRs, the Board previously rejected the assertion that the general disclosure of a class of TNFα antibodies in a prior art reference would have directed a POSA to select the specific TNFα antibody, D2E7, for inclusion in a formulation:

> We are unpersuaded that the inclusion of TNFα in a laundry-list of untested potential targets in Lam [Ex. 1012] would have provided sufficient direction to one of ordinary skill in the art to select TNFα, much less combine Lam's formulation with the teachings regarding D2E7 in Barrera [Ex. 1057], to achieve the claimed formulation (whether starting with Lam, or starting with Barrera).

Amgen '514 IPR, Paper 9 at 18; *Amgen* '517 IPR, Paper 9 at 19-20.

That is, the Board found a motivation to combine lacking in those prior IPR proceedings even though the class of TNFα antibodies (of which D2E7 is a member) identified in the Lam reference addressed in the *Amgen* IPRs is no less

specific than the generic group of "all IgG1 antibodies" discussed in Relton. The same conclusion regarding lack of motivation must also apply here. Relton's reference to "all IgG1 antibodies" would not have provided sufficient direction to a POSA to select *any* anti-TNFα antibodies from among the nearly infinitely broad class of IgG1 antibodies, and certainly not to select D2E7 in particular. Likewise, the uncharacterized antibodies that bind to CD4 or CD23 disclosed in Example 4 of Relton also would not have provided any direction to a POSA to select an antibody that binds TNFα, much less the specific D2E7 antibody. Thus, while a POSA had no reason to modify van de Putte in the first instance, even if he had, there would have been no reason to turn to Relton.[9]

[9] Notably, although Petitioner and Manning make use of Relton and van de Putte in their Petition when it suits their purpose, they did not find it necessary to cite either reference to this Office in connection with the prosecution of their Coherus-Manning Patents and currently pending applications directed to liquid formulations of D2E7, *i.e.*, adalimumab (*see* References Cited and Other Publications sections of U.S. Pat. Nos. 9,382,317; 9,346,880; 9,340,612 and 9,340,611, and prosecution histories of U.S. Serial Nos. 14/020,733; 14/661,849; 14/879,847; 14/879,885; 15/155,832; 15/155,925; 15/155,982; and 15/162,140, each titled, "Stable Aqueous

c. The "logical starting point" would have been the then-existing commercially available antibody formulations, not Relton

Against the backdrop of the complete lack of disclosure in Relton of any stable, high-concentration formulation or any mention of D2E7, Petitioner fails to establish why a POSA would have looked to Relton to develop a D2E7 formulation, as opposed to the then-existing commercial antibody formulations. To the contrary, Dr. Manning concedes that "[a] POSA would have focused on [the then-existing] commercial formulations as a logical starting point . . . for the development of stable high-concentration liquid formulations of D2E7." (Ex. 1002 at ¶ 145.) Alternatively, Dr. Manning admits that a "POSA would have considered *intravenous* formulations to be a logical starting point because, like subcutaneous formulations, they must be stable and isotonic." *Id.*

In view of these admissions, and for the other reasons discussed above,[10] Petitioner fails to meet its burden of establishing that a motivation existed to select

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Formulations of Adalimumab" (collectively "the Coherus-Manning Adalimumab Patents and Applications")).

[10] As detailed in Section III.A.1, because these existing commercial preparations were all either lyophilized or formulated at 10 mg/ml or less (see Exs. 2009–2016, 2039, 2040.), a POSA would have been steered away from the claimed high

and combine van de Putte and Relton to render obvious the claimed formulations. Rather, it is evident that Petitioner's selection of these two references is solely based on impermissible hindsight, using the '166 patent as a roadmap.

2. Van de Putte in combination with Relton would not have disclosed or suggested the claimed subject matter

Even were a POSA to combine van de Putte with Relton, it would not render the '166 patent claims obvious. Petitioner cherry-picks various claim elements from different contexts in van de Putte and Relton, but fails to demonstrate that the claimed subject matter when considered as a whole would have been obvious to a POSA in view of those references.

a. Van de Putte in combination with Relton does not disclose or suggest a *stable,* liquid, pharmaceutical formulation *of D2E7*

A POSA would not understand van de Putte and Relton, even in combination, to teach a liquid formulation *of D2E7* that is "stable" under the proper construction of that term. Van de Putte disclosed no formulation information whatsoever. Nevertheless, Petitioner asserts, without support, that "[a] POSA would have understood that these fixed dosages of D2E7 [described in van

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concentration liquid formulations of the '166 patent, and instead toward the development of either a lyophilized or a low-concentration, liquid formulation.

de Putte] had been formulated in stable, isotonic, and appropriately buffered single-use subcutaneous injections." (Pet. at 3.)

