Filed on behalf of: AbbVie Biotechnology Ltd.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SANDOZ INC.
*Petitioner*

v.

ABBVIE BIOTECHNOLOGY LTD.
*Patent Owner*

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Case IPR2017-01823
U.S. Patent No. 8,802,100

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**PATENT OWNER'S PRELIMINARY RESPONSE**

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## I. Introduction

The Petition of Sandoz Inc. ("Petitioner") seeking *inter partes* review of claims 1-29 of AbbVie Biotechnology Ltd.'s U.S. Patent No. 8,802,100 ("the '100 patent") should be denied. Petitioner recycles the same core references and repackages the same meritless arguments upon which other challengers unsuccessfully relied in three prior IPRs. Those earlier proceedings were against patents in the *same* family that had the *same* specification, *similar* claims directed to D2E7 formulations, and the *same* 2002 priority date as the '100 patent. After a thorough analysis, the Board correctly denied institution in all three prior proceedings.[1] Petitioner now tries once again, with the benefit of the Board's

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[1] *See Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01514, Paper 9 (PTAB Jan. 14, 2016) (Decision Denying Institution) (AbbVie's U.S. Pat. No. 8,916,157) ("*Amgen* '514 IPR"); *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01517, Paper 9 (PTAB Jan. 14, 2016) (Decision Denying Institution) (AbbVie's U.S. Pat. No. 8,916,158) ("*Amgen* '517 IPR") (collectively, the "*Amgen* IPRs"); *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-01018, Paper 10 (PTAB Nov. 7, 2016) (Decision Denying Institution) and Paper 12 (PTAB Feb. 2, 2017) (Decision Denying Request for Rehearing) (AbbVie's U.S. Pat. No. 9,114,166) ("the *Coherus* IPR").

decisions, to rehash the same basic prior art and arguments. This effort fares no better than those the Board previously rejected. The Board, however, need not and should not even reach Petitioner's arguments because the duplicative nature and timing of the Petition provides ample cause for the Board to deny institution under 35 U.S.C. §§ 314(a) and/or 325(d).

To the extent the Board does not decline to institute under §§ 314(a) and 325(d), it should deny the Petition on the merits. The claims of the '100 patent are directed to stable liquid aqueous antibody formulations of the anti-TNFα antibody D2E7 (a/k/a adalimumab) at the high concentrations of 45 to 150 mg/ml (claims 1-18) or 45 to 105 mg/ml (claims 19-29). Petitioner's sole asserted ground for challenging those claims as obvious relies on a combination of *five* references and is thoroughly tainted by hindsight. Indeed, the Board has previously condemned combinations involving this same prior art as "exercises in impermissible hindsight reconstruction." *Amgen* '514 IPR, Paper No. 9 at 18; *Amgen*, '517 IPR, Paper 9 at 20.

Petitioner starts off on the wrong foot by incorrectly characterizing its primary reference. Salfeld is not a formulation patent and lacks any working examples or data of a high concentration D2E7 formulation that might constitute a "lead" formulation. What Petitioner calls a "complete guideline" for the claimed formulations is little more than a compendium of dosage forms, routes of

administration, and ingredients. Nothing points a person of ordinary skill in the art ("POSA") toward high-concentration liquid antibody formulations suitable for subcutaneous administration, as opposed to more conventional approaches, such as low-concentration lyophilized formulations. Moreover, Salfeld fails to disclose or provide any specific guidance for at least five claim elements, including the claimed (i) D2E7 antibody concentration, (ii) surfactant type (polysorbate), (iii) polysorbate concentration, (iv) pH, and (v) stability.[2]

Petitioner attempts to compensate for Salfeld's many deficiencies by picking and choosing isolated disclosures from multiple references, using the '100 patent as a roadmap through the prior art. But Petitioner fails to establish that a POSA would have selected those isolated disclosures, much less had a reasonable expectation of successfully combining these disparate elements to achieve a stable, high-concentration, liquid formulation of D2E7, as claimed in the '100 patent. Petitioner cannot and does not overcome the well-known unpredictability and difficulties associated with preparing stable high-concentration liquid formulations that existed at the time of AbbVie's invention. In fact, the art taught away from

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[2] Petitioner concedes that many of these elements of the claim are missing from Salfeld. *See, e.g.*, Pet. at 16 (antibody concentration), 20 (surfactant type and concentration), 25-28 (polyol concentration), 28-29 (pH).

preparing such high-concentration, liquid formulations and instead toward low-concentration or lyophilized (*i.e.*, freeze-dried) formulations.

Finally, as in the prior challenges, Petitioner's positions flatly contradict prior statements by its own declarant, Dr. Remmele, and by Petitioner's parent company, Novartis, each of which previously agreed that "one cannot expect that an excipient that stabilizes one protein will predictably stabilize another protein" (Ex. 1044 at 1)[3] and that "each antibody formulation must be prepared and evaluated on a case-by-case basis" (Ex. 2037 at 14). Petitioner's contradictions and changed position show that its assertions about the state of the art do not reflect the views of a POSA at the time of the invention in 2002—as the Board has found *over a half dozen times* in the *Amgen* IPRs, the *Coherus* IPR, and other proceedings.

In short, the Petition is fatally flawed from start to finish. It belatedly retreads the same ground as prior petitions in a manner disfavored under §§ 314(a) and 325(d), and it fails to establish the required elements of obviousness with respect to any challenged claim. For either reason—or both—the Petition should be denied.

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[3] All citations herein refer to the exhibits' native page numbers, except IPR page numbers are used where the exhibits do not include native page numbers.

## 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 11.

### B. Claim Construction

#### 1. *"stable"*

In the prior *Amgen* IPRs and the *Coherus* IPR, which involved patents with the same specification as the '100 patent and similar claims (*see* Section V.A), the Board construed the term "stable" in the phrase "stable liquid aqueous pharmaceutical formulation" to mean a formulation in which "the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage and use as a pharmaceutical formulation." *Coherus* IPR, Paper 10 at 6; *see also Amgen* '514 IPR, Paper 9 at 6-8; *Amgen* '517 IPR, Paper 9 at 6-8. The same construction should apply here.

Petitioner does not dispute the Board's prior construction of "stable" (Pet. at 12), but nonetheless seeks to improperly redefine the Board's construction throughout its Petition as though it required only "some degree of stability," a "minimal level of stability," or a "minimal degree of stability" (Pet. at 33, 39, 40; *see also id.* at 9). The Board previously rejected this same argument—that stable means storage "for any period of time, no matter how short"—in the *Amgen* IPRs.

*Amgen* '514 IPR, Paper 9 at 7; *Amgen* '517 IPR, Paper 9 at 7. As the Board found, the specification "focuses on the need for a formulation 'with an extended shelf life,'" and a POSA "would have understood that a formulation would need to be stable for storage and use." *Amgen* '514 IPR, Paper 9 at 7; *Amgen* '517 IPR, Paper 9 at 7-8 (same). In the *Coherus* IPR, the Board further found that the claim term "stable" required that "the formulation must be sufficiently stable for use when administered subcutaneously to a human." *Coherus* IPR, Paper No. 10 at 6. Dr. Remmele expressed a comparable view as recently as 2015. Ex. 1064 at 46-47. Accordingly, a POSA would recognize that formulations that retain stability only for very short periods of time are not "stable" and would not satisfy the Board's prior claim construction.

## III. Background And State Of The Art

The '100 patent covers HUMIRA®, one of the top selling drugs in the world, used by over a million patients to treat rheumatoid arthritis and other inflammatory conditions. *See* Ex. 2022 at 187; *see also* Ex. 2001 at 3; Ex. 2002 at 15; Ex. 2028 at 1-2; Ex. 2023 at 1. HUMIRA's success was driven in no small part by (i) the ability of patients to self-administer a liquid antibody formulation via subcutaneous (s.c.) administration (*see* Ex. 1060 at 4) without the need for reconstitution of a lyophilized formulation, and (ii) the fact that its formulation is stable enough to be commercially viable (*e.g.*, to withstand shipping and storage for periods of time

typical for biologic therapies). These advances helped HUMIRA meet the long-felt need for easy self-administration.

### A. Before HUMIRA, No One Had Commercialized A Stable, Liquid, High-Concentration Antibody Formulation

HUMIRA's stable, liquid, high-concentration antibody formulation, which could be subcutaneously administered, was a major breakthrough. Prior to AbbVie's invention in 2002 of the formulations claimed in the '100 patent, only two types of monoclonal antibody formulations were commercially available: (i) low-concentration liquid formulations, and (ii) lyophilized (*i.e.*, freeze-dried) formulations. None was subcutaneously administered. The table below is adapted from Petitioner's list of available commercial antibody products (Pet. at 43-46) and identifies liquid and lyophilized formulations, as well as the concentrations of the formulations.

