UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SWISS PHARMA INTERNATIONAL AG,

Petitioners

v.

Patent Owner of
U.S. Patent No. 8,900,577 to Burke et al.
Appl. No. 13/605,590 filed Sept. 6, 2012
Issued Dec. 2, 2014

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IPR Trial No. TBD

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**PETITION FOR *INTER PARTES***
**REVIEW OF U.S. PATENT NO. 8,900,577**
**PURSUANT TO 35 U.S.C. § 312 AND 37 C.F.R. § 42.108**

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| Ex. 1014 | B. W. van Oosten, et al., Increased MRI Activity and Immune Activation in Two Multiple Sclerosis Patients Treated with the Monoclonal Anti-Tumor Necrosis Factor Antibody cA2, 47 Neurology 1531 (1996) | van Oosten |
| Ex. 1015 | Bruce E. Sands, et al., Infliximab in the Treatment of Severe, Steroid-Refractory Ulcerative Colitis: A Pilot Study, 7 Inflammatory Bowel Diseases 83 (2001) | Sands |
| Ex. 1016 | BLA 98-0012, Correspondence with FDA re Pharmacology Review of the infliximab BLA, dated 5/21/1998 | BLA Correspondence |
| Ex. 1017 | Fiona H. Gordon, et al., A Randomized Placebo-Controlled Trial of a Humanized Monoclonal Antibody to α4 Integrin in Active Crohn's Disease, 121 Gastroenterology 268 (2001) | Gordon |
| Ex. 1018 | U.S. Patent No. 5,840,299 to Bendig, issued 11/24/1998 | Bendig |
| Ex. 1019 | L.A. Sorbera, et al., Natalizumab Treatment of IBD Treatment of Multiple Sclerosis, 25 Drugs of the Future 917 (2000) | Sorbera |
| Ex. 1020 | John Stephen White, et al., Proteins, Peptides and Amino Acids: SourceBook 108-112 (2002) | White |
| Ex. 1021 | Larry M. Cummins, et al., Preparation and Characterization of an Intravenous Solution of IgG From Human Immunodeficiency Virus-Seropositive Donors, 77 Blood 1111 (1991) | Cummins |
| Ex. 1022 | Orthoclone®, in Physicians' Desk Reference 1837 (50th ed. 1996) | Orthoclone |

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| Ex. 1023 | Thomas Aversano, et al., A Chimeric IgG4 Monoclonal Antibody Directed Against CD18 Reduces Infarct Size in a Primate Model of Myocardial Ischemia and Reperfusion, 25(3) JACC 781 (1995) | Aversano |
| Ex. 1024 | Zenapax®, in Physicians' Desk Reference 2696 (54th ed. 2000) | Zenapax |
| Ex. 1025 | Jenny Bell & Jean Colaneri, Zenapax: Transplant's First Humanized Monoclonal Antibody, 25(4) ANNA Journal 429 (1998) | Bell |
| Ex. 1026 | Malathy Subramanian et al., Effect of Histidine Oxidation on the Loss of Potency of a Humanized Monoclonal Antibody, in AAPS Pharmsci S-29 (Oct. 2001) | Subramanian |
| Ex. 1027 | Xylocaine®, in Physicians' Desk Reference 638 (54th ed. 2000) | Xylocaine |
| Ex. 1028 | Naropin®, in Physicians' Desk Reference 609 (54th ed. 2000) | Naropin |
| Ex. 1029 | Pharmaceutical Formulation Development of Peptides and Proteins 146-47, 150-52, 160-65, 171(Sven Frokjaer and Lars Hovgaard eds., Taylor & Francis Ltd. 2000) | Frokjaer |
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| Ex. 1031 | Protein Formulation and Delivery Preface, 139-158 (Eugene J. McNally ed., Marcel Dekker, Inc. 2000) | McNally |
| Ex. 1032 | Remington: The Science and Practice of Pharmacy 250-51, 819, 1265 (2000) | Remington |

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| Ex. 1033 | Alfred Martin, et al., Physical Pharmacy 222-39, 391-92 (1983) | Martin |
| Ex. 1034 | Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists 8-32 (Kenneth A. Connors, et al., eds., 1986) | Connors |
| Ex. 1035 | Fundamental Immunology 47-57 (William E. Paul ed., Lippincott-Raven, 4th edition, 1999) | Paul |
| Ex. 1036 | Cellular and Molecular Immunology (Abul K. Abbas et al. W.B. Saunders Co., 3rd edition, 1997) | Abbas |
| Ex. 1037 | F. Mikulandra, The Effect of High Birth Weight (4000 g or More) on the Weight and Height of Adult Men and Women, 24 Coll. Antropol. 133-136 (2000) | Mikulandra |
| Ex. 1038 | Confidential Report, J. Deistung, P. Challis & R. Pardon, Preformulation Study on the Humanised Monoclonal Antibody (Sept. 1994) (on file with European Patent Office) | Preformulation Study |
| Ex. 1039 | Confidential Report, J. Deistung, P. Challis & R. Pardon, Preformulation Study on the Humanised Monoclonal Antibody (Sept. 1994) (from prosecution history of U.S. Patent No. 8,900,577) | '557 Preformulation Study |
| Ex. 1040 | Minutes of Oral Proceedings of May 21, 2010, by Examining Division, European Patent Office, with Andrea Schüssler, Representative for Applicants (June 7, 2010) (on file with European Patent Office) | EPO minutes |
| Ex. 1041 | Response to the Noting of loss of rights pursuant Rule 112(1) EPC dated November 24, 2015, in the prosecution of European Patent Application 10 005 235.6 – 1405, dated February 3, 2016. | EPO Response |

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| Ex. 1042 | Claims as filed for Appl. No. 12/572,978 dated 10/2/2009 | Original Claims |
| Ex. 1043 | Non-Final Rejection after for Appl. No. 13/605,590 dated 10/18/2012 | '590 Rejection |
| Ex. 1044 | U.S. Patent No. 6,914,128 to Salfeld, issued 7/5/2005 | Salfeld |
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| Ex. 1047 | Cleland et al., 10 Critical Reviews in Therapeutic Drug Carrier Systems, 307-377 (2000) | Cleland |
| Ex. 1048 | Notice of Allowance for Appl. No. 13/605,590 dated 7/28/2014 | '590 Allowance |
| Ex. 1049 | U.S. Patent Pub. No. US2015/0030590, published January 29, 2015 | Panzara |

Pursuant to 35 U.S.C. § 311 et seq. and 37 C.F.R. § 42.1 et seq., Swiss Pharma International AG ("Petitioner") hereby submits this petition for *inter partes* review ("Petition") of U.S. Patent No. 8,900,577 ("the '577 patent") (Ex. 1001). Petitioner respectfully submits that claims 1, 3-7 and 9-12 (the "Challenged Claims") of the '577 patent are unpatentable under 35 U.S.C. § 103 in view of the prior art discussed herein.

## I. INTRODUCTION

The Challenged Claims cover an old therapeutically active agent paired with a standard well-known formulation repeatedly and successfully used with numerous other therapeutically active agents from the same class of compounds. The therapeutically active agent is natalizumab, discovered years before the earliest effective filing date for the '577 patent. Natalizumab is a monoclonal antibody ("mAb") belonging to the immunoglobulin G ("IgG") class of compounds. The formulation recited by the Challenged Claims is also old. Numerous prior art IgG mAb formulations, including multiple FDA-approved prior art formulations, contain the exact same combination of three excipients recited by the Challenged Claims – (1) phosphate buffer, (2) NaCl and (3) polysorbate 80. Given the repeated success of this formulation with other IgG mAb actives, the rationale for its combination with natalizumab is strong. Further, protein formulators skilled in the art looked to this formulation with these other

IgG mAb actives because they reasonably expected it to work. Consequently, its combination with natalizumab in the Challenged Claims is obvious.

The remaining limitations, such as concentrations or the pH of the formulation, are either necessarily satisfied or recite nothing more than result effective variables subject to routine optimization. It is, of course, well-settled that differences in concentration and pH do not support patentability in the absence of some evidence of criticality or unexpected results. But nothing critical or unexpected is present here.

Indeed, the allegedly unexpected results Applicants relied upon during prosecution of the '577 patent to gain allowance arose from a "Preformulation Study" that Applicants themselves publicly admitted is inaccurate, non-reproducible and unsupportive of the conclusion of unexpected results. Specifically, on July 6, 2010, a few years before presenting the Preformulation Study during prosecution of the '577 patent, Applicants' representative admitted to the European Patent Office (EPO) that the study was "based on preliminary data which was not accurate . . . [and] could not be reproduced." (Ex. 1040 at 1.) Yet, Applicants never told the Examiner about this problem, and in fact relied on the Preformulation Study as a primary basis for overcoming the Examiner's repeated obviousness rejections. Unexpected results do not rescue the '577 patent here.

Thus, there is a reasonable likelihood that at least one, if not all, of the Challenged Claims of the '577 patent are obvious. Petitioners respectfully request that the Board institute an *inter partes* review of the '577 patent pursuant to 35 U.S.C. § 314 and 37 C.F.R. § 42.108.

## II. MANDATORY NOTICES (37 C.F.R. § 42.8)

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

Petitioner certifies that Swiss Pharma International AG is a real party-in-interest. Petitioner is a subsidiary that is owned by Medana Pharma SA, Polfa Warsaw SA (also known and registered as Warszawskie Zakłady Farmaceutyczne Polfa S.A.) and Pharmaceutical Works Polpharma SA (also known and registered as Zakłady Farmaceutyczne Polpharma SA). Polfa Warsaw SA and Medana Pharma SA are in turn owned by Zakłady Farmaceutyczne Polpharma SA (also known as Pharmaceutical Works Polpharma SA).

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

Petitioner is concurrently filing two additional petitions for *inter partes* review that will address certain claims of U.S. Patent Nos. 8,349,321 ("the '321 patent") and 8,815,236 ("the '236 patent"). The '321 and '236 patents are related to each other and to the '577 patent as continuations or divisionals.