Petitioner's conclusory speculation regarding what a POSA allegedly "would have understood" is contrary to the state of the art. For example, it wholly fails to account for, among other things, the possibility that the formulation used in the van de Putte clinical trial could have been a lyophilized formulation that was reconstituted just prior to injection, and therefore need not have even been a *liquid* pharmaceutical formulation at all, much less one that was stable for storage and use. Indeed, the only approved anti-TNFα antibody on the market at the time, REMICADE, was a *lyophilized* formulation (and included instructions to begin using it within 3 hours after reconstitution into liquid form). (Ex. 1002 at ¶¶ 144–145, *see also* Ex. 2014.)

In addition to speculating that a POSA would have understood van de Putte as disclosing a liquid aqueous formulation, Petitioner and Dr. Manning further speculate that "a single batch of drug product [would have been] given throughout the course of the study" (Ex. 1002 at ¶ 81) and, therefore, "the D2E7 formulations in van de Putte [must have been] stable for a sufficient period of time to allow these extended studies to be performed without significant degradation of the protein occurring" (*id*. at ¶ 83). Petitioner and Dr. Manning ignore the real possibilities that (i) multiple batches could have been made over the course of the

trial (*see, e.g.*, Ex. 2044 at 738 (noting multiple lots used in the clinical study); Ex. 2045 at 236 (creation of multiple batches)) and/or (ii) other measures were employed, such as keeping the D2E7 samples frozen until just before use (*id.* at 237), which would have obviated the need for a stable liquid pharmaceutical formulation. Certainly, nowhere does van de Putte state that only a single batch was used for the full study, and Petitioner and Dr. Manning offer no support for their speculation in this regard.[11] At best, the hindsight-based speculations of Petitioner and Dr. Manning concerning what a POSA allegedly "would have thought" about the formulation used in van de Putte based on its minimal disclosure are entirely conclusory, and therefore are entitled to little to no weight. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004); *Apotex Inc. v. Wyeth LLC*, No. IPR2015-00873 (P.T.A.B. Sept. 16, 2015), Paper 8 at 13.

Furthermore, Relton does not cure van de Putte's failure to teach or suggest

[11] Petitioner and Dr. Manning's assertions also ignore that pharmaceutical companies' formulation efforts are often ongoing over the course of their clinical development efforts, and that the formulations used for early stage clinical trials, *i.e.*, phase I or II clinical trials, do not have to be, and often are not the stable pharmaceutical formulations settled on for the final pharmaceutical product.

a stable liquid aqueous pharmaceutical formulation of D2E7. Relton's only discussion of stability is in the background section, discussing previously existing polyclonal antibody formulations. (*See, e.g.*, Ex. 1006 at 1:22–29; 2:15–19.) Relton does not mention the words stable or stability with regard to any of the particular monoclonal antibody formulations disclosed in Relton. And Relton does not provide any data concerning whether any of those formulations would be stable for storage and use for any monoclonal antibody, much less D2E7, and at the high 50 mg/ml concentration.

In particular, with regard to the only specifically identified subcutaneous formulations for antibodies disclosed in Relton—the low-concentration "Subcutaneous Formulation[s] for Anti-CD4 and Anti-CD23 Antibodies" disclosed in Example 4, which are the "exemplary subcutaneous formulations" that Petitioner relies on its claim charts (*see* Pet. at 50–51)—Relton provides no data of any kind. (*Id.* at 11:50–12:21.)

Examples 1–3 of Relton only provide examples where an ultrafiltration process was used to concentrate the anti-CDw52 antibody (Campath-1H) (Example 1; Ex. 1006 at 5:40–7:20) and anti-CD4 antibodies (Examples 2 and 3; *id.* at 7:22–

11:50).[12] There is no data in these examples showing that any of those particular preparations are "stable for storage and use." Rather, Example 1, for example, merely provides data concerning the aggregation and "[t]urbidity of the Campath-1H solution *during concentration*." (*id.* at 6:65–66.) Indeed, even though Relton concedes in its background section that "it is important that [an] antibody is sufficiently stable *on storage*" (*id*. at 3:8–9), particularly as some antibodies "have a tendency to aggregate during long term storage" (*id*. at 2:61–62), no attempt is made in Relton to assess the stability for storage and use of any of the antibody buffer preparations in any of the Examples 1–3 of Relton, such as by long term stability studies or freeze-thaw testing. Thus, a POSA would have no reason to believe that any of the antibody preparations resulting from the ultrafiltration process described in Examples 1–3, or the "Sub-cutaneous Formulation[s] for Anti-CD4 and Anti-CD23 Antibodies" in Example 4, are stable for storage and use.

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[12] Notably, nowhere does Relton describe the concentrated antibody preparations resulting from the ultrafiltration processes in Examples 1–3 as pharmaceutical formulations, much less as *stable* pharmaceutical formulations. Rather, it is only the low-concentration formulations in Example 4 that Relton describes as "Sub-cutaneous Formulations."