**Table 1. Commercially Available Antibody Formulations (as of 08/16/2002)**

| 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. |
| PROSTASCINT (capromab pendetide) *(anti-PSMA)* | Ex. 1031 | 0.5 mg/ml | i.v. |
| ZENAPAX (daclizumab) *(anti-IL2)* | Ex. 2014 | 5 mg/ml | i.v. |
| ZEVALIN (ibritumomab tiuxetan) *(anti-CD20)* | Ex. 1029 | 1.6 mg/ml | i.v. |
| ***Lyophilized* Formulations** | | | |
| REMICADE (infliximab) *(anti-TNFα)* | Ex. 2016 | 100 mg/vial (powder)<br>10 mg/ml reconstituted | i.v. |
| HERCEPTIN (trastuzumab) *(anti-HER2)* | Ex. 2017 | 440 mg/vial (powder)<br>21 mg/ml reconstituted | i.v. |
| WINRHO SDF *(gamma globulin)* | Ex. 2018 | 0.120-1 mg/vial (powder)<br>0.48-0.240 mg/ml reconstituted | i.v. or intra-muscular |
| SYNAGIS (palivizumab) *(anti-RSV protein F)* | Ex. 2019 | 50 or 100 mg/vial (powder)<br>100 mg/ml reconstituted | intra-muscular |
| SIMULECT (basiliximab) *(anti-IL-2Rα)* | Ex. 2020 | 20 mg/vial (powder)<br>4 mg/ml reconstituted | i.v. |

As this table shows, all commercially available liquid antibody formulations at the time had a concentration of 10 mg/ml or less—more than 4-fold lower than the concentrations recited in the '100 patent claims. *See* Exs. 1029, 1031, 2009-2012, 2014, 2016-2020.[4] Antibody formulations with higher concentrations were lyophilized—not stable, liquid formulations.

It is not an accident that no one had succeeded in commercializing a formulation like those claimed by AbbVie. In practice, 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 small injection volumes for single dose subcutaneous administration. *E.g.*, Ex. 1066 at 237; *see also* Ex. 2005 at 1905 (noting in 2007 that "[d]evelopment of these [high concentration antibody] formulations *poses a number of serious obstacles to commercialization*.")[5]; Ex. 2033 at 271 (noting in

[4] Even the non-antibody proteins cited by Dr. Remmele illustrate this point. Ex. 1002 at 28-29. Of the seventeen protein formulations listed, eight were lyophilized, one was provided as both lyophilized or a liquid formulation having a concentration of less than 10 mg/ml, and seven of the remaining eight had a concentration of 10 mg/ml or less. *E.g.*, Exs. 1026, 1053-1056.

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

2015 that "a considerable proportion of human monoclonal antibody candidates *fail formulation studies.*"); Ex. 2030 at 612.

### B. The Art Taught Away From Liquid Formulations And Toward Lyophilized Formulations

Recognizing the difficulties of making stable liquid antibody formulations, the prior art taught away from liquid formulations. By 2002, the literature specifically directed formulation scientists toward the development of *lyophilized* rather than liquid (aqueous) 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. 1022 at 109-110; *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."); *id.* at 188; Ex. 2032 at 365; Ex. 2024 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.").

Even as late as 2015—thirteen years after the priority date of the '100 patent—Dr. Remmele admitted that liquid formulations of certain monoclonal antibodies may be "technically unfeasible" due to their instability, meaning that lyophilization should be used. Ex. 1064 at 44, 46-47.

### C. Formulating Proteins, Particularly Antibodies, Was Complicated And Unpredictable In 2002

Antibody formulation was complicated and unpredictable in 2002, with little guidance or predictability about what might work in a particular circumstance, or whether a formulation would work at all. It was considered "not possible" to formulate "many proteins" as stable liquid formulations, much less at the high claimed concentrations of 45 to 150 (or 105) mg/ml. *E.g.*, Ex. 1022 at 109-110. Developing stable liquid antibody formulations, especially those at a concentration high enough to be suitable for subcutaneous administration, therefore required extensive scientific judgment and was highly unpredictable. *E.g.*, Ex. 1022 at 188. Before this IPR, Petitioner's own expert (Dr. Remmele) and parent company (Novartis (Ex. 2042)) consistently acknowledged the complex and unpredictable nature of protein formulation.

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

Among the many complexities of protein formulation were the large number of potential problems to solve and the even larger number of potential, but

unpredictable, avenues to try to address them. Perhaps the "most challenging task [wa]s the stabilization of a protein to achieve an acceptable shelf life." Ex. 1021 at 178. Typical stability problems observed in protein pharmaceuticals included (i) non-covalent aggregation, (ii) covalent aggregation, (iii) deamidation, (iv) cyclic imides, (v) cleavages, (vi) oxidation, and (vii) surface denaturation/adsorption. Ex. 1021 at 177-178; Ex. 1064 at 50. Multiple potential causes of these stability problems further complicated the situation. *E.g.*, Ex. 1022 at 13; Ex. 1021 at 145-153; Ex. 2003 at 117-118. Additionally, in attempting to overcome these challenges, "there [wa]s no single pathway to follow in selection of a suitable stabilizer(s)." Ex. 1021 at 178; *see also id.* at 164-167; Ex. 2021 at 307. The numerous alternatives included pH optimization, ionic additives, amino acids, surfactants, protein concentration, raw material purity, inhibitors, free radical scavengers, and active oxygen scavengers, among others. Ex. 1022 at 13; *see also* Ex. 1021 at 163-172, 177-178. A POSA was therefore presented with a wide array of potential problems and potential options.

Moreover, different antibodies have different degradation profiles. *E.g.*, Ex. 1022 at 185-186; *see also* Ex. 2008 at 386; Ex. 2033 at 270. As Dr. Remmele appreciated, there was no reliable approach to predict which, if any, formulation components might work for a particular protein or antibody. *E.g.,* Ex. 2027 at 200 ("Determination of the best candidate solutions that offer the greatest chances of

achieving optimal shelf-life can be difficult."). Others in the scientific community also acknowledged this lack of predictability. *See, e.g.,* Ex. 1021 at 163-172, 178; Ex. 2021 at 307 ("Predicting *a priori* the alteration of pharmaceutical properties caused by the three degradation routes [(*i.e.*, protein aggregation, deamidation, and oxidation)] is difficult and must be determined on a case-by-case basis."). Dr. Remmele admitted that "[s]olution conditions producing adequate stability for protein pharmaceuticals are often *empirically determined*, which is essentially *a 'hit' or 'miss' method* for developing stable formulations." Ex. 2029 at IPR2.

Dr. Remmele repeatedly reiterated these uncertainties during prosecution of his own patents related to liquid protein formulations, which had a 2002 priority date. *E.g.*, Ex. 2025 at 16. He noted that "even if the skilled person would have figured out the cause [of instability], s/he would not have known without inventive merit how to overcome that cause…since the skilled person would then have to [] select a suitable 'countermeasure' to fix the problem." Ex. 2026 at 24.

Even after the '100 patent's priority date, the plethora of formulation components available yielded "far too many possible sets of formulations to allow a purely empirical screening approach to be successful." Ex. 2005 at 1902; Ex. 2041 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"). In fact, Novartis argued to the PTO during

prosecution of its own antibody formulation patents, which claimed priority to 2008, that it was "legal error for the Office to assert that a skilled artisan would be motivated to *generally* optimize excipients, and would *eventually* strike upon the excipients recited in Applicants' claims." Ex. 2037 at 19-20 (emphasis in original).

Given the large number of potential formulation problems and still larger number of potential avenues to try to address them, 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 '100 patent.

### 2. *A formulation designed for one protein would not be expected to result in a stable formulation for a different protein*

Contrary to Petitioner's suggestion, there was no expectation that these problems could be overcome merely by swapping new proteins, such as novel antibodies, into existing formulations. Numerous scientific publications at the relevant time, including those by Dr. Remmele, acknowledged the difficulty of determining which of the many potential excipients, if any, might yield a stable liquid protein formulation, much less a stable, liquid, high-concentration formulation.

As noted, Dr. Remmele repeatedly described the "'hit' or 'miss'" unpredictability and "[c]hallenging problems" associated with making stable

aqueous protein formulations. *E.g.*, Ex. 2029 at IPR2; Ex. 2031 at Abstract; Ex. 2027 at 200. He admitted in 2008 that "if there were such a thing as a universal protein stabilizer, my current role would be redundant because the same stabilizer could be used for all proteins." Ex. 2034 at 1.

Dr. Remmele's statements reflect the consensus in the scientific community regarding such unpredictability. For example, a 1999 Wang review article explained that achieving acceptable stability is "the most formidable challenge in formulating a liquid protein pharmaceutical." Ex. 1021 ("Wang") at 178. Wang further explained that there is no one-size-fits-all approach: "[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 have to be evaluated on a *case-by-case basis*." *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. 2021 at 307; Ex. 2032 at 365 ("[A] comprehensive strategy to achieve stable liquid formulations has not yet emerged.").