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

Petitioner designates the following as lead and back-up counsel, all with Axinn, Veltrop & Harkrider LLP:

| Lead Counsel | Back-up Counsel |
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A power of attorney is submitted herewith pursuant to 37 C.F.R. § 42.10(b).

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

Service of any documents via hand-delivery may be made at the postal mailing addresses of lead and back-up counsel identified above with courtesy copies to the respective email addresses stated above. Petitioners consent to electronic service at these same email addresses.

## III. FEE PAYMENT AUTHORIZATION (37 C.F.R. § 42.103)

In accordance with 37 C.F.R. § 42.103(a), Petitioner authorizes the Patent Office to charge Deposit Account No. 013050 for the fees set forth in 37 C.F.R. § 42.15(a). If payment of additional fees is due during this proceeding, the Patent

Office is authorized to charge such fees to Deposit Account No. 013050, and credit any overpayment to the same account.

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

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '577 patent is available for *inter partes* review and that Petitioner is neither barred nor estopped from requesting *inter partes* review.

## V. IDENTIFICATION OF CHALLENGE AND GROUNDS (37 C.F.R. § 42.104(b))

Pursuant to 37 C.F.R. §§ 42.22(a)(1) and 42.104(b)(1)-(2), Petitioner respectfully requests *inter partes* review and cancellation of Challenged Claims 1, 3-7, 9-12. The Challenged Claims recite:

> 1. A stable, aqueous pharmaceutical formulation comprising from about 20 mg/ml to about 150 mg/ml of natalizumab, polysorbate 80 present in an amount of about 0.001% to 2% (w/v), about 10 mM phosphate buffer, and about 140 mM NaCl.
>
> 3. The formulation of claim 1, wherein the formulation is isotonic.
>
> 4. The formulation of claim 1, wherein the formulation is stable at a temperature of 2° C. to 8° C. for at least 6 months.
>
> 5. The formulation of claim 1, wherein the formulation has a pH of 3.0 to 7.0.
>
> 6. The formulation of claim 4, wherein the formulation has a pH of 5.5 to 6.5.
>
> 7. An article of manufacture comprising a container holding the stable, aqueous pharmaceutical formulation of claim 1.

9. An article of manufacture comprising a container holding the stable, aqueous pharmaceutical formulation of claim 3.

10. An article of manufacture comprising a container holding the stable, aqueous pharmaceutical formulation of claim 4.

11. An article of manufacture comprising a container holding the stable, aqueous pharmaceutical formulation of claim 5.

12. An article of manufacture comprising a container holding the stable, aqueous pharmaceutical formulation of claim 6.

(Ex. 1001 at 18:40-19:6)

### A. Effective Filing Date of the '577 Patent

The '577 patent was filed as Appl. No. 13/605,590 ("the '590 application") on September 6, 2012. It is a continuation of Appl. No. 12/572,978 ("the '978 application") filed on October 2, 2009, which issued as the '321 patent on January 8, 2013. The '978 application is a continuation of Appl. No. 10/773,406, filed on February 9, 2004, which in turn claims priority to provisional Appl. No. 60/445,818, filed on February 10, 2003. For purposes of this petition only, Petitioner has assumed that the earliest effective filing date of the Challenged Claims is February 10, 2003. Petitioners do not otherwise concede same for other purposes.

### B. Prior Art and Statutory Grounds for the Challenge (37 C.F.R. § 42.104(b))

The scope and content of the prior art is described in Section VII.A, and the two proposed grounds of invalidity are described in Sections VII.B and VII.C. The Declarations of Dr. Christian Schöneich (Ex. 1002) and Dr. Staley Brod (Ex. 1011) support each of these grounds. As more fully set forth in their declarations, Dr. Schöneich is an expert in protein formulation (Ex. 1002 at ¶¶ 5-10, 85) and Dr. Brod is a medical expert (Ex. 1011 at ¶¶ 5-14). Each is qualified to provide opinions as to what a person of ordinary skill in the art would have understood, known or concluded as of February 10, 2003.

Petitioner respectfully requests institution on each of the Challenged Claims based on two independent Grounds:

- **Ground 1** – Obviousness over either van Oosten (Ex. 1014) or Zenapax (Ex. 1024) in view of Sorbera (Ex. 1019); and
- **Ground 2** – Obviousness over Gordon (Ex. 1017) in view of either Orthoclone (Ex. 1022) or Aversano (Ex. 1023).

## VI. SUMMARY OF THE '577 PATENT AND PROSECUTION HISTORY

The '577 patent, like its parent, the '321 patent, relates to aqueous formulations comprising various therapeutically active proteins, especially antibodies and immunoglobulins. According to the '577 patent specification, "the invention provides for a stable, aqueous pharmaceutical formulation comprising an

immunoglobulin (or other protein), a phosphate buffer, a polysorbate and sodium chloride." (Ex. 1001 at 1:59-62.) The '577 patent uses the terms "sodium chloride" and "NaCl," the chemical formula for sodium chloride interchangeably. (Ex. 1002 at ¶ 21.) The '577 patent states that virtually all proteins are interchangeable in this formulation, stating that "[a]lthough discussion of the formulation is provided mainly in reference to an antibody or immunoglobulin, other proteins are contemplated as interchangeable in the formulations disclosed." (Ex. 1001 at 2:64-67.)

Although the originally-filed independent claims of the '577 patent specifically recited natalizumab, as a continuation of the '321 patent, its original independent claims trace back to the application leading to the '321 patent, all of which broadly recited protein or immunoglobulin formulations without restriction. (Ex. 1042 at 1, 4 and 5 (claims 1, 29 and 33).) The '577 patent thus never removed the '321 patent teaching concerning interchangeability of proteins and antibodies in the claimed formulations.

In the first substantive Office Action of the application leading to the '577 patent, the Examiner rejected the claims as being unpatentable over U.S. Pat. No. 6,914,128 ("Salfeld") (Ex. 1044) in view of Gordon (Ex. 1017). (Ex. 1043 at 4.) The Examiner explained that Salfeld discloses an aqueous pharmaceutical

formulation as claimed, and that although "[Salfeld] . . . does not particularly teach natalizumab," Gordon cures the deficiency. (Id. at 4-5).

In response, and notwithstanding the statements in the specification concerning interchangeability and their original decision to broadly claim formulations comprising any and all proteins and immunoglobulins in the parent '978 application, Applicants nevertheless argued that "one of skill in the art would appreciate that antibodies are not readily interchangeable in formulations. . . ." (Ex. 1045 at 5 (citing Ex. 1046; Ex. 1047).) Although unreported in the prior art, Applicants also argued that subsequent work (presumably its own work) on the Gordon formulation revealed it was unstable. (Id. at 7-8.)

Applicants also relied heavily on the aforementioned "Preformulation Study" (Ex. 1038),[1] as evidence that the "inclusion of . . . sodium chloride or . . . Tween [polysorbate] 80 had the effect of *accelerating the degradation process* . . ." concluding that phosphate buffer, polysorbate 80 and sodium chloride represented an "unlikely combination of excipients." (Ex. 1045 at 9-10, emphasis in original.) As explained in Section VII.F, starting at page 57, Applicants publicly

[1]During prosecution of EP Appln. No. 04709508.8 ("EP '508"), Applicants submitted to the EPO Ex.1038, the same document as the "Preformulation Study" (Ex. 1039) referenced by Applicants during the prosecution of the application leading to the '557 patent. (Ex. 1002 at ¶ 166.)

admitted the Preformulation Study "was not accurate . . . [and] could not be reproduced," but never made or disclosed that admission to the Examiner. (Ex. 1040 at 1.)

The Examiner did not provide reasons for allowance relating to its prior obviousness rejection, although Applicants' heavy reliance on the Preformulation Study just prior to withdrawal of the Examiner's obviousness rejection demonstrate that the study played a significant role. (Ex. 1045 at 8-10.)

### A. Level of Ordinary Skill in the Art

A person of ordinary skill in the art of the '577 patent would have held a Ph.D. or other post-graduate training in protein chemistry or a related field with at least a few years of practical industrial or academic experience preparing protein formulations. (Ex. 1002 at ¶ 83.) The experience includes practical familiarity with assays for assessing protein stability and solubility so as to optimize a protein formulation based on the results. One of ordinary skill could also confer with medical doctors who have at least three years of knowledge or experience in treating patients with Crohn's Disease or other disease states treatable with IgG mAbs. (Id. at ¶ 83.)

### B. Claim Construction (37 C.F.R. § 42.104(b)(3))

A patent claim term in *inter partes* review is to be given the "broadest reasonable construction in light of the specification" as commonly understood by

those of ordinary skill in the art. 37 C.F.R. § 42.100(b); see also In re Cuozzo Speed Techs., LLC, 793 F.3d 1268, 1275 (Fed. Cir. 2015), cert. granted 84 U.S.L.W. 3218 (U.S. Jan. 15, 2016) (No. 15-446). Consistent with this standard, and without conceding that these terms should be construed the same way in a district court proceeding, Petitioner provides proposed constructions of certain of the claim terms as set forth below for purposes of this Petition only.

**1. "Stable"**

The '577 patent expressly defines this term by stating that "[a] 'stable' formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. By 'stable' is also meant a formulation which exhibits little or no signs of instability, including aggregation and/or deamidation." (Ex. 1001 at 5:55-60.) Although this passage offers alternate definitions, the broadest reasonable interpretation of "stable" merely requires that the formulation retains any one of physical, chemical or biological stability upon storage. (Ex. 1002 at ¶ 26.)

**2. "Phosphate buffer"**

The '577 patent does not expressly define "phosphate buffer," but does expressly define "buffer" to mean "a buffered solution that resists changes in pH by the action of its acid-base conjugate components." (Id. at 6:39-41.) Accordingly, the broadest reasonable construction of "phosphate buffer" is "a

buffered solution comprising one or more phosphate salts that resists changes in pH by the action of its acid-base conjugate components." (Ex. 1002 at ¶ 28.)