In any event, given that, as explained in Sections III.A.3.b–c, different antibodies have wildly different degradation and stability profiles, a POSA also would have no way of knowing whether or to what extent Relton's data on aggregation or turbidity of Campath-1H (Example 1) or an anti-CD4 antibody (Examples 2-3) during the concentration process would apply to any other antibody. (*See* Ex. 2007 at 1, 14, 21; Ex. 1027 at 307; Ex. 1030 at 130, 178; *see also* Section III.A.3.) Such information, certainly would not inform a POSA about the stability for storage and use of D2E7 in any formulation disclosed in Relton.

Accordingly, even in combination, van de Putte and Relton would not have rendered obvious a *stable,* liquid, pharmaceutical formulation of D2E7.

b. Van de Putte in combination with Relton does not disclose or suggest a *stable,* liquid, pharmaceutical formulation of D2E7 *at the claimed concentration of 50 mg/ml*

A combination of van de Putte and Relton also fails to disclose or suggest a *stable,* liquid, pharmaceutical formulation of D2E7 *at the claimed concentration of 50 mg/ml*. In particular, Relton does not teach such. As discussed above, the particular formulations disclosed in Relton are for different antibodies and there is no indication that such formulations are stable for storage and use even for those antibodies. Moreover, the only purported subcutaneous pharmaceutical

formulations exemplified in Relton, which are set forth in Example 4, are *low*-concentration formulations (*1.5 mg/ml*).[13]

Likewise, a POSA would have no reason to believe that the formulation used in van de Putte was even a liquid formulation, much less a high concentration (*i.e.*, 50 mg/ml) liquid formulation. This is especially true given that, as described above, in 2002, the only two types of antibody formulations that were commercially available were: (i) low-concentration, liquid formulations, and (ii) lyophilized formulations.

Petitioner makes an elaborate argument as to how a POSA would have allegedly derived from van de Putte concentrations of between 20 mg/ml to 160

[13] Because Relton does not disclose any stable antibody formulations for subcutaneous injection with a 50 mg/mL concentration, contrary to Petitioner's assertion (Pet. at 5), Applicant need not have disputed the Examiner's description of Relton. Importantly, however, Petitioner recognizes that Relton was considered during patent prosecution, and the Examiner determined the issued claims were patentable over Relton. (Ex. 1003 at 196-202; 7/14/2015 Notice of Allowance at 5.)

m/ml based on its disclosure of total doses of 20 mg, 40 mg and 80 mg delivered.[14] Petitioner's argument, however, which spans no less than *nine pages* of the Petition and relies on *dozens of additional references,* impermissibly employs hindsight and relies on several speculative and demonstrably false assumptions. (Pet. at 6, 7, 20–27.)

For example, to support their hindsight-driven calculations, Petitioner and Dr. Manning assert in a conclusory manner that there "was a maximum volume (around 1 ml) that could be administered subcutaneously." (Pet. at 23 (citing Ex. 1002 at ¶¶ 71–73).) Likewise, Dr. Manning makes the unsupported assertion that "[w]hile it would have been possible to prepare a dose at a non-standard volume, such as at 1.6 ml, a POSA would have considered a volume that large to be

[14] Petitioner offers no explanation for how the disclosure in van de Putte of dosages of 20 mg, 40 mg and 80 mg would teach the particular claimed concentration of D2E7 at 50 mg/ml. Instead, it offers the unsupported and irrelevant allegation that that "[t]he 50 mg/ml D2E7 concentration of the challenged claims was merely a design choice within the disclosed range." (Pet. at 34.) Because for the reasons discussed herein, neither van de Putte nor Relton discloses any formulation having the D2E7 antibody at a range that would encompass a 50 mg/ml formulation of D2E7, the case law to which Petitioner cites to support its position is inapplicable.

unusual and/or impractical for a single subcutaneous self-administered dose (such as in van de Putte)." (Ex. 1002 at ¶ 76.) Petitioner's and Dr. Manning's conclusory assertions, however, are belied by the scientific literature at the time which clearly shows that volumes of up to 2.0 ml were routine for subcutaneous injections. (*See, e.g.*, Ex. 1030 at 175; Ex. 2030 at 612; Ex. 2046 at 721.)

In addition, Petitioner's and Dr. Manning's hindsight-inspired calculations rely on their conclusory assertion that a POSA would necessarily interpret van de Putte (Ex. 1007) as specifying that the doses were administered in a single injection volume. Again, there is no evidentiary basis for this speculation. Petitioner erroneously asserts that its speculative interpretation of van de Putte, as necessarily being delivered "subcutaneously in a single injection," would have been confirmed by Kempeni (Ex. 1017) and Lorenz (Ex. 1041). But, the sections of Kempeni and Lorenz on which Petitioner relies are directed to references other than van de Putte (Ex. 1007). Indeed, contrary to Petitioner's assertion, neither Kempeni nor Lorenz cites to, or interprets, van de Putte (Ex. 1007). (*See generally* Exs. 1017 and 1041.) And the only other reference Petitioner relies on for its speculative interpretation of van de Putte, Sorbera (Ex. 1008), also makes no mention of whether the van de Putte clinical trial formulation was delivered in single, as opposed to multiple, injections.