Dr. Remmele previously relied on Wang to argue the same points. In prosecuting his own patent with a 2002 priority date (Ex. 1037), he stated:

> [O]ne cannot expect that an excipient that stabilizes one protein will predictably stabilize another protein. In other words, there is no

> universal stabilizer for liquid formulations of pharmaceutical proteins. … This fact is recognized in the art. [The authors of Wang (Ex. 1021)] state that 'although antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior.'

Ex. 1044 at 1-2 (*citing* Ex. 1021 at Abstract).[6] The same arguments were repeatedly made during prosecution of Dr. Remmele's other patents. *E.g.*, Ex. 2006 at 6 (*citing* Ex. 1021 at 178); Ex. 2025 at 16 ("[T]he teaching relating to one protein cannot simply be transferred to other proteins."); *id.* at 17 ("[T]he skilled person would not simply apply the teaching relating to one protein to a different protein." (emphasis in original)).

The broader scientific literature reported the same unpredictability as recently as 2012. Protein folding and physical instability are "complex

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[6] The Board should accord no weight to Petitioner and Dr. Remmele's attempt to walk-back and distinguish Dr. Remmele's prior statements by arguing that "the '702 patent is directed to the discovery that a particular excipient is capable of stabilizing a particular protein in solution and refers to long-term storage." Pet. at 41 n.35. Such arguments flatly contradict Dr. Remmele's prior writings and the '702 patent itself.

phenomena," and "[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. 2040 at 1326 ("Each protein is unique both chemically and physically and therefore *will exhibit unique stability behavior*."); Ex. 1066 at 244; Ex. 2030 at 613; Ex. 2033 at 270; Ex. 2008 at 386 ("Exposed surface residues of each antibody are unique and require specific formulation excipients to provide maximal stability… .").

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. 1022 at 185-186.

### 3. *Formulating antibodies was particularly difficult because antibodies with similar sequences often have different instability issues*

Antibodies are particularly unsuitable for a one-size-fits-all approach to formulation because even small changes in antibody amino acid sequence can have a large impact on stability. For example, during prosecution of Dr. Remmele's patent claiming priority to 2002, it was noted that "even very similar antibodies may differ in aggregation behavior and stability requirements … due to the

differences in surface-exposed amino acids that mediate antigen specificity." Ex. 2006 at 6 (citations omitted); *see also* Ex. 2025 at 17-18. Dr. Remmele also "point[ed] to additional support in the literature" showing that "even antibodies, which as a class can share distinct structural similarities[,] will respond differently in solution" (Ex. 2036 at 8), as did Novartis (*e.g.,* Ex. 2037 at 13; *id.* at 14).

The literature continued to stress well after the '100 patent's priority date that "the interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity." Ex. 2035 at 690; Ex. 2007 at 1, 14, 21 ("Due to the significant difference in the primary sequence among different antibodies, the relative severity of [] degradation pathways can be significantly different."). Thus, "[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… ." Ex. 2007 at 21.

Dr. Remmele likewise admitted as recently as 2015 that differences in antibody sequences can have significant and varying effects on protein stability:

> Although formulation has some impact, clearly a vital consideration is the primary sequence of the protein itself. … [T]here are significant differences in stability and aggregation propensity among antibodies related to Fab differences and the particular antigen specificity of the mAb.

Ex. 2003 at 128; *see also, e.g.*, *id.* at 116, 117, 128; Ex. 1064 at 47, 50, 52.

For all these reasons, and as determined by this Board on at least three separate occasions for patents in this family, a POSA would not have reasonably expected a formulation designed for one antibody to be a stable formulation for a different antibody.

## IV. Summary Of The Asserted References

Petitioner relies on a combination of *five* references. Other than Remington, which is merely a general pharmaceutical sciences reference with no specifics as to D2E7, all of this art was previously argued in the three earlier IPRs.

### A. Salfeld

Salfeld is an antibody patent that is disclosed on the face of the ’100 patent, was thoroughly discussed during prosecution, and was considered by the Board in multiple proceedings. *See Amgen* ’514 IPR, Paper 9; *Amgen* ’517 IPR, Paper 9; *see also* Ex. 1001 at IPR1; Ex. 2043 at 14-19.

Salfeld fails to teach or disclose the stable, high-concentration, liquid antibody formulations disclosed and claimed in the ’100 patent. Instead, Salfeld generally states that formulations may be made and provides long lists of potential dosage forms (*e.g.*, injectable and infusible solutions, dispersions or suspensions, tablets, pills, powders, liposomes, and suppositories, *etc.*), routes of administration (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular, oral, and

transdermal), and broad categories of ingredients (called "carriers," including "solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying and the like that are physiologically compatible"). Ex. 1003 at 20:57-22:39.

Salfeld provides no working example of a stable, high-concentration adalimumab formulation. Indeed, Salfeld fails to disclose or provide any specific guidance regarding at least five claim elements, including the claimed D2E7 antibody concentration, surfactant type, polysorbate concentration, pH, and stability. Salfeld's recitation of numerous formulation forms and components offers nothing to counter the strong preference that POSAs had in 2002 for lyophilized compositions rather than liquid formulations.

**B. Van de Putte**

Van de Putte is an abstract for an early stage (phase II) clinical trial directed to showing the clinical responsiveness of patients following weekly subcutaneous self-administration of total doses of 20, 40 or 80 mg of D2E7 (or placebo). The 1999 van de Putte abstract cited by Petitioner (Ex. 1004) is essentially identical to the 2000 van de Putte abstract (Ex. 2056) reviewed by the Board in the *Coherus* IPR, except that the 1999 abstract includes only three-month efficacy data rather than the additional six-month efficacy data.

Van de Putte provides no guidance on the development of any pharmaceutical formulation. With the exception of disclosing subcutaneous administration of D2E7, van de Putte is completely silent as to the limitations of the claims of the '100 patent and provides no details as to: (i) the injection volume or antibody concentration, (ii) the formulation ingredients, (iii) whether it was administered as a single injection or multiple injections, (iv) whether the formulation was a liquid or lyophilized, or (v) whether the formulation used was stable, and for what period of time or under what conditions.

The Board fully reviewed the substance of van de Putte (in the form of the 2000 abstract) and expressly found all of these deficiencies when it denied institution in the *Coherus* IPR, concluding that "van de Putte offers no guidance as to how a person of ordinary skill in the art would prepare a stable, liquid formulation of 50 mg/ml D2E7." *Coherus* IPR, Paper 10 at 10.

### C. Barrera

Barrera is a journal publication that is disclosed on the face of the '100 patent and was fully reviewed in the *Amgen* IPRs. *E.g.*, *Amgen* '514 IPR, Paper 9; *Amgen* '517 IPR, Paper 9; Ex. 1001 at 3. It reports on an early clinical trial that involved "administering a single dose of D2E7 to study short-term effects in rheumatoid arthritis patients, using a preparation of '25 mg/ml D2E7 mAb in 1.2% mannitol, 0.12% citric acid, 0.02% sodium citrate' in an *intravenous* infusion."

*Amgen* ’514 IPR, Paper 9 at 16-17; *Amgen* ’517 IPR, Paper 9 at 18. The antibody concentration in Barrera is less than that claimed in the ’100 patent. Barrera fails to disclose whether the formulation was a liquid or lyophilized. Barrera also “does not expressly discuss the stability of its formulation” and “is silent as to pH and whether it includes a surfactant.” *Amgen* ’514 IPR, Paper 9 at 17; *Amgen* ’517 IPR, Paper 9 at 18.

**D. Lam**

Lam is disclosed on the face of the ’100 patent and was previously reviewed by the Board in the *Amgen* IPRs. *E.g.*, *Amgen* ’514 IPR, Paper 9; *Amgen* ’517 IPR, Paper 9; Ex. 1001. Other than formulations for two antibodies unrelated to D2E7 (namely, antibodies to CD18 and CD20), Lam lists only dozens of distinct antigens against which antibody formulations might be developed, without disclosing a specific formulation or amino acid sequence for any of these other antibodies. S*ee* Ex. 1005 at 10:5-63. The Board previously identified these deficiencies and was “unpersuaded that the inclusion of TNFα in a laundry-list of untested potential targets in Lam 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.” *Amgen* ’514 IPR, Paper 9 at 18; *Amgen* ’517 IPR, Paper 9 at 19.

### E. Remington

Remington is a pharmaceutical sciences reference that provides only broad, general disclosure regarding pharmaceutical formulations. Remington makes no mention of D2E7 and provides no formulations for D2E7. Indeed, the formulation information of Remington that Petitioner cites is not directed to any specified proteins or antibodies, but rather is merely general information with regard to *any* potential pharmaceutical formulation.