### 3. "Isotonic"

The '577 patent expressly defines the claim term "isotonic" to mean "that the formulation of interest has essentially the same osmotic pressure as human blood." (Id. at 6:33-34.) The '577 patent further states that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm," which may be measured using an "ice-freezing type osmometer." (Id. at 6:33-38.)

### 4. "Container"

The '577 patent does not expressly define "container," but makes clear that a container is any article that holds the formulation, citing "an intravenous solution bag" and a "vial" as examples. (Id. at 5:48-52.)

## VII. DETAILED EXPLANATION (37 C.F.R. § 42.104(b)(4)-(5))

As mentioned, this case is about a known therapeutically active agent provided in a known formulation. At the time of the earliest effective filing date of the '577 patent, the IgG mAb natalizumab and its indications, including treatment of CD, were known. And the three excipients recited in the Challenged Claims – phosphate buffer, NaCl and polysorbate 80 – were also known.

For example, prior art by von Oosten (Ex. 1014) teaches an aqueous formulation containing these very same excipients with an IgG mAb that, like natalizumab, was known to treat CD. Furthermore, Gordon teaches a natalizumab formulation containing a buffer and polysorbate 80 which later undergoes dilution with saline thus adding NaCl. (Ex. 1017 at 7.) The buffer used in that formulation served the same buffering function as phosphate buffer.

For the foregoing reasons, and as discussed in more detail below, the scope and content of the prior art points directly to the claimed subject matter of the '577 patent.

### A. Scope and Content of the Prior Art

The Declarations of Scott Bennett (Ex. 1005) and Rachel J. Watters (Ex. 1008) establish the prior art status of all printed publications identified in this section of the Petition. Unless otherwise indicated, all such publications were publicly available prior to February 10, 2002 – one year before the earliest possible effective filing date of the '577 patent – qualifying them as prior art under 35 U.S.C. 102(b). Furthermore, with the exception of Gordon (Ex. 1017) and Bendig (Ex. 1018), none of the prior art relied upon here appears in the references cited section of the '577 patent.

### 1. The IgG mAb Natalizumab

Natalizumab was known at least as early as November 24, 1998. (Ex. 1018 at Figs. 6 and 7; Ex. 1049 at ¶ 0051 (stating Natalizumab was described in Ex. 1018); see also Ex. 1002 at ¶ 66.) The prior art classified natalizumab as a humanized IgG mAb. (Ex. 1018 at 2:44-48; Ex. 1017 at 6; Ex. 1019 at 2.) As Dr. Schöneich explains, a person of ordinary skill would have known that all IgG mAbs, including natalizumab, share key structural characteristics that impact their general compatibility with the excipients used in aqueous formulations. (Ex. 1002 at ¶ 34 and discussed further at p. 39, below.) The prior art, specifically Sorbera, also confirms the efficacy (at least 3 mg/kg) and safety (up to 6 mg/kg) of natalizumab for the treatment of CD. (Ex. 1019 at 3-4.)

### 2. Prior Art IgG Formulations

The prior art is replete with IgG and IgG mAb formulations having the same excipients as those in the Challenged Claims at the same or similar concentrations.

#### a. Prior Art IgG Formulations Comprising Phosphate Buffer and NaCl

Commercial protein manufacturers routinely stored and shipped IgG antibodies in formulations containing phosphate buffered saline, often abbreviated as PBS. (Ex. 1020 at 14 (USBio I19903-31 using "PBS"), 16 (Sigma F7381 using "phosphate buffered saline"); publicly available as of April 2002 (Ex. 1005 at 54).) A person of ordinary skill recognizes that PBS contains phosphate buffer and

saline, which is an aqueous solution containing sodium chloride. (Ex. 1002 at ¶ 37.) White discloses numerous such formulations, many of which employed the same or similar concentrations recited by the Challenged Claims. For example, White discloses 20 mg/ml IgG formulations that use 10 mM phosphate buffered saline. (Ex. 1020 at 16 (Sigma F 7381, F 9636 and F 7256).) These excipients help ensure the long-range stability of the IgG active drug substances. (Ex. 1002 at ¶ 36.) For example, Cummins reports 12 month stability (0° to 8°C storage) of a 5% (50 mg/ml) IgG solution in normal saline, disclosing "no changes detected in pH, [or] percentage of monomeric IgG." (Ex. 1021 at 6, 8; Ex. 1002 at ¶ 79.) Similarly, White discloses several IgG formulations comprising 20 mg/ml concentration of IgG in 5 mM or 10 mM PBS. (Ex. 1020 at 14 (USBio I1903-31) and 16 (Sigma F 7381, F 9636 and F 7256).)

**b. Prior Art IgG mAb Formulations Containing Sodium Phosphate, NaCl and Polysorbate 80**

Because IgG mAb actives may aggregate, and thereby compromise stability, it was also well-known in the art to include a surfactant with such formulations. (Ex. 1002 at ¶¶ 59-60 (discussing Ex. 1029 at 18).) As Dr. Schöneich explains, typical prior art IgG mAb formulations include a buffer to maintain a specific pH over time, NaCl to provide tonicity and a surfactant to disperse the IgG mAb and

thereby prevent aggregation. (Ex. 1002 at ¶¶ 41, 49-50, 59-60 (discussing Ex. 1029 at 12-13, 15-20; Ex. 1031 at 13-15; Ex. 1032 at 6, 9; Ex. 1033 at 8).)

At least four prior art IgG mAb formulations employ phosphate buffer, NaCl and the surfactant polysorbate 80, as recited by the Challenged Claims. Furthermore, these prior art formulations employ these excipients at nearly the same concentrations as the Challenged Claims:

**Table 1: Prior Art IgG mAb Formulations**[2]

| Ingredient | Claim | Orthoclone | Aversano | van Oosten | Zenapax |
|---|---|---|---|---|---|
| IgG mAb | ~ 20 to ~ 150 mg/ml | 1 mg/ml | 5 mg/ml | 10 mg/ml | 5 mg/ml |
| Polysorbate 80 | 0.001% to 2% (w/v) | 0.02% | 0.01% | 0.01% | 0.02% |
| Phosphate Buffer | ~ 10 mM | 16.4 mM | 10 mM | 10 mM | 67 mM |
| NaCl | ~ 140 mM | 147 mM | 150 mM | 150 mM | 78.7 mM |
| pH | 5.5 to 6.5 | 7.0 ±0.5 | 6.5 | 7.2 | 6.9 |

[2] Dr. Schöneich provides routine conversions of units of measurement to compare reported values in the prior art to the claims. (Ex. 1002 at ¶¶ 65-79.)

***Orthoclone (Ex. 1022)***

Orthoclone, approved by FDA in 1992, is a formulation comprising the IgG mAb muromonab-CD3. (Ex. 1022 at 3; Ex. 1030 at 1.) The formulation contains 1 mg/ml muromonab-CD3, 0.45 mg/ml monobasic sodium phosphate and 1.8 mg/ml of dibasic sodium phosphate – equivalent to 16.4 mM phosphate buffer (see Ex. 1002 at ¶ 71; see also p. 11, above for construction of phosphate buffer), 147 mM NaCl and 0.02% polysorbate 80 in water for injection. (Ex. 1022 at 3.) The formulation has a pH of 7.0 ±0.5 and is supplied in ampules. (Id.) The formulation is stored at 2º C to 8º C. (Id. at 7.) Because Orthoclone was FDA approved, it retained its biological activity, i.e., was stable, at least long enough to be shipped from the manufacturer to the site of use. According to Remington, Orthoclone had a shelf-life of one year. (Ex. 1032 at 8.)

***Aversano (Ex. 1023)***

Aversano, published in 1995, discloses a formulation comprising the IgG mAb designated CLB54. (Ex. 1023 at 4, 5.) The formulation contains 5 mg/ml CLB54, 10 mM phosphate buffer, 150 mM NaCl and 0.01% polysorbate 80. (Ex. 1023 at 5; Ex. 1002 at ¶ 72.) The formulation has a pH of 6.5 and is supplied in vials. (Ex. 1023 at 5.)

***van Oosten (Ex. 1014)***

van Oosten, published in 1996, discloses a formulation containing the IgG mAb infliximab. (Ex. 1014 at 5 ("[e]ach vial contained . . . 10 mg/ml cA2.")); Ex. 1015 at 4 (disclosing that cA2 is also known as "infliximab").) Like natalizumab, infliximab was known to treat Crohn's Disease ("CD"). (Ex. 1014 at 4.) The formulation contains 10 mg/ml infliximab, 10 mM phosphate buffer, 150 mM NaCl and 0.01% (0.1 mg/ml) polysorbate 80. (Ex. 1002 at ¶ 73.) The formulation has a pH of 7.2. (Ex. 1014 at 5.)

***Zenapax (Ex. 1024)***

Zenapax, approved by FDA in 1997, is a formulation comprising the IgG mAb daclizumab. (Ex. 1024 at 2; Ex. 1030 at 3.) The formulation contains 5 mg/ml daclizumab, 3.6 mg sodium phosphate monobasic monohydrate and 11 mg sodium phosphate dibasic heptahydrate – equivalent of 67 mM of phosphate buffer (see Ex. 1002 at ¶ 74), 78.7 mM NaCl and 0.02% polysorbate 80. The formulation has a pH of 6.9. (Ex. 1024 at 2.) According to another prior art reference by Bell, the "[s]helf life of Zenapax is 1 year" and "[v]ials should be stored between 36° – 46° F" (equivalent to 2º C to 8º C). (Ex. 1025 at 4; Ex. 1002 at ¶ 75.)