That van de Putte involved multi-dose therapy is not a mere hypothesis. Multi-dose therapy is not only contemplated by Relton (Ex. 1006 at 5:6–7), but frequently used in clinical trials (*see, e.g.*, Ex. 2047 (patients administered ten daily s.c. injections per dose of campath-1); Ex. 2048 (two s.c. injections per dose).)

Indeed, after spending four pages attempting to justify his conclusory assertion that patients must have been given "a single subcutaneous injection" in a "volume range of 0.5 to 1.0 ml," Dr. Manning concedes that, in fact, his assertion, and therefore his hindsight inspired calculations, are likely wrong. (Ex. 1002 at ¶ 78; *see also* Pet. at 37, n. 3.) This is because Ex. 1087 provides the results of a separate clinical trial using D2E7, in which the same 20, 40 or 80 mg dose of D2E7 disclosed in van de Putte (Ex. 1007) was "given every other week s.c. for up to 24 weeks[, and each] dose of study drug was administered as *two s.c. injections of 1.6 mL each*."

Of course, if van de Putte had involved a multi-dose therapy, the formulation for each dose would only require a fraction of the antibody concentration, as previously appreciated by this Board in the *Amgen* IPRs. (*Amgen* '514 IPR, Paper 9 at 22; *Amgen* '517 IPR, Paper 9 at 23 ("[O]ne factor that could skew Amgen's concentration calculations is whether a single-dose or a multi-dose therapy is assumed.").

In short, notwithstanding Dr. Manning's hindsight-driven speculations and calculations, van de Putte does not expressly or implicitly teach a high-concentration formulation. Thus, van de Putte and Relton, alone or in combination, do not disclose or suggest any specific stable monoclonal antibody formulations *at all*, much less any stable liquid formulations of D2E7 at a concentration of *50 mg/ml*.

3. The Petition fails to demonstrate a reasonable expectation of success in applying a formulation of Relton to the D2E7 antibody of van de Putte (or vice versa)

Even were a POSA to combine van de Putte and Relton (which he wouldn't), Petitioner fails to provide any basis for a POSA to reasonably expect that any formulations disclosed in Relton would stabilize the D2E7 antibody of van de Putte. Petitioner similarly fails to establish that there would be a reasonable expectation of success in making the claimed stable, liquid formulation of D2E7 at a concentration of 50 mg/ml. Petitioner and Dr. Manning instead make the bald assertion that Relton's failure to mention D2E7 is irrelevant "because the IgG1 subclass disclosed in Relton includes D2E7 and nothing in the prior art or the '166 patent indicates that D2E7 had any unusual properties that made it more difficult to

formulate than any other IgG1 antibody."[15] (Pet. at 35 (citing Ex. 1002 at ¶¶ 162–163).)

In so arguing, Petitioner improperly tries to shift away from itself the burden of proving that the prior art established a reasonable expectation of success. Furthermore, Petitioner again relies on the false premise that there is a one-size-fits-all approach to antibody formulation such that a single formulation would be expected to work for all antibodies. But, as discussed in Sections III.A.1–4, this argument is directly contrary to the state of the art in 2002 and prior admissions by both Petitioner and Dr. Manning. (*See, e.g.*, Ex. 1025 at 185–186; Ex. 2022 at 2; Ex. 2023 at 4; 2026 at 6; Ex. 1060 at 365; Ex. 1030 at 130, 152, 178; Ex. 2008 at 405; Ex. 2034 at 6109; Ex. 1012 at 22:13–17, 42:64–65.) Thus, there was no expectation, based on the asserted references and the art as a whole, that a 50 mg/ml stable liquid formulation of D2E7 could be achieved.

Notably, this Board twice rejected these same lines of argument in the *Amgen* IPRs. As described above, this Board *has already recognized* that there was a high degree of *unpredictability* in preparing liquid antibody formulations in

[15] Notably, none of the antibodies in any of the examples of Relton— including the "Anti-CD4 and Anti-CD23 Antibodies" in Example 4—is identified as being an IgG1 antibody.

2002, and that a skilled artisan at that time would not have had a reasonable expectation of success in arriving at a stable liquid formulation of D2E7 at the high concentration of 20 to 150 mg/ml. *Amgen* '514 IPR, Paper 9 at 14–15; *Amgen* '517 IPR, Paper 9 at 15–16. Moreover, the Patent Owner also successfully overcame this argument during prosecution of the '166 patent with the *exact same* primary reference, *i.e.*, Relton, being cited.