## V. Institution Should Be Denied Under 35 U.S.C. §§ 314(a) And 325(d) Because The Patentee Overcame Petitioner's Arguments During Three Prior IPR Proceedings And The Petition Provides Nothing New

### A. Institution Should Be Denied Under § 325(d) Because Petitioner Presents Substantially The Same Prior Art And Arguments Previously Presented To The Office

The Board may decline to institute where "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). That is exactly the situation here. The *Amgen* IPRs and *Coherus* IPR involved patents in the same family with the same specification and the same priority date as the '100 patent. The table below provides a summary of the prior proceedings with exemplary claims from the challenged patents.

| *Amgen* '514 IPR<br>U.S. Pat. No. 8,916,157 | *Amgen* '517 IPR<br>U.S. Pat. No. 8,916,158 | *Coherus* IPR<br>U.S. Pat. No. 9,114,166 | The Present IPR<br>U.S. Pat. No. 8,802,100 |
|---|---|---|---|
| 1. A stable liquid aqueous pharmaceutical formulation comprising | 1. A stable liquid aqueous pharmaceutical formulation comprising | 1. A stable liquid aqueous pharmaceutical formulation comprising | 1. A stable liquid aqueous pharmaceutical formulation comprising |
| (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof,<br><br>at a concentration of 20 to 150 mg/ml, | (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof,<br><br>at a concentration of 20 to 150 mg/ml, | a human anti-human Tumor Necrosis Factor alpha (TNFα) IgG1 antibody<br><br>at a concentration of 50 mg/ml, | (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof,<br><br>at a concentration of 45 to 150 mg/ml, |
| (b) a tonicity agent, | (b) a polyol, | | (b) a polyol, |
| (c) a surfactant, and | (c) a surfactant, and | | (c) a polysorbate at a concentration of 0.1 to 10 mg/ml, and |
| (d) a buffer system having a pH of 4.0 to 8.0, | (d) a buffer system having a pH of 4 to 8, | [and] a buffer system[], and has a pH of 4.0 to 8.0[,] | (d) a buffer system having a pH of 4.5 to 7.0, |
| wherein the antibody comprises<br><br>the light chain variable region and the heavy chain variable region of D2E7. | wherein the antibody comprises<br><br>the light chain variable region and the heavy chain variable region of D2E7. | wherein the antibody comprises<br><br>the light chain variable region and the heavy chain variable region of D2E7… . | wherein the antibody comprises<br><br>the light chain variable region and the heavy chain variable region of D2E7. |
| *Asserted Grounds Rejected by the Board:*<br><br>Obviousness over<br><br>(1) Lam and Barrera<br><br>(2) Salfeld and Heavner | *Asserted Grounds Rejected by the Board:*<br><br>Obviousness over<br><br>(1) Lam and Barrera<br><br>(2) Salfeld and Heavner | *Asserted Grounds Rejected by the Board:*<br><br>Obviousness over<br><br>(1) van de Putte and Relton | *Asserted Grounds:*<br><br>Obviousness over<br><br>(1) Salfeld, van de Putte, Lam, Barrera and Remington |

As can be seen, there are significant parallels between the claims in those prior proceedings and the claims of the ’100 patent. Petitioner nonetheless shuffles the same basic combinations of references asserted in those prior petitions to make obviousness arguments that the Board has already rejected. The only new reference Petitioner cites, Remington, is merely a general pharmaceutical sciences reference with no specific reference to D2E7 at all. Adding that one small variation does not change the fact that the four core references relied on by Petitioner were previously considered in the *Amgen* IPRs and the *Coherus* IPR.

The Board has made clear that merely recycling references and arguments considered during prior proceedings before the Office may be grounds for denial of institution under 35 U.S.C. § 325(d). *See, e.g.*, *Unified Patents Inc. v. Berman*, No. IPR2016-01571, Paper 10 at 9, 12-13 (PTAB Dec. 14, 2016). Absent “a compelling reason why [the Board] should readjudicate substantially the same prior art and arguments,” retreading the same ground already covered is simply not “an efficient use of Board resources.” *Id.* at 12. That is exactly what the Petition requests here, and the Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d).

### B. The *General Plastic* Factors Strongly Favor Denial Of Institution Under 35 U.S.C. § 314(a)

Even where a petition is not rejected under § 325(d), institution of an *inter partes* review remains discretionary, and the Board may decline to institute under § 314(a). In *General Plastic*, an expanded panel set forth a non-exhaustive list of seven factors to provide a framework for determining whether to exercise the Board's discretion to deny institution of an *inter partes* review under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a). *General Plastic Indus. v. Canon Kabushiki Kaisha*, No. 01357/-01358/-01359/-01360/-01361, Paper 19 at 9-10 (PTAB Sept. 6, 2017) (Decision Denying Request for Rehearing) (designated precedential). These factors collectively support denying institution here.

***Factor 1: Prior Petition.*** Factor 1, which addresses whether a petitioner previously filed a petition directed to the same claims of the same patent, favors denying institution. While the *Amgen* IPRs and the *Coherus* IPR were not directed to "the same patent" as in the current proceeding, they involved patents in the same family having the same priority date and the same specification as the '100 patent. As discussed above, there are significant parallels between the claims in those prior proceedings and the claims of the '100 patent and, accordingly, extensive duplication in the prior art and arguments presented by Petitioner. This "high degree of similarity" of issues and arguments substantially "reduces the weight" of

the fact that Sandoz was not a petitioner or real-party-in-interest in the prior IPRs. *Samsung Elecs. Co. v. ELM 3DS Innovations, LLC*, No. IPR2017-01305, Paper 11 at 18-19 (PTAB Oct. 17, 2017) (Decision Denying Institution). The Board's "discretion under 35 U.S.C. § 314(a) and 37 C.F.R § 42.108(a) is not limited to situations where the same party files multiple petitions." *NetApp Inc. v. RealTime Data LLC*, No. IPR2017-01195, Paper 9 at 10 (PTAB Oct. 12, 2017) (Decision Denying Institution). The situation here may not be quite as egregious as when the same petitioner challenges the same claims with exactly the same art. But the degree of duplication here triggers the same fairness and efficiency concerns repeatedly recognized by the Board and thus weighs in favor of denying institution.

***Factor 2: Awareness of Newly Asserted Prior Art.*** Factor 2 also counsels in favor of denying institution. Factor 2 considers whether, at the time of the first petition's filing, the petitioner knew of the prior art asserted in the second petition or should have known of it. As explained above, rather than presenting new and different art of which prior petitioners may not have been aware, the Petition here essentially repackages the same art previously presented by others.

***Factors 3 and 4: Timing.*** Factors 3 and 4 both weigh heavily in favor of denying institution. Factor 3 asks whether, at the time the second petition is filed, the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first

petition. Factor 4 addresses the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition.

Here, the timing of the Petition in relation to other relevant events supports denial of institution. The petitions in the *Amgen* IPRs had an effective filing date of July 20, 2015, and institution was denied on January 14, 2016. The *Coherus* IPR had an effective filing date of May 11, 2016, and institution was denied on November 7, 2016. Coherus' rehearing petition was denied on February 2, 2017. The Petition at issue here has an effective filing date of August 14, 2017. Accordingly, it was filed more than *two years* after the first two petitions by Amgen with which it substantially overlaps, and more than *fifteen months* after the filing of the third petition by Coherus. Furthermore, Petitioner inexplicably waited *sixteen months* after denial of institution in the *Amgen* IPRs and more than *eight months* after the denial in the *Coherus* IPR before filing its own Petition, in which essentially the same arguments were recycled.

Petitioner thus had the benefit of "receiving and having the opportunity to study" (i) Patent Owner's prior responses to challenges by the other unsuccessful petitioners using the same prior art references and arguments as in the present proceeding, (ii) the three decisions denying institution in the *Amgen* IPRs and the *Coherus* IPR, and (iii) the additional decision denying the request for rehearing in

the *Coherus* IPR. *General Plastic*, No. IPR2016-01357, Paper 19 at 17. Petitioner admitted as much, alleging that its Petition "addresses the Board's reasons for not instituting trial on these prior petitions, including arguments raised by AbbVie in its preliminary responses." Pet. at 4. In fact, Petitioner repeatedly attempts to preemptively rebut arguments made by Patent Owner in the prior proceedings with respect to the same prior art references now recycled in the current proceeding. *E.g.*, Pet. at 20, 29-33, 35 n.32, 39-49. Petitioner's knowledge from other proceedings and use of such information in its Petition to reargue old points "weighs strongly in favor of exercising [the Board's] discretion to deny institution." *Samsung*, No. IPR2017-01305, Paper 11 at 21.

***Factor 5: Explanation for Time Lapse***. Factor 5 also weighs in favor denying institution. This factor assesses whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent. Petitioner has offered no explanation for the significant delay in filing its Petition. Nor could it, given the degree of duplication with the *Amgen* IPRs and the *Coherus* IPR.