### 3. Prior Art Natalizumab Formulations

In August 2001, clinical researchers reported a natalizumab formulation containing a buffer and the surfactant polysorbate 80, which later undergoes dilution with saline to add NaCl. (Ex. 1017 at 7.) Gordon reports results from a clinical trial for the treatment of CD with an aqueous natalizumab formulation comprising 5 mg/ml natalizumab, "50 mmol/L of histidine buffer and 0.02% polysorbate 80, adjusted to pH 6.0."[3] (Id.) This formulation then undergoes dilution through the addition of 0.9% saline (NaCl and water). Post-dilution, Gordon further teaches that "[p]atients received a single 3 mg/kg intravenous infusion of natalizumab." (Id.)

The buffer employed by Gordon was histidine, used to maintain the formulation pH at 6.0. (Id.) According to scientifically authoritative prior art texts, only a few buffers were suitable for the pH disclosed in Gordon, including phosphate, citrate and histidine buffers. (Ex. 1029 at 13.)

Shortly after Gordon published, in October 2001, Subramanian reported that the use of both histidine and citrate buffers in an IgG mAb formulation containing polysorbate 80 results in "accelerated potency loss" of the IgG mAb active drug. (Ex. 1002 at ¶ 77; Ex. 1026 at 4.) According to Subramanian, histidine

[3] As Dr. Schöneich explains, Gordon teaches a formulation containing natalizumab, histidine and polysorbate 80 stored in a vial. (Ex. 1002 at ¶ 68.)

undesirably reacts with polysorbate 80 to form an impurity that oxidizes the IgG mAb. (Ex. 1026 at 4.) This helps explain Applicants' later alleged discovery that Gordon was unstable. (Ex. 1002 at ¶ 77.) And given that Subramanian did not criticize phosphate buffer in this way, suggests how one of ordinary skill could fix it. (Id.)

Furthermore, although Gordon teaches dilution of its natalizumab formulation with saline prior to administration, nearly all the prior art aqueous IgG formulations include NaCl as part of the commercial formulation. In fact, it was well known that formulating at isotonic conditions was highly desired to allow for patient comfort. (Ex. 1011 at ¶ 22; Ex. 1032 at 6.) Isotonic formulations are highly desirable because non-isotonic formulations, i.e., those that are hyper or hypotonic, "cause tissue irritation, pain on injection, and electrolyte shifts." (Ex. 1032 at 6.) "An isotonic solution, therefore, is the choice as a vehicle for many drugs which have to be administered parenterally." (Id. at 9.) To make that choice, skilled formulators could simply follow the teachings of Andya, which states that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm" and that "[i]sotonicity can be measured using a[n] . . . ice-freezing type osmometer." (Ex. 1010 at ¶ 0051.) The '577 patent appears to have copied this passage directly from Andya. (Ex. 1001 at 6:33-38.)

### B. Ground 1 – The Challenged Claims are Obvious under 35 U.S.C. § 103(a) over van Oosten or Zenapax in view of Sorbera

Each of the primary references in Ground 1 – van Oosten (Ex. 1014) and Zenapax (Ex. 1024) – discloses an IgG mAb formulation comprising the identical excipients recited by the claims –phosphate buffer, sodium chloride and polysorbate 80. Although van Oosten and Zenapax respectively contain infliximab and daclizumab as opposed to natalizumab, a single modification through the secondary reference – Sorbera (Ex. 1019) – cures this deficiency. Sorbera teaches that natalizumab, like the infliximab of van Oosten, is an IgG mAb that is useful for treating CD. In other words, these actives qualify as simple substitutes under the case law. In addition, modifying Zenapax with Sorbera combines known elements (the Zenapax excipients and natalizumab) according to known methods of manufacture. (Ex. 1002 at ¶ 92.) Each combination of prior art references thus discloses all of the structural limitations recited by the Challenged Claims as exemplified by claim 1:

| Claim 1 | Prior Art |
|---|---|
| A stable, aqueous pharmaceutical formulation comprising | **van Oosten:** "Each vial contained . . . 10.0 mg/ml cA2. . . ." (Ex. 1014 at 5.)<br>**Zenapax:** "Each milliliter of ZENAPAX contains 5 mg of Daclizumab. . . ." (Ex. 1024 at 2.)<br>**Sorbera:** "2 i. v. infusions (3 mg/kg) of natalizumab given 4 weeks apart." (Ex. 1019 at 3.) |
| from about 20 mg/ml to about 150 mg/ml of natalizumab, | **van Oosten:** "Each vial contained . . . 10.0 mg/ml cA2. . . ." (Ex. 1014 at 5.)<br>**Zenapax:** "Each milliliter of ZENAPAX contains 5 mg of Daclizumab. . . ." (Ex. 1024 at 2.) |

| | |
|---|---|
| | **Sorbera:** "2 i. v. infusions (3 mg/kg) of natalizumab given 4 weeks apart." (Ex. 1019 at 3.) |
| polysorbate 80 present in an amount of about 0.001% to 2% (w/v), | **van Oosten:** "Each vial contained . . . 0.01% polysorbate 80. . . ." (Ex. 1014 at 5.)<br>**Zenapax:** "Each milliliter of ZENAPAX contains . . . 0.2 mg polysorbate 80. . . ." (Ex. 1024 at 2.) |
| about 10 mM phosphate buffer, | **van Oosten:** "Each vial contained . . . 0.01 M sodium phosphate." (Ex. 1014 at 5.)<br>**Zenapax:** "Each milliliter of ZENAPAX contains . . . 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptabydrate. . . ." (Ex. 1024 at 2.) |
| about 140 mM NaCl. | **van Oosten:** "Each vial contained . . . 0.15 M sodium chloride. . . ." (Ex. 1014 at 5.)<br>**Zenapax:** "Each milliliter of ZENAPAX contains . . . 4.6 mg sodium chloride. . . ." (Ex. 1024 at 2.) |

The only other limitations are result effective variables subject to routine optimization. As the C.C.P.A. long ago explained, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955). See also In re Applied Materials, Inc., 692 F.3d 1289, 1295-96 (Fed. Cir. 2012). That is, optimization of result effective variables is "within the grasp of one of ordinary skill in the art." Id. There is no such evidence of criticality or unexpected results here as discussed further below.

### 1. Challenged Claim 1

The limitations of independent claim 1 are recited in the headings of sub-paragraphs (a) through (e) below:

**a. "A stable, aqueous pharmaceutical formulation"**

The preamble is not limiting because the body of claim 1 fully sets forth all of the limitations, and the preamble merely states the intended purpose of those limitations. See Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999).

To the extent the preamble is a limitation, van Oosten and Zenapax disclose formulations that are necessarily aqueous. van Oosten, for example, teaches that its formulation is a "solution," which necessarily requires a solvent. (Ex. 1002 at ¶ 95; Ex. 1014 at 5.) Similarly, Zenapax teaches a colorless concentrate in a volume of 5 milliliters. (Ex. 1024 at 2.) Absent identification of a specific solvent in both, a person of ordinary skill in the protein formulation art would have recognized that the solvent in question is necessarily water and the formulation is thus aqueous. (Ex. 1002 at ¶ 95.) Water is of course safe for pharmaceutical administration and routinely used in parenteral formulations. (Id.) Indeed, other IgG mAb formulations, e.g., Orthoclone, teach ampules containing buffered solutions "in water for injection." (Ex. 1022 at 3.)

With respect to the "stable" limitation, van Oosten reports favorable efficacy on CD, which demonstrates that its formulation necessarily retained its biological activity after storage and prior to administration. (Ex. 1002 at ¶ 96.) Zenapax

likewise qualifies as stable, with Bell expressly teaching that Zenapax has a shelf life of 1 year. (Ex. 1025 at 4.)

It is also a basic and fundamental goal of formulation science to prepare stable formulations that retain their biological activity under storage. (Ex. 1002 at ¶ 36; Ex. 1031 at 7 ("This book is written to assist pharmaceutical scientists in the development of stable protein formulations.").) For the same reasons the claimed formulations achieve that goal, so do the modified natalizumab formulations in Petitioner's proposed combinations. Stable formulations containing various IgG mAbs and the claimed excipients at similar concentrations were well-known in the prior art and approved by FDA on multiple occasions, e.g., Zenapax and Orthoclone. (Ex. 1024 at 2; Ex. 1022 at 3.) In addition, Cummins reports the extended stability of a 50 mg/ml IgG formulation containing just phosphate buffer and sodium chloride for a full twelve months. (See Ex. 1021 at 6, 8.) As Dr. Schöneich thus explains, the combination of natalizumab and the claimed excipients at optimized concentrations would necessarily or inherently create a stable formulation, especially under the broad definition of "stable" provided by the '577 patent. (Ex. 1002 at ¶ 144.) Indeed, an otherwise obvious formulation claim cannot become non-obvious simply by adding an inherent property to its limitations. See Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012).

### b. "from about 20 mg/ml to about 150 mg/ml of natalizumab"

There are various reasons why one of ordinary skill would replace the IgG mAbs in either van Oosten (infliximab) or Zenapax (daclizumab) with natalizumab. First, the prior art motivates the exchange because infliximab and natalizumab are known substitutes that treat the same disease states. And second, substitution of daclizumab for natalizumab combines known elements according to known methods.

van Oosten teaches that administration of its infliximab formulation results in significant improvement in patients with CD. (Ex. 1014 at 4.) Because Sorbera (Ex. 1019) teaches that natalizumab effectively treats CD, the prior art motivates one of ordinary skill to substitute it for infliximab. See In re Huellmantel, 324 F.2d 998, 1000 (C.C.P.A. 1963) (finding substitution of one steroid for another obvious because they share similar physiological activity). Infliximab and natalizumab qualify as simple substitutes because their function, i.e., treatment of CD, was well-known in the art.