4. Petitioner's recourse to "routine" optimization or "common" excipients cannot salvage its obviousness argument

Having failed to explain how a specific formulation from Relton would reasonably be expected to stably formulate D2E7 from van de Putte (or *vice versa*), Petitioner cannot compensate for the deficiencies in its position by conclusory references to so-called "routine" optimization or "common" excipients. (*See, e.g.*, Pet. at 1–2 (citing Ex. 1002 at ¶¶ 64, 80–82), 11, 13 (citing Ex. 1002 at ¶¶ 89–90, 95–102), 38, 39, 40 (citing Ex. 1002 at ¶ 94), 45 (citing Ex. 1002 at ¶ 102).)

As an initial matter, focusing on the fact that certain excipients existed in the art is the viewpoint of a person looking backward after an event happened. This is classic hindsight, rather than a proper forward looking analysis that views the prior art as a whole in 2002 without the benefit of the '166 patent's teachings. In fact, Petitioner's hindsight approach—locating a single claimed formulation element in the prior art, and then asserting that inclusion of the element would have been

"expected" because it was "common" and "routinely added" to formulations (s*ee, e.g.*, Pet. at 13)—is a lens through which virtually any valid invention would appear obvious.

In any event, Petitioner's attempts to import "routine" optimization or the use of "common" excipients to fill gaps in its obviousness combinations (*see, e.g.*, Pet. at 11, 13, 38–40, 46) are unavailing. For instance, Dr. Manning argues that:

> [A]s of August 16, 2002, a POSA would have focused on *a limited set* of excipients to include in a D2E7 formulation. In other words, a POSA trying to formulate an antibody for subcutaneous injection in August 2002 would be working with a *limited number of potential buffers and excipients.*

(Ex. 1002 at ¶¶ 103, 104.) But Relton's extensive disclosure of formulation parameters hardly presents a "limited set."[16] Indeed, Relton discloses extensive

[16] Petitioner also resorts to improperly incorporating by reference vast numbers of additional pages of the Manning Declaration, which, in turn, cite dozens of additional references. (*See* Section IV.) As this Board previously determined, this is improper, and the Board should "consider only those arguments that [Petitioner] presents squarely in its Petition." *Amgen* '514 IPR, Paper 9 at 13–14, n. 10. But even these improperly incorporated references do not help because, like Relton, they offer no scientific basis from which a POSA could have reasonably expected

lists, spanning several columns, of possible formulation components available in the art. (Ex. 1006 at 3:18–5:39.) This allows for a virtually endless number of combinatorial possibilities, without any guidance as to what combination of formulation components might stabilize any particular antibody. *See Leo Pharm.*, 726 F.3d at 1356 (affirming Board's finding that certain claimed pharmaceutical formulations were nonobvious and noting "the breadth of these choices and the numerous combinations indicate that these disclosures would not have rendered the claimed invention obvious to try.").

Relton adds further complication by including: all types of antibodies (Ex. 1006 at 3:19–22; 3:28–41); various routes of administration (*id.* at 4:10–16); numerous formulation buffers (*id.* at 3:45–58); buffer concentrations (*id.* at 4:38–39); pH ranges (*id.* at 4:26–27), as well as optional "additional ingredients such as buffers, salts, Polysorbate and/or EDTA" (*id.* at 5:26-27). Such extensive inventories of components and ranges effectively *teach away* from any specific formulation. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011); *Novartis*, 611 F. App'x at 996; *BioDelivery Sci. Int'l, Inc. v. MonoSol Rx, LLC*, No. IPR2015-00167 (P.T.A.B. May 20, 2015), Paper 6 at 19–20. (*See*

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to succeed in making a formulation of D2E7 within the scope of the patent claims, particularly in view of the state of the art in 2002. (*See* Sections III.A.1–4.)

also Section III.A.3.) Thus, had a POSA been motivated to create a stable, liquid formulation for D2E7, a POSA equipped with Relton is effectively no better off than a POSA *without* Relton.

Petitioner's recourse to routine optimization is also flatly contradicted by Petitioner and Dr. Manning's numerous prior inconsistent statements, as well as the state of the art in 2002, which constitute powerful proof that their newly formed, IPR-inspired positions do not reflect the views of a POSA at the time of the invention. (*See, e.g.*, Ex. 2022 at 2; Ex. 2005 at 1902; Ex. 1063 at 1554; Ex. 2023 at 4; *see also* Sections III.A.1–4.) As discussed, Petitioner's own prior statements and the scientific literature, including publications by Dr. Manning, demonstrate that a vast number of possible choices and potential pitfalls existed, and that for many antibodies it was simply not possible to create stable, liquid formulations, much less high-concentration ones. (*See, e.g.*, Ex. 1063 at 1554; Ex. 2022 at 2–3; Ex. 2025 at 6–7; *see also* Ex. 2005 at 1902; Ex. 2027 at 2720–21; Section III.A.3.)