***Factor 6: Impact on Board Resources***. Factor 6 also favors denying institution. This factor requires consideration of the Board's finite resources. Petitioner's strategy of trying to paper over gaps in prior failed arguments is disfavored because "us[ing] [the Board's] decisions on institution as a roadmap,

until a ground is advanced that results in review is a practice that would tax Board resources, and force patent owners to defend multiple attacks." *Ube Maxell Co., Ltd. v. Celgard, LLC*, No. IPR2015-01511, Paper 10 at 11 (PTAB Jan. 7, 2016) (Decision Denying Institution) (*citing Conopco, Inc. v. Procter & Gamble Co.*, No. IPR2014-00506, Paper 25 at 4 (PTAB Dec. 10, 2014) (Decision Denying Request for Rehearing) (designated informative)). And even without that particular concern, addressing duplicative prior art and arguments is not "an efficient use of Board resources." *Unified Patents*, No. IPR2016-01571, Paper 10 at 12.

***Factor 7: Impact on Timing of Decision***. Finally, Factor 7 addresses the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution of review. Although the current Petition would not interfere with the Board's ability to decide the earlier IPRs in a timely fashion, this is only because of the lengthy amount of time that elapsed between the completion of the prior IPRs and the filing of the latest Petition. Factor 7 is therefore neutral.

In sum, the majority of the *General Plastic* factors weigh in favor of the Board exercising its discretion under 35 U.S.C. § 314(a) to deny institution, and the remainder are neutral. Petitioner unfairly benefitted from having the opportunity to study Patent Owner's prior responses and Board decisions in the *Amgen* IPRs and the *Coherus* IPR. It then used that information to repackage and

assert the very same references, as well as preemptively rebut the prior arguments and decisions related to those same references, in its own Petition. Declining to institute review will avoid the resulting inequity to Patent Owner and improper burden on the Board.

## VI. The Challenged Claims Would Not Have Been Obvious Over Salfeld In Combination With Van De Putte, Barrera, Remington And Lam

Even if considered on its merits, Petitioner's asserted ground does not warrant institution because Petitioner 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. Petitioner's Hindsight-Driven Approach Improperly Relies On The '100 Patent To Thread Its Way Through The Prior Art And Fails To Overcome The Unpredictably That Doomed The *Amgen* IPRs And The *Coherus* IPR

Petitioner's approach relies on filling gaps in Salfeld by locating individual elements of the claimed formulations in *four* other prior art references and then asserting that inclusion of each element is "typical" or "common," but this approach uses a hindsight lens through which virtually any valid invention would appear obvious. In particular, to arrive at the claimed invention, Petitioner argues that a POSA would (1) choose to pursue a stable liquid formulation from among the varied dosage forms and routes of administration mentioned in ***Salfeld***, even though the art at the time recommended lyophilized powders rather than liquid

formulations; (2) speculate as to the concentration of D2E7 in ***van de Putte*** using unreasonable and selective assumptions about numbers of injections and injection volumes; (3) selectively choose a polyol, a surfactant, and a buffer from ***Salfeld***'s extensive disclosure of formulation components, while at the same time ignoring all the other disclosed optional excipients to combine with D2E7; (4) identify the type and amount of surfactant based on ***Remington***'s teaching that polysorbate is the most widely used surfactant and ***Lam***'s teaching of a polysorbate concentration from 0.01% to 0.1%; and for certain claims, also (5) choose to use mannitol in the formulation from ***Remington***'s general disclosure of tonicity agents; and (6) choose the concentration of mannitol based on ***Barrera***'s disclosure of a completely different, lower-concentration D2E7 formulation for *intravenous* administration having 12 mg/ml mannitol. Pet. at 2-3.

Here, as in the three prior IPRs, Petitioner is attempting to use "the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *Amgen* '514 IPR, Paper 9 at 19 (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)); *Amgen* '517 IPR, Paper 9 at 20 (same). In fact, with its reliance on *five* different references, the combination Petitioner proposes is even more complicated and attenuated than the grounds rejected in the prior IPRs.

Petitioner also fails to overcome the unpredictably that doomed the *Amgen* IPRs and the *Coherus* IPR. As discussed in Section III above and the Board's decisions denying institution in the prior IPRs, the antibody formulation art was highly unpredictable in 2002. *Amgen* '514 IPR, Paper 9 at 15 ("Wang suggests a high degree of *un*predictability in the antibody formulation art.") (emphasis in original); *Amgen* '517 IPR, Paper 9 at 16 (same); *Amgen* '514 IPR, Paper 9 at 19 ("[T]he difficulty of formulating liquid antibodies as described in the Wang article and the dearth of high-concentration, stable liquid antibody formulations available at the time of the invention together appear to paint a prior art landscape of unpredictability."); *Amgen* '517 IPR, Paper 9 at 20 (same).[7]

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[7] Petitioner attempts to distinguish "literature reviews," such as Wang (Ex. 1021) and Carpenter 2002 (Ex. 1022), on the ground that they "did not address" the alleged "minimal level of stability" required by the '100 patent or "the teachings of stable high antibody concentration formulations" in Petitioner's cited references. Pet. at 39. As discussed above, however, the Board previously explained that the properly construed claims are not drawn to a "minimal" level of stability (*see* Section II.B), and the literature reviews are highly probative of the state of the art, including the Petitioners' cited references, as it was understood before AbbVie made its invention.

The Board explicitly found that such unpredictability foreclosed a POSA in 2002 from having a reasonable expectation of success in developing stable, high-concentration, liquid formulations of D2E7. *See Amgen* '514 IPR, Paper 9 at 14 ("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* '517 IPR, Paper 9 at 15 (same); *Coherus* IPR Paper 10 at 11 ("Given this uncertainty in the art, we are not persuaded … that a skilled artisan would have had a reasonable expectation of success in preparing a stable, liquid formulation of D2E7."); *see also id.* at 11-13; *Coherus* IPR, Paper 12 at 3-5.

The Board has similarly cited and relied on the high unpredictability in the formulation art in other IPR proceedings as well. For example, it has observed that, even in 2007, "'there was a general consensus in the art that formulation that worked for one antibody … would *not* be predicted to work for a different antibody (such as adalimumab).'" *Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2017-00822, Paper 14 at 23 (PTAB Sept. 7, 2017) (Decision Denying Institution) (emphasis in original).[8]

[8] *See also Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2017-01008, Paper 11 at 19 (PTAB Sept. 7, 2017) (Decision Denying Institution);

Indeed, even Dr. Remmele and Novartis repeatedly admitted in prior statements that unpredictability precluded the type of obviousness analysis offered here. *See* Section III. Petitioner's and Dr. Remmele's attempt to walk away from these statements should be disregarded as an IPR-inspired tactic. *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, No. IPR2014-00654, Paper 69 at 25 (PTAB Sept. 21, 2015) (Final Written Decision) (discrediting expert testimony in view of contradictory statements by Petitioner's expert that formulating a reliable dosage form was "very difficult"); *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 prior representations to the USPTO, whether viewed "as judicial estoppel, an admission, waiver, or simply hoisting [the party] by its own petard").

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*Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2017-01009, Paper 11 at 20 (PTAB Sept. 7, 2017) (Decision Denying Institution); *Momenta Pharm., Inc. v. Bristol-Myers Squibb Co.*, No. IPR2015-01537, Paper 37 at 7 (PTAB Dec. 22, 2016) (Final Written Decision) (The Wang (Ex. 1021) reference "suggests a trial-and-error approach to protein formulation. … We do not agree that because the approach was known, it was necessarily expected to be successful.").

As discussed below, nothing in the art or arguments presented by Petitioner comes close to overcoming this acknowledged uncertainty in the prior art and establishing motivation to combine with a reasonable expectation of success.

### B. Salfeld Is Not A "Complete Guideline" Or "Roadmap" To The Claimed Formulations Of D2E7

Contrary to Petitioner's contention (Pet. at 1, 15, 20), Salfeld is not a "complete guideline" or "roadmap" to the claimed formulations. If it were, Petitioner would not need to combine *four* additional references with Salfeld to cobble together its obviousness arguments. Salfeld is an antibody patent, and its generic "formulation" disclosure consists merely of broad lists that identify multiple potential formulation types, routes of administration, and formulation ingredients. Salfeld's recitation of such ingredients lacks specific guidance concerning certain elements and provides no examples of any high-concentration, liquid antibody formulation. *See* Section IV.A. There is no teaching or direction as to which, if any, of the combinations of ingredients in Salfeld would likely be successful or stable, a particular problem for Petitioner given the strong preference in the art for lyophilized rather than stable liquid antibody formulations. *See* Section III.B. Salfeld thus provides a shaky foundation for the sole ground presented in the Petition

### 1. *Petitioner fails to identify a reference formulation*

Petitioner stumbles at the outset by failing to identify a specific starting point for its obviousness analysis. In the context of a composition or formulation patent, an obviousness analysis should be based on a "reference composition," similar to the lead compound analysis for chemical patents. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361-62 (Fed. Cir. 2011). After identifying a reference composition, a patent challenger must demonstrate a motivation to modify that composition to arrive at the patented invention with a reasonable expectation of success. *See id.* at 1363; *see also Astrazeneca AB v. Apotex Corp.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008). But Petitioner fails to identify, much less analyze, a reference formulation. Without a specific formulation in Salfeld to optimize, a POSA would not even have had a starting point, let alone a rational motivation to modify the reference composition with any expectation of success.