And this simple substitution would have yielded the predictable result of achieving that function. (Ex. 1002 at ¶ 99.) Indeed, the scope and content of the prior art demonstrates that the excipients employed in the van Oosten formulation were compatible and worked well with various IgG mAb actives. (Id. at ¶ 100.) For example, each of van Oosten (Ex. 1014 at 5), Zenapax (Ex. 1024 at 2),

Aversano (Ex. 1023 at 5) and Orthoclone (Ex. 1022 at 3) relied upon this same combination of excipients to create stable, pharmaceutically acceptable formulations. (Ex. 1002 at ¶ 100.) The result of pairing these same excipients with natalizumab is no different.[4] (Id. at ¶ 101.) In fact, the '577 patent teaches that all proteins are "interchangeable" with these excipients. (Ex. 1001 at 2:62-65.)

Alternatively, adding the natalizumab of Sorbera to the Zenapax excipients (which are identical to those of the Challenged Claims) merely combines known elements according to known methods. More than ten years before the earliest effective filing date, formulators prepared commercial formulations of Orthoclone using these very same excipients. (Ex. 1002 at ¶ 102; Ex. 1030 at 1.) And, the Zenapax formulation was approved in 1997, more than 5 years before the earliest effective filing date. (Ex. 1030 at 3.) Thus, to achieve the claimed natalizumab formulation, one of ordinary skill would have needed only to follow well-known

[4] The fact that FDA ultimately approved a lyophilized powder as opposed to the aqueous infliximab formulation of van Oosten does not teach away. Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013) ("A reference does not teach away . . . [if it] does not criticize, discredit, or otherwise discourage investigation into the invention claimed."). Further, the NDA holder for infliximab publicly stated that "there were no significant differences between the liquid and the two lyophilized formulations of cA2." (Ex. 1016 at 12.)

methods for creating the final formulation, i.e., combining the IgG mAb in question with optimized excipient solutions. (Ex. 1002 at ¶ 102.)

One of ordinary skill would also have recognized that each ingredient in the Petitioner's modified formulations would retain its original function. (Id. at ¶ 103.) And, because the modified formulations would be stable, natalizumab would retain its function. (Ex. 1011 at ¶ 21.) Sodium phosphate would buffer the formulation to a certain pH. (Ex. 1002 at ¶ 103.) Polysorbate 80 would prevent agglomeration of the IgG mAb. (Id.) And NaCl would provide the desired isotonicity for the IgG mAb. (Id.)

Finally, for the same reasons substitution of natalizumab in place of infliximab yields predictable results, so is the substitution of natalizumab for daclizumab. (Id. at ¶ 102.) After all, as stated in the '577 patent, antibodies in general are "interchangeable" in the claimed formulation. (Ex. 1001 at 2:64-67.)

With respect to the "about 20 mg/ml to about 150 mg/ml" limitation – this is nothing more than routine optimization of a result effective variable. The "normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003). While van Oosten and Zenapax include IgG mAb concentrations of 10 mg/ml and 5 mg/ml, respectively (Ex. 1014 at 5; Ex. 1024 at 5), IgG

formulations containing between 5 and 50 mg/ml were known in the art. (Ex. 1017 at 7; Ex. 1020 at 16 (e.g., Sigma F 7381 F 9636 or F 7256); Ex. 1021 at 6). One of ordinary skill would have simply calculated the appropriate concentration of natalizumab for storage in vials over a range of volumes. (Ex. 1002 at ¶ 106; Ex. 1011 at ¶ 20.)

For example, Sorbera discloses that 3 mg of natalizumab per kg of body weight (3 mg/kg) is therapeutically effective. (Ex. 1019 at 3.) Because the average adult male weighs 78.5 ±11.8 kg, 235.5 mg (3 mg/kg * 78.5 kg) of natalizumab would have been considered necessary for a single treatment. (Ex. 1002 at ¶ 107 (citing Ex. 1037 at 6, Table 1).) Given that vials for aqueous protein formulations come in a range of different volumes, including, for example, 5, 10, 20 and 50 ml (see Ex. 1024 at 2; Ex. 1027 at 3; Ex. 1028 at 6), a person of ordinary skill in the art would have routinely tested natalizumab over a range of concentrations that fall within the 20 mg/ml to 150 mg/ml range recited in the Challenged Claims. (Ex. 1002 at ¶ 108.) No single concentration is critical because a single vial or multiple vials in combination are added to standard intravenous infusion bags for administration of 3 mg/kg. (Ex. 1011 at ¶ 20.)

**c. "polysorbate 80 present in an amount of about 0.001% to 2% (w/v)"**

Both van Oosten and Zenapax expressly satisfy the claim limitation reciting "in an amount of about 0.001% to 2%." (Ex. 1014 at 5 (reciting 0.1 mg/ml

(0.01%)); Ex. 1024 at 2 (reciting 0.2 mg/ml (0.02%)).) "It is . . . an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." Aventis Pharma S.A. v. Hospira, Inc., 675 F.3d 1324, 1333 (Fed. Cir. 2012) (citing Titanium Metals Corp. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985).)

**d. "about 10 mM phosphate buffer"**

van Oosten discloses that its aqueous formulation comprises 10 mM phosphate buffer. (Ex. 1014 at 5; Ex. 1002 at ¶ 112.) van Oosten thus expressly teaches this limitation.

Zenapax discloses an aqueous pharmaceutical formulation comprising 67 mM phosphate buffer. (Ex. 1024 at 2.) This concentration is unnecessarily high (as it provides more than 1000 times the necessary buffering capacity) and is subject to routine optimization. (Ex. 1002 at ¶¶ 113-15.)

As an initial matter, buffer concentration is a result effective variable because it was known in the art to maintain the pH of pharmaceutical formulations over time. (Ex. 1002 at ¶ 41 (discussing Ex. 1029 at 12-13).) In line with existing IgG mAb formulations, pH varies between 6.0 (Ex. 1017 at 7) and 7.2 (Ex. 1014 at 5). One of ordinary skill seeking to maintain pH in this range would thus explore the minimum buffer capacity necessary to achieve this pH range through basic mathematical calculations. According to Dr. Schöneich, buffer capacity (β) is

routinely calculated using the following well-known equation: $\beta = \Delta A / \Delta pH$, where $\Delta A$ is the change in acid brought about by degradation and ΔpH is the change in pH that can be tolerated. (Ex. 1002 at ¶ 44 (citing Ex. 1033 at 13).) Applying this equation to Zenapax and taking into account the level of degradation of the active drug expected over time,[5] Dr. Schöneich calculates that only a minimum of about 0.065 mM phosphate buffer would have been required to maintain a pH of 6.9 ±0.1. (Ex. 1002 at ¶113.)

Protein formulators, however, routinely seek to maintain pH by including excess buffer concentrations. (Id. at ¶ 45.) van Oosten, for example, requires a minimum buffer concentration of about 0.116 mM phosphate buffer, but sets its phosphate buffer concentration at 10 mM – an excess of about 86 times. (Id. at ¶ 46 (discussing Ex. 1014 at 5).) Further, a commercially available research formulation of an IgG antibody that contains 20 mg/ml protein, in 10 mM phosphate buffered saline at a pH of 7.4 would have required only 0.24 mM phosphate buffer, but contains an excess of about 40 times. (Ex. 1002 at ¶ 47 (citing Ex. 1020 at 16 (Sigma F 7381 F 9636 or F 7256, for example)).)

With respect to 20 mg/ml of natalizumab at pH 6.0 (as disclosed in Ex. 1017 at 7) or pH 6.1 (Petitioner's optimized formulation), one of ordinary skill would

[5] If not stated otherwise, shelf life allows for no more than 10% degradation. (Ex. 1002 at ¶ 45 (discussing Ex. 1034 at 11).)

calculate the minimum buffer concentration of phosphate buffer to equal 1.036 mM and 0.85 mM, respectively, and would have routinely tested a range of excess buffer concentrations to ensure proper maintenance of the desired pH. (Id. at ¶ 114.) One of ordinary skill would thus explore a buffer concentration between 10 and 100 mM phosphate buffer to achieve the claimed concentration. (Id.)

Finally, a buffer concentration of about 10 mM is in no way critical. According to Dr. Schöneich, once a minimum amount of phosphate buffer has been ascertained, amounts in excess of the minimum, even up to 10 to 100 times the required minimum buffering capacity, will not negatively impact the formulation. (Id. at ¶ 115; see also Ex. 1014 at 5; Ex. 1020 at 16; Ex. 1033 at 14.) Indeed, the '577 patent specification discloses a wide range of buffer acceptable concentrations:

> Additional liquid formulations of antibody at high concentrations, from 20-200 mg/mL may consist of phosphate or other suitable buffer (such as histidine, citrate acetate or succinate) in the concentration range of 2 to 50 mM, to provide buffering in the pH range of 3.0 to 7.0.

(Ex. 1001 at 17:41-46.) Dr. Schöneich confirms that a buffer concentration of "about 10 mM" does not represent the only concentration that will maintain a pH of about 6.0 or 6.1 for a 20 mg/ml antibody formulation. (Ex. 1002 at ¶ 115.)

### e. <u>"about 140 mM NaCl"</u>

van Oosten and Zenapax respectively teach concentrations of NaCl of 150 mM and 78.7 mM. (Ex. 1014 at 5; Ex. 1024 at 2.) One of ordinary skill would, however, routinely optimize the concentration of NaCl after inclusion of natalizumab to achieve isotonicity because the prior art motivates a person of ordinary skill to formulate to isotonic conditions. (Ex. 1011 at ¶ 22; Ex. 1032 at 6, 9.)