Accordingly, a POSA would not have had a reasonable expectation that a stable, liquid pharmaceutical formulation of the D2E7 antibody of the type claimed in the '166 patent could be arrived at by mere routine experimentation based on existing formulations and ingredients. (*Id.*)

5. The dependent claims would not have been obvious in view of van de Putte and Relton

Beyond the deficiencies in the Petition as a whole, Petitioner further fails in its attack on the challenged dependent claims. Petitioner barely addresses the additional elements in the dependent claims, as set forth below.

a. The Petition is deficient with respect to the pH ranges recited in dependent claims 4, 7 and 8

Dependent claims 4, 7 and 8 limit the formulation pH range—which Dr. Manning calls "the most important formulation variable" (Ex. 1002 at ¶ 91)—to between "4.8 to 5.5" (claims 4 and 7) and "5.0 to 5.2" (claim 8).

Neither of the references relied upon by Petitioner discloses these claim limitations. There is no mention whatsoever of pH (or any other formulation components) in van de Putte, and to the extent they are disclosed in Relton, each of the antibody preparations has a pH of 6.0. (Ex. 1006 at 7:29, 9:29; *see also* Pet. at 42.)[17]

Recognizing these deficiencies, Petitioner's only response is to rely on Dr. Manning for the conclusory assertion that "a POSA would not have selected an

[17] Even to the extent that claim 6 recites a pH of 4.5 to 6.0, for the reasons detailed, *e.g.*, in Section III.B.1-4 above, van de Putte and Relton also fail to render this claim obvious.

extreme pH" or that "a POSA would have been able to determine the claimed pH ranges by routine optimization." (Pet. at 40 (citing Ex. 1002 at ¶ 94).) However, although Petitioner concedes that the pH of a particular formulation is "critical" in controlling both solubility and stability (Pet. at 39, 41), Petitioner ignores the art's recognition that identification of a pH, along with the other formulation components, that will result to a stable pharmaceutical formulation for a particular antibody—if such was even possible—was not a routine task. (*See, e.g.*, Ex. 1030 at 164.)

Finally, like Relton, all the commercially available protein formulations identified by Petitioner (Pet. at 26) and all commercial antibody formulations, to the extent any pH was identified in the label (*see* Table 1 *supra*), were formulated at a pH of 6.0 or above. In other words, the art *taught away* from claims directed to pH ranges below 6.0, such as claims 4, 7 and 8 which relate to pH's lower than 6 – i.e., "4.8 to 5.5" or "5.0 to 5.2." Accordingly, Petitioner completely fails to explain why a POSA would choose the narrow ranges of the dependent claims to formulate the D2E7 antibody, particularly in view of Relton and the commercially available antibody formulations at the time.

b. The Petition is also deficient with respect to the remaining dependent claims

The Petition is also defective with respect to the other elements set forth in

the dependent claims of the ’166 patent. For example, claims 2, 3 and 14 require specific buffer systems, and other claims require specific excipients in the formulation, such as tonicity agents (claims 10, 13, 16 and 23), surfactants (claims 24–26), or a chelating agent (claim 28).

In an attempt to satisfy these limitations, Petitioner merely argues that “it was widely known” that various types of excipients existed or were “common” and should be used in pharmaceutical formulations. (Pet. at 45–46 (tonicity agents); *id.* at 46 (surfactants); *id.* at 47 (organic acids as buffers); *id.* at 48 (chelating agents).) This is insufficient. Petitioner fails to explain why *any* of these specific types of excipients would be selected from the many possibilities available in the art to formulate a stable liquid pharmaceutical formulation of D2E7 with any reasonable expectation of success.

Petitioner’s arguments also flatly contradict positions taken during prosecution of the Coherus-Manning Patents. For example, here Petitioner alleges that the challenged claims “merely recite art-required formulation properties, along with the most common excipients routinely added to protein formulations.” (Pet. at 13.) But as recently as 2015, Petitioner conceded that “protein stabilization is an extremely unpredictable art, and therefore, agents that stabilize some proteins, will not stabilize others.” (Ex. 2022 at 2; *see also* Ex. 2023 at 4 (“Slight modifications of excipients may lead to widely varying results.”).) Similarly, here Petitioner

alleges that "it was widely known" that various types of "common" excipients existed or that it was "not surprising" they were included in the formulations of the '166 patent (*See, e.g.*, Pet. at 45–48, 56), Yet, in pursuing the Coherus-Manning Patents, Petitioner is taking the completely opposite position that these same "common" excipients result in the "surprising finding" of stable adalimumab formulations. (*See, e.g.*, Ex. 2024 at 9 ("The claimed invention is directed to the surprising finding that a combination of adalimumab, histidine buffer, salt, polysorbate 80 and glycine and/or mannitol or sorbitol results in a stable adalimumab formulation.").) As explained in Section III.A.4, the Board should not permit Petitioner in this proceeding to contradict its prior representations to this Office. At a minimum, its new and contradictory positions should not be accorded any weight.