Petitioner does not contend that Salfeld teaches a stable liquid formulation with a high antibody concentration in the ranges claimed in the '100 patent. Nor does it contend that Salfeld provides any examples or data concerning such stable liquid formulations. *Cf.* Pet. at 15, 34. Instead, Petitioner relies on Salfeld's vague and general statement that "[t]herapeutic compositions *typically must be sterile and stable*" as purportedly disclosing stable formulations of D2E7. *Id.* at 34 (citing Ex.

1003 at 21:28-29).[9] But that statement is simply a desired characteristic and says nothing about, for example, making a high-concentration, *liquid* formulation as opposed to a *lyophilized* formulation.

"[K]nowledge of the goal does not render its achievement obvious." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008); *see also Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need."). A POSA would not have understood from Salfeld's statement about a "stable" composition that high-concentration, stable, liquid formulations of D2E7 could be achieved and, if so, what the ingredients of the formulation might be.

As for the argument that "Salfeld's teaching of stability is entitled to a legal presumption that it is correct" (Pet. at 34), Petitioner misconstrues *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). As previously noted in the *Coherus* IPR, "'[u]nder § 103, … a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein.'" *Coherus* IPR, Paper 12 at 6 (quoting *Amgen v. Hoechst*, 314 F.3d at 1357). But Salfeld does

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[9] Petitioner also appears to rely on Salfeld's broad "pharmaceutical composition" claim 29 (Pet. at 14-15, 53-56), but as Petitioner concedes (*id.* at 15, n.21), this claim does not require a stable, liquid aqueous formulation.

not teach or suggest all the elements of the claim, and no presumption can substitute for that missing disclosure.

Because Salfeld discloses no formulation stability data and no exemplary high-concentration D2E7 formulations, Petitioner's assertion that a POSA would have had a reasonable expectation of success with respect to making the claimed D2E7 formulations is unsupported speculation and entitled to no weight. *See* 37 C.F.R. § 42.65(a); *TRW Automotive US LLC v. Magna Elecs, Inc.*, No. IPR2014-00258, Paper 18 at 11 (PTAB Aug. 27, 2014) (recognizing "the Board's well-established discretion to give little weight to conclusory, unsupported expert testimony"). Indeed, "in light of the prior art as a whole," the Board previously held in the *Coherus* IPR that a "generic disclosure" of antibody formulations does not "translate[] to a reasonable expectation of success in formulating a stable, liquid, high-concentration D2E7." *Coherus* IPR, Paper 12 at 6.

#### 2. *Using hindsight, Petitioner improperly cherry-picks elements from Salfeld's broad disclosure*

In keeping with its general approach to the prior art, Petitioner improperly plucks disclosures from Salfeld's many lists of possibilities even though Salfeld provides no direction as to which, if any, should be combined or are likely to be successful. As an example of its improper hindsight approach, Petitioner chooses "liquid solutions" from a list of possible dosage forms, including dispersions,

tablets, liposomes, transdermal patches, and lyophilized powders. Ex. 1003 at 21:13-16, 63; *see also id.* at 21:29-32, 40-45. But a POSA would have been just as likely, indeed more likely, to select from the lists to create a lyophilized formulation or a formulation with a lower concentration because the art taught away from high-concentration, liquid formulations. *See, e.g.*, Section III.B; Ex. 2024 at 545-547; Ex. 2039 at 167; Ex. 2007 at 18. Petitioner likewise selects "subcutaneous" from a lengthy list of possible routes of administration. *Id.* at 21:18-27, 56-57, 60-64.

This approach of selectively choosing elements from multiple lists is symptomatic of Petitioner's impermissible hindsight analysis. Petitioner admitted during prosecution of its own protein formulation patents that such unguided choices among lists of possible formulation components do not render obvious a specific combination of such components. Ex. 2047 at 8; *id.* at 10 (long lists of a "large genus … does not render obvious the species"). The broad disclosures in Salfeld similarly provide no "roadmap," particularly in view of the unpredictability in the antibody formulation art. Salfeld does not indicate a preference for any particular dosage form or route of administration, but rather merely invites experimentation with these and other parameters. Salfeld does not even identify the *goal* of creating a stable, high-concentration, liquid formulation of IgG1 antibodies having D2E7 light and heavy chain variable regions. *See, e.g.*, *Novartis Pharm.*

*Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015) (in discussing impermissible hindsight, "[w]ithout the knowledge of a problem, one of skill in the art would not have been motivated to modify [the prior art]"). It also lacks disclosure of several elements recited in the '100 patent claims. Petitioner's reliance on Salfeld is therefore misplaced and improperly relies on the '100 patent to pick and choose elements from Salfeld with the benefit of hindsight.

#### 3. *Salfeld does not disclose the claimed formulation pH*

Petitioner concedes that Salfeld does not teach formulation pH. Pet. at 28-29. Nonetheless, Petitioner attempts to read a pH teaching into Salfeld, alleging that because excipients should be "physiologically compatible," they must require a pH of between 4.5 and 7. *See id.* at 28. Such allegations by Petitioner are entirely conclusory and should be given no weight.

### C. Salfeld And Van De Putte Do Not Teach D2E7 Concentration, Let Alone The Claimed Stable, High-Concentration, Liquid Formulations Of D2E7

Petitioner concedes that Salfeld does not teach antibody concentration. *See* Pet. at 16. Although Salfeld states that "[t]he composition can be formulated as a solution … suitable to high drug concentration" (Ex. 1003 at 21:29-32), the term "high drug concentration" is neither defined nor explained. The Board has already indicated that it is "not persuaded" that "Salfeld's dose information teaches an antibody concentration range [of 20 to 150 mg/ml]." *Amgen* '514 IPR, Paper 9 at

21; *Amgen* '517 IPR, Paper 9 at 23. The same holds true for the narrower range of 45 to 150 mg/ml (or 45 to 105 mg/ml) claimed in the '100 patent.

Nevertheless, using hindsight, Petitioner attempts to fill the gaps in Salfeld by citing van de Putte. However, even if a POSA would have somehow turned to van de Putte's meager disclosure, a POSA would not have, as Petitioner contends, "know[n] exactly what to do." Pet. at 24. Beyond noting the subcutaneous administration of D2E7, van de Putte is completely silent as to claimed limitations of the '100 patent.

### 1. *Van de Putte does not disclose whether a stable liquid pharmaceutical formulation was used*

Petitioner fails to establish that a POSA would have thought, based on van de Putte's barebones disclosure, that a stable, liquid pharmaceutical formulation had been used. Petitioner also fails to account for the possibility that the formulation used in van de Putte could have been a lyophilized formulation reconstituted prior to injection—that is, not a liquid pharmaceutical formulation at all, much less one stable for storage and use. As the Board previously stated:

> van de Putte does not disclose whether the administered D2E7 formulation was in liquid form or lyophilized form. Nor does van de Putte teach the concentration of antibody in the formulation, the ingredients of the formulation, or whether it was administered as a single-dose or multi-dose delivery. Thus, van de Putte offers no

> guidance as to how a person of ordinary skill in the art would prepare a stable, liquid formulation of 50 mg/ml D2E7.

*Coherus* IPR, Paper 10 at 10.

In fact, a POSA would have expected that the formulation used in van de Putte was more likely a lyophilized formulation based on the prior art's preference for lyophilized forms and the nature of the then-existing commercially available antibody products (*i.e.*, low-concentration, liquid formulations or lyophilized formulations). *See* Sections III.A and III.B. The only approved anti-TNFα antibody on the market at the time, REMICADE, was a lyophilized formulation for intravenous (i.v.) administration and included instructions to begin using it within three hours after reconstitution into liquid form. Ex. 2016 at 1181.

Petitioner also ignores other possibilities. For example, multiple formulation 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 236-237 (creation of multiple batches). Nowhere does van de Putte state that only a single batch was used for the full study, and Petitioner and Dr. Remmele offer no support for their speculation in this regard. Other measures, such as keeping the D2E7 samples frozen until just before use, could also have been employed. Ex. 2045 at 237. These steps would have obviated the need for a stable liquid pharmaceutical formulation. Petitioner bears the burden of proof, and hindsight-based speculations

concerning either a POSA's beliefs about van de Putte's formulation or what a POSA could have "easily ascertained" (Pet. at 21) with a "reasonable assumption" (*id.* at 24) are entirely conclusory, and entitled to little or no weight.