It was known in the art, per the teachings of Andya, that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm" and that "[i]sotonicity can be measured using a[n] . . . ice-freezing type osmometer." (Ex. 1010 at ¶ 0051.) For example, each of Orthoclone, van Oosten and Aversano teach isotonic formulations. (Ex. 1002 at ¶ 58.) As Dr. Schöneich explains, 250 to 350 mOsm is present when a solution has a freezing point between -0.46° C and -0.64° C. (Ex. 1002 at ¶ 53 (citing the cryoscopic method, Ex. 1033 at 23-25).) To determine the appropriate concentration of NaCl, one of ordinary skill would simply calculate the concentration of sodium chloride necessary to depress the freezing point of the solution to within that range. (Ex. 1002 at ¶ 55.) Using this method, Dr. Schöneich calculated that a natalizumab formulation comprising a 10 mM phosphate buffer concentration requires a NaCl concentration between 127 mM and 180 mM, which encompasses the claimed

concentration. (Id. at ¶ 118.) Furthermore, the exact concentration of NaCl cannot be critical because isotonicity permits a range of NaCl concentrations, confirmed not only by Dr. Schöneich's calculations but also by Challenged Claim 1 itself, which requires "about 140 mM NaCl."

**2. Challenged Claim 3**

Claim 3 depends from claim 1 and further requires that the formulation is "isotonic." Not only does the prior art motivate the preparation of such an isotonic formulation through routine optimization, the modified prior art formulations that meet the limitations of claim 1 are inherently isotonic because the combination of 10 mM phosphate buffer and 140 mM NaCl make them so. (Ex. 1002 at ¶ 124.)

The prior art expressly motivates one of ordinary skill to prepare isotonic formulations to facilitate patient compliance and comfort. (Ex. 1011 at ¶ 22.) As previously mentioned starting at page 32 above, the goal of parenteral formulation development is to prepare isotonic formulations. As Remington's authoritative text explains, isotonicity is "the choice as a vehicle for many drugs which have to be administered parenterally" because it avoids tissue irritation and pain at the site of injection. (Ex. 1032 at 9, see also at 6.) One of ordinary skill would, therefore, calculate the concentration that, when combined with 10 mM phosphate buffer,

achieves isotonicity. (Ex. 1002 at ¶ 56.) Based on Dr. Schöneich's calculations, that concentration is between 127 mM and 180 mM NaCl. (Id. at ¶ 57.)

Furthermore, Petitioner's modified natalizumab formulation is inherently isotonic. Specifically, both the prior art (Andya) and the '577 patent specification state that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm," and that "[i]sotonicity" may also be measured by an "ice-freezing type osmometer." (Ex. 1010 at ¶ 0051; Ex. 1001 at 6:32-36.) As explained above starting at page 32, 250 to 350 mOsm is present when a solution has a freezing point between -0.46° C and -0.64° C. (Ex. 1002 at ¶ 53 (citing Ex. 1033 at 23-25).) Dr. Schöneich determined that a 10 mM phosphate buffered formulation requires between 127 mM and 180 mM NaCl to achieve isotonic conditions as defined by the '577 patent. (Ex. 1002 at ¶ 57.) Claim 3 thus does not add any further limitation not inherently present in claim 1 and therefore qualifies as equally obvious. See Santarus, 694 F.3d at 1354.

### 3. Challenged Claim 4

Claim 4 depends from claim 1 and further requires that the formulation is "stable at a temperature of 2° C. to 8° C. for at least 6 months."

It is a basic and fundamental tenet of formulation science to prepare stable formulations that retain their biological activity under storage. (Ex. 1002 at ¶ 36; Ex. 1031 at 7.) Stability is of course critical to the commercial manufacture of

protein formulations, which often need to be shipped around the world and maintained under storage for extended periods. (Ex. 1002 at ¶ 126.) That is why standard stability tests have existed in the prior art for decades. (Id.) According to Bell, the "[s]helf life of Zenapax is 1 year" and "[v]ials should be stored between 36° – 46° F" (equivalent to 2º C to 8 º C). (Ex. 1025 at 4.) Cummins reports 12 month stability (0° to 8°C storage) of a 50 mg/ml IgG solution in normal saline alone. (Ex. 1021 at 8.) Similarly, White discloses several commercially available formulations ready for shipment around the country, each comprising 20 mg/ml concentrations of IgG in 5 mM or 10 mM PBS. (Ex. 1020 at 14 (USBio I1903-31) and 16 (Sigma F 7381, F 9636 and F 7256).)

Against that backdrop, Petitioner's modified formulation would ensure the stability of natalizumab active under the conditions specified in claim 4. Indeed, as Dr. Schöneich explains, the teachings of Zenapax, Cummins, and White indicate that a 20 mg/ml natalizumab formulation with NaCl, phosphate buffer and polysorbate 80 would retain its biological activity for greater than six months under the conditions specified by claim 4 of the '577 patent. (Ex. 1002 at ¶ 126.)

Furthermore, because Petitioner's modified prior art formulations satisfy all limitations of claim 1, they necessarily achieve the same stability as set forth in claim 4. See Santarus, 694 F.3d at 1354; In re Spada, 911 F.2d 705, 708 (Fed. Cir.

1990) ("products of identical chemical composition cannot have mutually exclusive properties").

#### 4. Challenged Claims 5 and 6

Claim 5 depends from claim 1 and further requires a "pH of 3.0 to 7.0." Claim 6 depends from claim 4 and further requires that the formulation has a "pH of 5.5 to 6.5." van Oosten and Zenapax both teach maintaining their formulations at a set pH. Zenapax explicitly discloses a pH of 6.9, which is encompassed by the claimed range of claim 5. (Ex. 1024 at 2.) van Oosten discloses a pH of 7.2. (Ex. 1014 at 5.)

Further, optimizing the pH of a formulation containing natalizumab would have been a matter of routine optimization accomplished through stability and solubility studies known in the art for decades. (Ex. 1002 at ¶ 127.) As Dr. Schöneich explains, formulation pH has long been known to impact the stability and solubility of the therapeutically active antibody. (Ex. 1002 at ¶ 39 (discussing Ex. 1031 at 13-14).) Those of ordinary skill routinely tested protein formulations, including antibody formulations, within a pH range of 4 to 9, preferably 5 to 7. (Id. (citing Ex. 1031 at 13).) Prior art formulations of other IgG mAbs confirm widespread usage and knowledge of this preferred pH range, spanning 6.0 to 7.2. (See, e.g., Ex. 1017 at 7; Ex. 1024 at 2; Ex. 1014 at 5; Ex. 1022 at 3; Ex. 1023 at

5.) In fact, Gordon teaches that its natalizumab formulation is at a pH of 6.0. (Ex. 1017 at 7.)

### 5. Challenged Claims 7, 9-12

Claims 7 (depends from claim 1), 9 (depends from claim 3), 10 (depends from claim 4), 11 (depends from claim 5), and 12 (depends from claim 6) each add "a container" for holding the stable, aqueous pharmaceutical formulations of other respective claims. van Oosten states that its infliximab formulation was stored in a "vial." (Ex. 1014 at 5.) Similarly, Zenapax teaches that its daclizumab formulation is supplied in a 5 ml "vial." (Ex. 1024 at 3.)

### 6. Reasonable Expectation of Success

A person of ordinary skill in the art would have had at least a reasonable expectation of producing a stable formulation by substituting natalizumab for van Oosten's infliximab and Zenapax's daclizumab. (Ex. 1002 at ¶ 130.) As the Federal Circuit has repeatedly explained, absolute predictability is not required: "[o]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). In this case, the prior art demonstrates the stability of IgG mAb formulations containing the excipients recited by the Challenged Claims of the '577 patent. Further, key

overlapping structural characteristics shared by IgG mAbs means they behave comparably in formulations containing identical excipients.

As discussed above in Section VII.B.1-5, one of ordinary skill would have reasonably expected that the claimed natalizumab formulation could have been made through routine experimentation. Each and every excipient recited by the claims –phosphate buffer, NaCl and polysorbate 80 – was not only individually known but had been repeatedly and successfully used together in prior art IgG mAb formulations to create stable formulations years before the '577 patent. (Ex. 1002 at ¶ 130.) Furthermore, given the extensive literature discussing how to optimize concentrations for such excipients, one of ordinary skill could have readily prepared the claimed formulation through routine testing. (Id. at ¶ 130; Ex. 1031 at 9, 10.)

Similarly, one of ordinary skill would have reasonably expected such an optimized formulation to achieve its intended purpose of remaining "stable" under storage, especially under the '577 patent's broad definition of this term. (Ex. 1002 at ¶ 131.) Stable formulations containing various IgG mAbs and the claimed excipients were both well-known in the prior art and approved by FDA on multiple occasions, e.g., Orthoclone and Zenapax. (Ex. 1022 at 3; Ex. 1024 at 2.) Cummins reports 12 month stability (0° to 8°C storage) of a 50 mg/ml IgG solution in normal saline. (Ex. 1021 at 8.) And White discloses several commercially

available formulations ready for shipment around the country, each comprising 20 mg/ml concentrations of IgG in 5 mM or 10 mM PBS. (Ex. 1020 at 14 (USBio I1903-31) and 16 (Sigma F 7381, F 9636 and F 7256).)

According to Dr. Schöneich, the existence of prior art formulations employing such high concentrations of IgG actives leads a person of ordinary skill to expect that a 20 mg/ml natalizumab formulation comprising these same excipients would also retain biological activity under storage. (Ex. 1002 at ¶ 126.) One of ordinary skill would, therefore, have reasonably expected the combination of natalizumab with the claimed excipients at optimized concentrations to support a stable final formulation.

Furthermore, IgG mAbs represent a specific population of proteins sharing key structural characteristics germane to formulation development. These shared characteristics would have provided a person of ordinary skill in the art with a reasonable expectation that a formulation useful for one IgG mAb would be useful for another. (Ex. 1002 at ¶ 34.)

Among those characteristics are the primary amino sequence and secondary, tertiary and quaternary structures of the antibodies. (Ex. 1002 at ¶ 34 (discussing Ex. 1035 at 8-23; Ex. 1036 at 11-21).) As Dr. Schöneich explains, IgG mAbs share essentially identical secondary, tertiary and quaternary structures, which structures are important to ensuring comparable behavior in identical formulations.