(1) The Petition is deficient with respect to the tonicity agents recited in dependent claims 10, 13, 16 and 23

Petitioner points to Relton as disclosing the use of sodium chloride in its subcutaneous formulations (Pet. at 46 (citing Ex. 1006 at 11:50–12:23)), which Petitioner characterized as "not surprising since sodium chloride was one of the most common tonicity agents added to subcutaneous formulations" (*id.* (citing Ex. 1002 at ¶ 112 and Ex. 1031 at 317)). However, a reference cited by Petitioner concedes that not all proteins can be stabilized by salts. (Ex. 1030 at 148.) Indeed,

art cited by Petitioner actually teaches away from sodium chloride because it "may cause the antibody to precipitate and/or may result in oxidation at low pH." (Ex. 1012 at 22:32–36; *see also* Ex. 2049 at 1224-25 ("[i]f salts are added to adjust the tonicity this will influence both stability and solubility. These effects can be dependent on pH, the type and concentration of salt, the nature of the interaction between salt and proteins, and on the amount of charged residue in the protein"); Ex. 1025 at 67.) The same holds true for other tonicity agents, including sugars and polyols. (Ex. 1030 at 166.) Certainly, Petitioner identifies no basis by which a POSA would have had a reasonable expectation of success that the inclusion of these excipients would have resulted in the claimed stable, liquid, pharmaceutical formulations of D2E7 at the high concentration of 50 mg/ml. Accordingly, the Petition has not shown that dependent claims 10, 13, 16 and 23 are obvious.

(2) The Petition is deficient with respect to the surfactants recited in dependent claims 24–26

Petitioner cites Relton as including polysorbate 80 in "all of its subcutaneous formulations. (Pet. at 46.) Petitioner further asserts that there is "nothing inventive or surprising about including a surfactant, or, more specifically, polysorbate-80 in the challenged claims" because "[i]t was widely known that surfactants contribute to protein stability, and it would have been common for a POSA to add a surfactant to a subcutaneous formulation" (Pet. at 46–47.) Petitioner also asserts that "by

August 2002, 'polysorbate 80 was the most commonly used surfactant in pharmaceutical formulations.'" (*Id.* at 46 (citing Ex. 1002 at ¶ 115.)

However, the mere fact that polysorbate 80 existed says nothing about the desirability or motivation to include it in stable liquid pharmaceutical formulations of D2E7. A POSA would have also appreciated that surfactants, such as polysorbates, had numerous, well-known drawbacks. (*See, e.g.*, Ex. 1025 at 14-15, 169; Ex. 2020 at 2253; Ex. 2021 at 679; *see also* Ex. 2050 at 511, 515, 514 ("[P]olysorbate has an opposite or detrimental effect on aggregation.").) In fact, one of Petitioner's own references teaches away from using polysorbates in formulations. (*See* Ex. 1025 at 15 ("The use of excipients… *e.g.*, Tweens… should be avoided if possible").)

Finally, even if a POSA did wish to apply Relton's polysorbate teachings to D2E7, Petitioner's cited art specifically teaches that surfactant concentrations cannot simply be transferred from one formulation to another because the optimal concentrations of surfactant "depend on the mechanism(s) by which a particular protein is protected from damage by surfactant addition." (Ex. 1025 at 170; *see also* Ex. 1027 at 353; Ex. 1029 at 74.) Accordingly, the Petition has not shown that dependent claims 24-26 are obvious.

(3) The Petition is deficient with respect to the chelating agent recited in dependent claim 28

Petitioner further asserts that "[t]he use of a chelating agent in protein formulations was very common." (Pet. at 48.) Petitioner further cites Relton as "unsurprisingly" teaching the use of EDTA as a chelating agent. (*Id.*)

However, the mere fact that chelating agents, such as EDTA, were known in the art, says nothing about the desirability or motivation to include it in D2E7 formulations. A POSA would have also appreciated that chelating agents, such as EDTA, may not be effective and had drawbacks. (*See, e.g.*, Ex. 1029 at 66–67; Ex. 1030 at 150.) Accordingly, the Petition has not shown that dependent claim 28 is obvious.

C. Secondary Considerations Support the Nonobviousness of the Challenged Claims

Objective indicia "help inoculate the obviousness analysis against hindsight," and help "turn back the clock and place the claims in the context that led to their invention." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378–79 (Fed. Cir. 2012); *see also Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). Here, the invention is supported by evidence of commercial success, unexpected results, and long-felt need.

Notwithstanding the complexities and unpredictability of the formulation art, AbbVie was the first to invent and commercialize a stable, liquid, high-

concentration antibody formulation for subcutaneous administration. This formulation, which is covered by the ’166 patent and is sold as HUMIRA was a marked advance over the low-concentration and lyophilized formulations of its day. (*See* Ex. 1041 at 187; Ex. 2001 at 3; Ex. 2002 at 15; Ex. 2028 at 1–2.)