### 2. *Van de Putte does not disclose the concentration of any formulation*

In an approach similar to one that the Board rejected in the *Coherus* IPR, Petitioner makes an elaborate argument as to how a POSA would have allegedly derived from van de Putte the range of concentrations between 45 to 150 mg/ml (or 45 to 105 mg/ml) claimed in the '100 patent. Pet. at 16, 24-25. But as the Board has already held, "van de Putte [does not] teach the concentration of antibody in the formulation, the ingredients of the formulation, or whether it was administered as a single-dose or multi-dose delivery." *Coherus* IPR, Paper 10 at 10. Rather, van de Putte merely discloses the delivery of three doses of 20, 40 and 80 mg. A POSA would have no basis to know the concentrations at which such doses were delivered, or if all doses were delivered at the same concentration.

Petitioner and Dr. Remmele nonetheless labor—over no less than five and twelve pages, respectively—to derive a "range of concentrations" allegedly found in van de Putte. *See* Pet. at 29-33; Ex. 1002 at 26-37. But Petitioner's so-called "reasonable assumptions" concerning the number of injections and injection volumes that may have been used in van de Putte are mere speculation. Pet. at 24-

25. Van de Putte does not disclose any volumes or numbers of injections, and a POSA would have had no way to derive them with any certainty. There is simply no reason other than hindsight for a POSA to believe that van de Putte would have used concentrations in the claimed range, particularly since such high concentrations were unknown in commercial formulations at the time. *See* Section III.A.

For example, if van de Putte had involved multiple injections, the formulation for each injection would require only a fraction of the antibody concentration. *See 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.").[10] Along these lines, a December 2002 publication by Kempeni (Ex. 1035) 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. 1004) was "given every other week s.c. [subcutaneously] for up to 24

[10] Even Dr. Remmele admits that the dose could have been split across four injections (1.6 ml at 12.5 mg/ml), rather than one or two. Ex. 1002 at ¶85. Although he calls four injections "extreme," such dosing has been part of the HUMIRA label for Crohn's disease since 2007. Ex. 2057 at 447 ("dose can be administered as four injections in one day").

weeks" and each "dose of study drug was administered as two s.c. injections of 1.6 mL each." Ex. 1035 at 34. Unlike van de Putte, Kempeni provides sufficient information to determine the antibody concentrations used. Tellingly, the concentrations were 6.25 mg/ml (20 mg total dose), 12.5 mg/ml (40 mg total dose), and 25 mg/ml (80 mg total dose). All are well below the claimed concentrations of 45 to 150 mg/ml (or 45 to 105 mg/ml).

In short, notwithstanding Petitioner's and Dr. Remmele's flawed speculation and calculations, van de Putte does not expressly or implicitly teach a high-concentration formulation.

### D. Salfeld, Remington, And Barrera Do Not Disclose Polyols In The Claimed Compositions Or Concentrations

Petitioner's failure to identify and justify the selection of a specific lead formulation in Salfeld defeats Petitioner's attempt to pluck individual teachings regarding polyols from other references. Salfeld's brief reference to tonicity agents, among many other disclosures, would not have led a POSA to look to either Remington or Barrera as suggesting success with the claimed polyol-containing compositions.

In any event, the combined teachings of the cited references are inadequate. Petitioner concedes that Salfeld does not teach a polyol concentration. *See* Pet. at 16, 25-28. The suggestion that a POSA would turn to Remington's "teaching of

tonicity agents to understand their purpose and how much to use" (Pet. at 25) does not fill this gap because Remington does not disclose the claimed concentration of polyols. Instead, Petitioner attempts to rely on "common amounts" using "routine adjustments" that are "within the range of amounts that could be used" to further fill the gaps. Pet. at 26. This rationale is flawed.

Remington contains only a broad and very general disclosure regarding, among many other things, tonicity in injectable solutions. The solutions of Remington do not even specifically relate to proteins or antibodies, but rather to all injectable solutions. Moreover, Remington's extensive lists of possible components available in the art would have yielded millions of possible combinations. Given the number of possibilities, together with the complete lack of guidance as to which of the many combinations would work for any high concentration antibody formulation (much less D2E7), a POSA equipped with Remington would have effectively been no better off than a POSA without Remington. The mere fact that polyols were known in the art says nothing about their desirability or the motivation to include one in D2E7 formulations.

Attempting to fill the gaps of Salfeld and Remington, Petitioner alleges that a POSA would turn to "Barrera's use of '1.2% mannitol' in its D2E7 formulation and be encouraged that this amount was compatible with D2E7." Pet. at 27. However, Barrera discloses an early clinical trial with a formulation of D2E7

outside the scope of the '100 patent claims because it lacks any surfactant. Barrera is also silent as to pH, as Petitioner concedes. Pet. at 17. Barrera further fails to disclose whether its formulation was stable, or even whether it was a liquid or lyophilized formulation.

On top of all this, the Barrera formulation is administered via i.v. infusion. Petitioner has failed to establish that a POSA would turn to Barrera's i.v. formulation to create a *subcutaneous* formulation. Formulation considerations are different in the two contexts, as Novartis acknowledged during prosecution of its own patent. Ex. 2048 at 6 (distinguishing subcutaneous formulations: "[t]he intravenous formulations … are not suitable for subcutaneous administration because syringe-ability and formulation stability prior to entry into the vasculature are not concerns for intravenous formulations").

Petitioner's reliance on Remington and Barrera, despite all these omissions and uncertainties, once again illustrates that it is working backward from the '100 patent, rather than describing what POSA would have believed in 2002.

### E. Salfeld, Remington, And Lam Do Not Disclose Polysorbate In The Claimed Compositions Or Concentrations

Petitioner concedes that, while Salfeld broadly mentions that surfactants can be used in formulations, it fails to disclose "the surfactant type and concentration." Pet. at 20. Petitioner therefore attempts to rely on Remington as disclosing that

"polysorbate 20 and polysorbate 80 [were] two common polysorbates" and Lam as "confirm[ing] that polysorbate is a leading example of a commonly used surfactant in pharmaceutical formulations." Pet. at 19, *see also id.* at 27. As discussed above, however, Remington's general disclosure, the lack of a lead formulation in Salfeld, and the unpredictability in the art meant that Remington added no meaningful guidance or teaching for the skilled artisan.

Petitioner's reliance on Lam is also unavailing. Lam discloses formulations for only two antibodies (anti-CD18 Fab and anti-CD20 chimeric antibody). Thus, contrary to Petitioner's suggestion (Pet. at 27-28), a POSA would not have been motivated to look to Lam either for a complete D2E7 antibody formulation or individual components like polysorbates. The Board in the *Amgen* IPRs explained:

> We are unpersuaded that the inclusion of TNFα in a laundry-list of untested potential targets in Lam 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 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.

Moreover, the fact that certain surfactants were known says nothing about their desirability or any motivation to include them in D2E7 formulations. Lam does not disclose that surfactants, such as polysorbate, would increase stability in

the case of D2E7. Pet. at 28. Rather, Lam explicitly suggests decreasing concentration to improve stability. *E.g.*, Ex. 1005 at 22:13-17, 42:64-65. And a POSA would have known that surfactants/polysorbates had numerous well-known drawbacks. *E.g.*, Ex. 1022 at 169 (showing that non-ionic surfactants may have the "opposite effect" and cause aggregation); *id.* at 14-15 (noting that even high grade surfactant may cause stability problems); *id.* at 15 ("The use of excipients…(e.g., Tweens)…should be avoided if possible due to the risk associated with transmissible diseases").

Even if a POSA had wished to apply Lam's polysorbate teachings to D2E7, the art taught that surfactant concentrations used for one antibody formulation cannot reliably be applied to a formulation for a different antibody because the requisite concentrations of surfactant "depend on the mechanism(s) by which a particular protein is protected from damage by surfactant addition." Ex. 1022 at 170; Ex. 2021 at 353; Ex. 2049 at 74. This was consistent with a POSA's general understanding that formulations designed for one antibody cannot be applied to other antibodies with a reasonable expectation of success. *See* Section III.C.

The Board has already rejected the argument that claims to high-concentration liquid formulations of D2E7 would be rendered obvious in light of the disclosure of D2E7 and various formulation elements in one reference (Barrera in the *Amgen* IPRs, or here, Salfeld) combined with Lam. *Amgen* '514 IPR, Paper

9 at 18-19; *Amgen* '517 IPR, Paper 9 at 19-20. Petitioner has provided no basis for deviating from that sound determination here.