(Ex. 1002 at ¶ 34.) In addition, the primary amino acid sequence of different IgG mAb actives can share 95% identity. (Id. at ¶ 34.) But even when the primary acid amino acid sequence differs by a greater percentage, many of the amino acid changes are conservative and would not affect the behavior of the IgG mAb actives within the same formulation. (Id.) For example, the four prior art IgG mAbs that were developed for clinical use have differences in subtype ($IgG_1$ vs. $IgG_4$) and species (humanized vs. chimeric vs. mouse). (Ex. 1002 at ¶ 131 (referring to Ex. 1024; Ex. 1023; Ex. 1014; Ex. 1022).) Yet, all four formulations (see Table 1, above at p. 16) were successfully formulated with the same three excipients, phosphate buffer, NaCl and polysorbate 80. (Ex. 1002 at ¶ 131.) Thus, a person of skill would have had a reasonable expectation that one IgG mAb would exhibit similar behavior as another in the optimized formulation.

Accordingly, a person of ordinary skill in the art would have had at least a reasonable expectation that natalizumab formulated with a combination of phosphate buffer, NaCl and polysorbate 80 would result in a stable, aqueous natalizumab formulation, as recited in claim 1 of the '577 patent. (Id. at ¶ 131.)

Applicants' contrary argument during prosecution based on Wang (Ex. 1046) and Cleland (Ex. 1047) not only overstates the teachings of those references, but also ignores express statements in the '577 patent regarding "interchangeable" proteins and antibodies. Wang and Cleland do not stand for the

proposition that the knowledge and experience of skilled antibody formulators can be swept aside during development of comparable antibody formulations employing different IgG mAb actives. Although Wang and Cleland generically discuss issues when formulating proteins in general, neither focuses on formulations comprising IgG mAbs in particular. And neither states that antibodies in general, let alone IgG mAbs, are not readily interchangeable in formulations. (Ex. 1002 at ¶ 134.) Perhaps more importantly, there is no indication that Wang or Cleland appreciated that multiple IgG mAb prior art formulations successfully relied upon the exact same excipients at similar concentrations. (Id.) Furthermore, this tribunal should not permit Patent Owner to reinstate its arguments over Wang and Cleland given its prior representation to the Patent Office that all proteins are "interchangeable" in such formulations. (Ex. 1001 at 2:64-67.)

Given the foregoing, the general disclosures in Wang and Cleland cannot rebut the reasonable expectation of success created by Petitioner's combination of prior art. If that were the case, all new protein formulations would qualify as non-obvious and patentable. But that simply is not law:

> A rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt … would be separately patentable, simply because the formation and properties of each salt must be

verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Pfizer, 480 F.3d at 1364. Like the situation in Pfizer, Patent Owner cannot claim that every new protein formulation is non-obvious simply because testing would be required to determine whether the protein actives are interchangeable.

### C. Ground 2 – The Challenged Claims are Obvious under 35 U.S.C. § 103(a) over Gordon in View of Orthoclone or Aversano

Gordon teaches a natalizumab formulation containing all of the claimed excipients, with the exception of histidine buffer in place of phosphate buffer. Each of the secondary references, Orthoclone or Aversano, teaches IgG mAb formulations with precisely the same excipients recited by the Challenged Claims – phosphate buffer, NaCl and polysorbate 80. A person of ordinary skill would have been motivated to replace the histidine buffer of Gordon with phosphate buffer of the secondary references because Subramanian reported that formulations containing histidine buffer combined with polysorbate 80 impair the biological activity of an IgG mAb. Not only had phosphate buffer worked with numerous prior art IgG mAb formulations, such a modification represents simple substitution of one known element for another. The following chart reflects these combinations, as exemplified by claim 1.

| Claim 1 | Prior Art |
|---|---|
| A stable, aqueous pharmaceutical | **Gordon:** "Natalizumab (5 mg/mL) was formulated in a solution." (Ex. 1017 at 7.) |

| | |
|---|---|
| formulation comprising | **Orthoclone:** "The antibody is a biochemically purified $IgG_{2a}$ immunoglobin" and that "[e]ach 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution." (Ex. 1022 at 3.)<br>**Aversano:** "The chimeric CLB54 monoclonal antibody used in this study is a human/mouse genetic reconstruction of a murine monoclonal IgG4 molecule that binds selectively to the neutrophil CD18 receptor." (Ex. 1023 at 5.) "It was supplied as a sterile, nonpyrogenic solution of 5 mg of monoclonal IgG4 per milliliter of buffer solution." (Id.) |
| from about 20 mg/ml to about 150 mg/ml of natalizumab, | **Gordon:** "Natalizumab (5 mg/mL) was formulated in a solution." (Ex. 1017 at 7.)<br>**Orthoclone:** "The antibody is a biochemically purified $IgG_{2a}$ immunoglobin" and that "[e]ach 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution." (Ex. 1022 at 3.)<br>**Aversano:** "The chimeric CLB54 monoclonal antibody used in this study is a human/mouse genetic reconstruction of a murine monoclonal IgG4 molecule that binds selectively to the neutrophil CD18 receptor." (Ex. 1023 at 5.) "It was supplied as a sterile, nonpyrogenic solution of 5 mg of monoclonal IgG4 per milliliter of buffer solution." (Id.) |
| polysorbate 80 present in an amount of about 0.001% to 2% (w/v), | **Gordon:** "[S]olution . . . [had] 0.02% polysorbate 80." (Ex. 1017 at 7.)<br>**Orthoclone:** "Each 5 mL ampule . . . contains . . . polysorbate 80 (1 mg). . . ." (Ex. 1022 at 3.)<br>**Aversano:** "[S]terile, nonpyrogenic solution . . . contain[s] . . . 0.01% of polysorbate 80. . . ." (Ex. 1023 at 5.) |
| about 10 mM phosphate buffer, | **Gordon:** "[S]olution [had] 50 mmol/L histidine buffer." (Ex. 1017 at 7.)<br>**Orthoclone:** "Each ampule contains a buffered solution (pH 7.0 ±0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg). . . ." (Ex. 1022 at 3.)<br>**Aversano:** "[S]terile, nonpyrogenic solution . . . |

| | |
|---|---|
| | contain[s] . . . 0.01 mol/liter of sodium phosphate. . . ." (Ex. 1023 at 5.) |
| about 140 mM NaCl. | **Orthoclone:** "Each 5 mL ampule . . . contains a buffered solution [of] . . . sodium chloride (43 mg) . . . in water." (Ex. 1022 at 3.)<br>**Aversano:** "[S]terile, nonpyrogenic solution . . . contain[s] 0.15 mol/liter of sodium chloride. . . ." (Ex. 1023 at 5.) |

### 1. Challenged Claim 1

The features of independent Claim 1 appear in the headings of sub-parts (a) through (e) below:

#### a. "A stable, aqueous pharmaceutical formulation"

To the extent the preamble limits claim 1, Gordon teaches that its formulation is in "solution," which necessarily requires a solvent. (Ex. 1017 at 7.) As previously mentioned, absent identification of a specific solvent, a person of ordinary skill in the protein formulation art would have recognized that the solvent in question is necessarily water and the formulation is thus aqueous. (Ex. 1002 at ¶ 143.) Water is of course safe for pharmaceutical administration and routinely used in parenteral formulations. (Id.) Furthermore, Orthoclone and Aversano also disclose this limitation. As mentioned, Orthoclone teaches a buffered solution "in water for injection." (Ex. 1022 at 3.) Like Gordon, Aversano teaches that its formulation is in "solution," which necessarily requires a solvent, for the same reasons as described for Gordon. (Ex. 1023 at 5.)

Further, the prior art teaches the importance of stable formulations and a skilled formulator would know how to create them. Under the broad definition for "stable," Gordon qualifies as stable inasmuch as the formulation was necessarily stored prior to administration. (Ex. 1002 at ¶ 144.) Gordon's formulation was made and shipped from "Elan Pharma Ltd." in England. (Ex. 1017 at 6.) Aversano and Orthoclone also disclose stable formulations. Aversano's formulation was made and shipped from "Centocor, Inc." (Ex. 1023 at 5.) As an FDA-approved formulation shipped around the country, Orthoclone also qualifies as "stable." In fact, Remington's indicated that Orthoclone had a shelf-life of 1 year. (Ex. 1032 at 8.) (Ex. 1002 at ¶ 144.) As Dr. Schöneich also points out, various prior art formulations comprising the identical combination of claimed excipients qualified as stable. (Ex. 1002 at ¶ 144 (citing Ex. 1014; Ex. 1024; Ex. 1022; and Ex. 1023).) According to Dr. Schöneich, the combination of natalizumab and the claimed excipients at optimized concentrations create a stable formulation, especially under the broad definition provided by the '577 patent. (Ex. 1002 at ¶ 144.) Indeed, the modified Gordon formulation substituting phosphate buffer for histidine, which satisfies all limitations of claim 1, is inherently stable. See Santarus, 694 F.3d at 1354.

**b. "from about 20 mg/ml to about 150 mg/ml of natalizumab"**

Although Gordon only discloses that the aqueous formulation includes 5 mg/ml natalizumab (Ex. 1017 at 7), this difference in concentration represents nothing more than routine optimization of a result effective variable. In this regard, Petitioner incorporates by reference its discussion starting on page 27 above.

**c. "polysorbate 80 present in an amount of about 0.001% to 2% (w/v)"**

Gordon's natalizumab formulation includes 0.02% polysorbate 80 (Ex. 1017 at 7), Aversano discloses a formulation with 0.01% polysorbate 80 (Ex. 1017 at 5), and Orthoclone discloses a formulation with 0.02% polysorbate 80 (Ex. 1022 at 3) all within the claimed range. (Ex. 1002 at ¶ 146.)

**d. "about 10 mM phosphate buffer"**

Gordon's natalizumab formulation includes a histidine buffer, which one of ordinary skill would have readily exchanged with the phosphate buffer of Orthoclone or Aversano because (1) the classic teaching/suggestion/motivation or "TSM" rationale points directly toward use of phosphate buffer and, independently (2) such use is no more than a simple substitution of one known buffer for another with predictable results.