A clear nexus exists between HUMIRA’s commercial success and the formulation claimed in the ’166 patent. HUMIRA’s success was driven in large part by (i) the ability of patients to self-administer a liquid antibody formulation via single dose subcutaneous administration (*see* Ex. 2003 at 4) without lyophilization and the accompanying need for reconstitution, and (ii) the fact that it is stable enough to be commercially viable (*e.g.*, to withstand shipping and storage for periods of time typical for biologic therapies). In short, HUMIRA was the first of its kind, permitting easy self-administration. The stable, liquid, high-concentration formulations claimed in the ’166 patent are necessary to provide the easy subcutaneous single-dose self-administration that AbbVie unexpectedly achieved, yielding this commercial success.

IV. The Petition’s Violation of PTAB Rules Supports Denial of Institution

In its stated grounds, the Petition identifies only two references. But in reality, Petitioner attempts to rely on no less than *ninety* exhibits—styled as the “state of the art”—to fill gaps left by its asserted combinations. For example, in an attempt to support its assertions regarding what a POSA would allegedly have

understood from van de Putte's meager disclosure, Petitioner relies on *twelve paragraphs* of Dr. Manning's Declaration (Pet. at 20–23 (citing Ex. 1002 at ¶¶ 57–64, 66, 67, 75)) and *ten additional references* (Exs. 1008, 1017, 1018, 1037–1041, 1045, 1091). Similarly, for the seemingly simple assertion that there was a motivation to try various pH ranges, Petitioner's arguments *spans seven pages*, citing *eighteen paragraphs* of Dr. Manning's Declaration (Pet. at 39–45 (citing Ex. 1002 at ¶¶ 26, 87, 91–102, 108, 125, 147, 161), which in turn cites at least *ten additional exhibits* (Exs. 1024, 1028, 1032, 1034, 1035, 1056, 1060, 1076, 1077, 1080).). (*See also* Pet. at 33–34 (citing Ex. 1002 at ¶¶ 45, 64, 68–74, 151–157, 174–182, which in turn cite at least *11 additional references* (Exs. 1001, 1026, 1027, 1029, 1031, 1047, 1052, 1072, 1088–1090)).)

Petitioner fails to address with specificity where and how the additional references it relies on would suggest attaining the claimed subject matter with a reasonable expectation of success. For example, Petitioner argues that a "POSA would not have thought formulating D2E7 with a buffer system as the only specified requirement posed any special challenges compared to other IgG_1 antibodies," and cites to ¶¶ 128–129 of Dr. Manning's Declaration. (Pet. at 35 (citing Ex. 1002 at ¶¶ 128–129).) On closer review, ¶¶ 128–129 refer through nested citations back to ¶¶ 93 and 98–102 and, taken together, span over three pages and refer to *13 additional exhibits* (Exs. 1023, 1025, 1027, 1029, 1033,

1034, 1049, 1071, 1073, 1074, 1077, 1078, 1080), and Petitioner makes no attempt to show how these references address the difficulty of achieving the formulation.

Petitioner's reliance on numerous extraneous references and its inability to point out concise statements from the references Dr. Manning cites to support its arguments not only reveal the deep flaws in its obviousness analysis, but these practices violate the requirements of (i) 37 C.F.R. § 42.104(b)(2); (ii) 37 C.F.R. § 42.22(a)(3); (iii) 37 C.F.R. § 42.6(a)(3); and (iv) 37 C.F.R. § 42.24(a)(1)(i). Petitioner's blatant violations of each of these rules mandates denial of institution. At a minimum—the Board should do as it did when it denied institution in the two *Amgen* IPRs and "consider only those arguments that [Petitioner] presents squarely in its Petition." *Amgen* '514 IPR, Paper 9 at 13–14, n. 10; *Amgen* '517 IPR, Paper 9 at 14, n. 10.

V. Conclusion

The Board should deny institution of the Petition because the asserted grounds are fundamentally deficient, driven by hindsight, and contradicted by contemporaneous publications as well as by Petitioner's prior statements and those of its expert. The Petition fails to show that any challenged claim is obvious, including failing to present any motivation to combine references, and failing to set forth any reasonable expectation of success in doing so. The flaws in Petitioner's argument are even more dramatic for dependent claims. For all these reasons, the

Petition fails to raise a reasonable likelihood that even one challenged claim is unpatentable.

Dated: August 9, 2016

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Preliminary Response to Petition complies with the applicable type-volume limitations of 37 C.F.R. § 42.24 (b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Petition, including footnotes, contains 13,977 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(i).

Date: August 9, 2016

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing Patent Owner's Preliminary Response and accompanying Exhibits thereto were served electronically by filing these documents through the PTAB E2E System, as well as by e-mailing copies the following counsel of record for Petitioner Coherus Biosciences, Inc.:

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