### F. The Remaining References And Examples Cited By Petitioner Also Fail To Support That A POSA Would Have Had A Reasonable Expectation Of Success In Achieving The Claimed Stable, High-Concentration, Liquid Formulations Of D2E7

Petitioner fails to carry its burden to prove that a POSA would have reasonably expected to achieve a 45 mg/ml or higher concentration liquid formulation as recited in the present claims. In fact, Lam and other cited art *teach away* from such a high concentration liquid formulation. Petitioner's own table of then-existing commercial antibody formulations shows that all commercial *liquid* antibody formulations available at the time had a concentration between 1 and 10 mg/ml, *i.e.*, between *only 1/5 and 1/150 of the claimed concentrations*. *See* Section III.A. There was no suggestion in the art to quintuple (or more) these commercial antibody concentrations to 45 mg/ml in a liquid formulation for a D2E7 antibody. To the contrary, the practice for higher concentrations was to use lyophilized formulations. Petitioner fails in its attempt to overcome this teaching away and does not show that a POSA would have had any reasonable expectation of success in arriving at the claimed stable, high-concentration liquid formulations of D2E7.

### 1. *Petitioner's purported examples of stable, high-concentration antibody formulations do not establish a reasonable expectation of success*

None of the six references cited by Petitioner as allegedly exemplifying stable, high-concentration antibody formulations would have provided a POSA with a reasonable expectation of successfully arriving at the claimed formulations of the '100 patent. Pet. at 35-36. Two of the six cited references—Heavner (Ex. 1012) and Lam (Ex. 1005)—were already fully considered and rejected by the Board in the *Amgen* IPRs. *Amgen* '514 IPR, Paper 9 at 18-23; *Amgen* '517 IPR, Paper 9 at 19-25.

Heavner generally relates to a different TNFα antibody that is separate and distinct from D2E7. *See, e.g.*, Ex. 1012 at claim 1. Like Salfeld, Heavner includes bulk recitations of potential formulation ingredients and covers virtually every imaginable route of administration, concentration, excipient, and the like. *See id.* at 42:59-48:4. The Board previously noted that Heavner offers no guidance on how to actually select from this massive number of possible combinations to prepare any antibody—much less a D2E7 antibody—as a stable liquid formulation. *Amgen* '514 IPR, Paper 9 at 23 ("[T]he lack of teachings regarding specific pharmaceutical formulations in Heavner would have left one of ordinary skill in the art 'with an utter lack of guidance as to which of the many combinations would work.'"); *Amgen* '517 IPR, Paper 9 at 24 (same).

Lam includes an example of a different antibody formulated at 40 mg/ml, but it expressly advises avoiding potential aggregation problems by *reducing* protein concentration. *See, e.g.*, Ex. 1005 at 22:13-17, 42:64-65. Petitioner's attempt to downplay this teaching (Pet. at 42) merely repeats its flawed effort to dilute the Board's claim construction. *See* Section II.B.

Andya (Ex. 1020) and two other references cited by Petitioner (Exs. 1017 & 1018) are inapposite because they disclose only *lyophilized* formulations. Novartis has previously stressed that directing claims "to liquid formulations" is "*an extremely important distinction from lyophilized formulations*, which do not suffer the same stability issues as high-concentration liquid antibody formulations and which are considered easier to prepare." Ex. 2038 at 9-10. Novartis therefore stressed that "teachings related to … lyophilized formulations … are *not relevant to the analysis of the currently claimed liquid formulations*." Ex. 2038 at 9-10. The three lyophilized formulations cited by Petitioner (Exs. 1017, 1018 & 1020) are likewise irrelevant to the high concentration liquid antibody formulations claimed in the '100 patent. *See also Amgen* '514 IPR, Paper 9 at 14-15; *Amgen* '517 IPR, Paper 9 at 15-16.

In fact, Novartis cited both Lam and Andya as demonstrating the "*art-understood unpredictability*" in preparing *liquid* antibody formulations in 2008—*six years after* the priority date of the '100 patent. Ex. 2037 at 11. Novartis cited

both again later in prosecution to show that "each antibody must be formulated on a case-by-case basis" and that "there were not a finite number of solutions, the solutions were not predictable, and success was not anticipated." Ex. 2038 at 7; *see also id*. at 8.

The final reference cited by Petitioner (Ex. 1014) relates to IL-12 antibodies. Similar to Salfeld and Heavner, this reference generally discloses that IL-12 antibody formulations may be made, but it does not provide a working example of any formulation or provide any guidance to produce a stable, high-concentration antibody formulation. More importantly, even if there had been such a disclosure for IL-12 antibodies (and there was not), it would provide no reasonable expectation of success to a POSA looking to formulate D2E7 because it was well known that a formulation developed for one antibody could not reasonably be expected to result in a stable, high-concentration, liquid formulation when transferred to another antibody. *See* Section III.C.

In sum, none of the references cited by Petitioner, either alone or in combination, would have provided a POSA with a reasonable expectation of successfully arriving at the stable, high-concentration, liquid antibody formulations of the '100 patent.

### 2. *Petitioner fails to explain away the lack of commercial, high-concentration, liquid antibody formulations for subcutaneous administration*

Prior to AbbVie's invention of the formulations claimed in the '100 patent, only two types of antibody formulations were commercially available: (i) low concentration liquid formulations, and (ii) lyophilized formulations. *See* Section III.A. Attempting to explain away this compelling evidence of non-obviousness, Petitioner asserts that there was "little reason for a drug manufacturer to develop a high concentration subcutaneously injectable formulation for patients who will undergo a short course of treatment under the direct supervision of medical professionals at the time of drug administration." Pet. at 42-48. This statement lacks support and is contradicted by subsequent developments in the field.

In fact, the same intravenous injectable antibodies cited by Petitioner as only useful for short course treatment under physician supervision were subsequently developed or tested as subcutaneous therapies, although in some instances the concentration was still kept low. These include RITUXAN (Ex. 2051 at 329 ("If subcutaneous administration is safe and effective, it could be more convenient for patients than intravenous treatment and would make fractionated dosing over prolonged periods possible.")); HERCEPTIN 600 mg solution for injection in vial (Ex. 2050 at IPR4 (describing "administer[ing] subcutaneously over 2-5 minutes every three weeks."); and CAMPATH (Ex. 2055 at 772 (tests of low concentration

subcutaneous formulation showed that "[a]cute administration-related events … appeared to be rare or absent"). Even after reformulation, these medications still required monitoring pre- or post-dosing, belying Petitioner's suggestion that under such circumstances, subcutaneous formulation would be useless. *See, e.g.*, Ex. 2053 at IPR3-4; Ex. 2050 at IPR1-2; Ex. 2052 at 3-5; *cf.* Pet. at 42-48.

Accordingly, the most reasonable conclusion is that such formulations did not exist in the prior art because they were difficult to achieve, not because they lacked clinical utility. Dr. Remmele admitted as recently as 2015—*thirteen years after* the priority date of the '100 patent—that high concentration liquid antibody formulations for subcutaneous injection *still* posed "significant challenges." Ex. 1064 at 44. It was only well after HUMIRA paved the way that such formulations became more common

Similar unsupported speculation underlies Petitioner's assertion that "[o]nce a determination is made that a drug should be administered intravenously, there is no need to develop a high concentration formulation" because the same "volume constraints" do not exist. Pet. at 48. Centocor-supported researchers published a subcutaneously administered infliximab (REMICADE) formulation well after HUMIRA and the '100 patent priority date. Ex. 2054 at 847-849. Tellingly, they used a lyophilized rather than a stable liquid formulation. *See* Ex. 1064 at 46 ("If stabilization as a liquid appears technically unfeasible, a lyophilized formulation is

developed."). Petitioner's additional argument that infliximab doses were too high to allow subcutaneous administration (Pet. at 48) can be discounted as it is grounded in contradictory testimony from Dr. Remmele. He opines that achieving a therapeutic amount of infliximab would require fourteen separate injections delivered in a 1.0 ml volume at 50 mg/ml concentration, but earlier in his declaration he admitted that a 1.6 ml volume was reasonable and identified 150 mg/ml as the expected limit on antibody concentration. *See, e.g.*, Ex. 1002 at 37 n.11 & ¶ 76; Pet. at 48. Using Dr. Remmele's own more generous assumptions, the necessary amounts of REMICADE could be delivered in only one to three injections—not fourteen—and well within the "up to 4" injections considered by Petitioner and Dr. Remmele to be an acceptable number of subcutaneous injections per dose. Pet. at 33; Ex. 1002 at ¶85.

In sum, the absence of *any* commercially available high concentration liquid antibody formulations in 2002 reflects the understanding at the time that such formulations were unpredictable and difficult to prepare. Petitioner's arguments to the contrary are not plausible.

## VII. Conclusion

The Board should deny institution of the Petition because the asserted grounds rely on recycled arguments and references, and are duplicative of prior petitions, driven by hindsight, and contradicted by contemporaneous publications

and Dr. Remmele's prior writings. The Petition fails to show that any challenged claim is obvious, including failing to prove motivation to combine references and reasonable expectation of success in doing so.

Dated: November 13, 2017

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 12,778 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).

Dated: November 13, 2017

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**CERTIFICATE OF SERVICE**

I hereby certify that on this 13th day of November 2017, true and correct copies of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE AND EXHIBITS THERETO were served by electronic mail upon the following counsel of record for Petitioner Sandoz Inc.:

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