Turning first to TSM – shortly after Gordon published, Subramanian taught those of ordinary skill that histidine buffer combined with polysorbate 80 caused accelerated degradation of IgG mAb actives. (Ex. 1026 at 4.) One of ordinary skill looking for an alternative to histidine buffer would quickly zero in on phosphate buffer. (Ex. 1002 at ¶ 148.) As discussed at length above in the scope and content, numerous IgG mAb formulations repeatedly and successfully used polysorbate 80 with a phosphate buffer and NaCl. In fact, FDA approved two of these formulations – Orthoclone and Zenapax – and the combined use of these excipients was common practice in the field for antibody and other protein formulations. (Ex. 1002 at ¶ 148.)

Such extensive and successful use of these inactive ingredients with other IgG mAbs would have motivated one of ordinary skill reviewing Gordon, which discloses natalizumab along with polysorbate 80 and the problematic histidine buffer, to incorporate phosphate buffer in place of histidine. (Ex. 1002 at ¶ 148.) The skilled artisans' choices were limited, given that only a few buffers had been previously approved by FDA for maintaining a pH of about 6.0, including, for example, histidine, phosphate buffer and sodium citrate. (Ex. 1029 at 13.)

Furthermore, unlike the histidine and citrate buffers criticized by Subramanian, phosphate buffer was known to be compatible with both IgG mAbs and polysorbate 80 without the prospect of accelerated potency loss. (Ex. 1002 at

¶ 148 (citing Ex. 1022 at 3; Ex. 1024 at 2).) Even putting Subramanian aside, there exists a rationale for selection of the phosphate buffer of Orthoclone inasmuch as this excipient qualifies as a simple substitute for Gordon's histidine. It was well-known that both histidine and phosphate buffer were safe buffers whose function was to maintain the pH of IgG mAb formulations over time. (Ex. 1002 at ¶ 149.) Indeed, Frokjaer teaches that both phosphate and histidine buffers were among the group of a few buffers used in protein formulations at pH of about 6.0. (Ex. 1029 at 13.)

Further, simple substitution of histidine with phosphate buffer would lead to the predictable result of a stable formulation. (Ex. 1002 at ¶ 150.) Numerous stable formulations comprising an IgG mAb active along with the combination of excipients polysorbate 80, NaCl and phosphate buffer, were known in the prior art. At least two of these formulations were FDA-approved. (Ex. 1022; Ex. 1024.) Thus, simple substitution of histidine with phosphate buffer would have led to the predictable result of a stable formulation. (Ex. 1002 at ¶ 150.)

The about 10 mM concentration is also subject to routine optimization. As discussed starting at page 29 above, those of ordinary skill routinely calculated optimal buffer concentrations using mathematical equations well-known in the prior art and such concentration is not critical. Aversano, for example, uses 10 mM phosphate buffer. (Ex. 1023 at 5.)

### e. **“about 140 mM NaCl”**

To answer whether Gordon satisfies the NaCl limitation, some brief background is necessary. More specifically, Gordon expressly teaches two formulations – (1) a pre-dilution formulation and (2) a post-dilution formulation. (Ex. 1017 at 7.) To be clear, Petitioner’s focus for purposes of Ground 2 is the pre-dilution formulation.

The prior art motivates NaCl addition to the pre-dilution formulation because isotonic conditions are necessary for patient comfort. (Ex. 1002 at ¶ 153; Ex. 1011 at ¶ 22; Ex. 1032 at 6.) As discussed above starting at page 32, the prior art teaches that “[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm.” (Ex. 1010 at ¶ 0051.) And NaCl was the excipient of choice for achieving isotonic conditions. (Ex. 1002 at ¶ 50; Ex. 1032 at 9.) In addition, numerous IgG mAb formulations employing phosphate buffer and polysorbate 80 also include NaCl for this very reason. For example, multiple FDA-approved prior art formulations, including both Orthoclone and Zenapax, include NaCl. (Ex. 1022 at 3; Ex. 1024 at 2.) Thus, a person of ordinary skill in the art would have added NaCl to the formulation prior to dilution.

It also bears noting that a person of ordinary skill reading Gordon would have understood its pre-dilution formulation to necessarily contain NaCl. Extrinsic sources, including Bendig and the ‘577 patent itself, confirm that Gordon’s pre-

dilution formulation contains NaCl. See Schering Corp. v. Geneva Pharm., 339 F.3d 1373, 1382-83 (Fed. Cir. 2003) (evidence external to a prior art reference, created after the patent-in-suit was filed, may be used to establish that each claimed element was necessarily present in the prior art). Bendig, assigned to Elan Pharmaceuticals (Ex. 1030 at 5), the same entity sponsoring Gordon's research (Ex. 1017 at 12; Ex. 1002 at ¶¶ 65, 68), discloses a preferred formulation of natalizumab, 50 mM histidine buffer and 150 mM NaCl at a pH of 6.0 without dilution. (Ex. 1018 at 14:18-21.) The '577 patent, also originally filed by Elan Pharmaceuticals, reports that polysorbate 80 was added to the original formulation used in clinical trials, i.e., the Bendig formulation. (Ex. 1001 at 12:1-8.) The inference is thus strong that Gordon built on the work of Bendig and added polysorbate 80 to Bendig's pre-dilution formulation containing histidine buffer and 150 mM NaCl.

Moreover, a person of ordinary skill would have recognized the presence of NaCl in the pre-dilution formulation because without it the post-dilution formulation would not qualify as isotonic. The prior art of course teaches that isotonic conditions are highly desirable for intravenous administration. (Ex. 1011 at ¶ 22; Ex. 1032 at 6.) As the '577 patent itself states, "[i]ntravenous administration requires the final formulation to be isotonic." (Ex. 1001 at 11:67-12:1.) If Gordon's pre-dilution formulation truly does not contain salt, its dilution

with 0.9% saline would result in an undesirably hypotonic solution. (Ex. 1002 at ¶ 153.) That is because the amount of saline added is insufficient to bring the diluted solution within the range of osmotic pressures identified by the prior art as isotonic. (Ex. 1010 at ¶ 0051; Ex. 1002 at ¶ 153.) Thus, the only way the post-dilution solution could qualify as isotonic is if the pre-dilution formulation already contained sufficient NaCl to make it so. (Ex. 1002 at ¶ 153.) According to Dr. Schöneich, a person of ordinary skill reading Gordon would conclude that the pre-dilution formulation already included NaCl. (Id.)

Finally, as to the concentration of about 140 mM NaCl, as discussed above starting at page 32, the concentration of NaCl required by Challenged Claim 1 is subject to routine optimization. As Dr. Schöneich explains, achieving isotonic conditions for a 10 mM phosphate buffered formulation requires NaCl to be at a concentration of between 127 mM and 180 mM, which encompasses the claimed concentration. (Ex. 1002 at ¶ 57.) For these reasons, a formulator with Gordon in hand would have included a sufficient concentration of NaCl in the pre-dilution formulation before placing it in a vial. (Ex. 1002 at ¶ 155.)

**2. Challenged Claim 3**

Claim 3 further requires that the formulation of claim 1 is isotonic. For the same reasons discussed above starting at page 33, the prior art motivates one of ordinary skill to formulation to isotonicity. One of ordinary skill would adjust the

concentration of sodium chloride by calculating the NaCl concentration necessary to formulate at isotonicity. According to Dr. Schöneich's calculations, the optimized formulation includes a sodium chloride concentration of 127 mM and 180 mM, which would qualify as isotonic. (Id. at ¶ 57.) Indeed, the modified Gordon formulation is necessarily isotonic because the combination of 10 mM phosphate buffer and 140 mM sodium chloride is an isotonic formulation. (Id. at ¶ 159.) Claim 2 thus does not add any further limitation not inherently present in claim 1 and is, therefore, equally obvious. See Santarus, 694 F.3d at 1354.

### 3. Challenged Claim 4

Claim 4 further requires that the formulation is "stable when stored at about 2° C. to about 8° C. for greater than 6 months." As explained above starting at page 34, Petitioner's modified natalizumab formulations, which satisfy all limitations of claim 1, are stable under these conditions. Not only does the prior art motivate skilled formulators to prepare formulations with extended stability and shelf life, numerous prior art formulations containing the same excipients recited by the Challenged Claims exhibited such stability. (Ex. 1002 at ¶¶ 126, 160; see also, Ex. 1022; Ex. 1024.) Furthermore, just like claim 3, claim 4 adds a limitation inherently present in claim 1 and is, therefore, equally obvious. See Santarus, 694 F.3d at 1354.

### 4. Challenged Claim 5 and 6

Claim 5 depends from claim 1 and further requires a "pH of 3.0 to 7.0." Claim 6 depends from claim 4 and further requires that the formulation has a "pH of 5.5 to 6.5." Gordon's natalizumab formulation has a pH of 6.0. (Ex. 1017 at 7.) Gordon's specific disclosure of a pH of 6.0 therefore renders the claimed range obvious to one of ordinary skill in the art. Regardless, as discussed above starting at page 36, pH is a result effective variable subject to routine optimization.

### 5. Challenged Claims 7, 9-12

Claims 7 (depends from claim 1), 9 (depends from claim 3), 10 (depends from claim 4), 11 (depends from claim 5), and 12 (depends from claim 6) each add "a container" for holding the stable, aqueous pharmaceutical formulations of other respective claims. Gordon states "[n]atalizumab (5 mg/ml) was formulated in a solution of 50 mmol/L histidine buffer and 0.02% polysorbate 80 adjusted to pH 6.0 with hydrochloric acid and was diluted to 100 ml in 0.9% saline for administration." (Ex. 1017 at 7.) According to Dr. Schöneich, the 5 mg/ml natalizumab formulation necessarily resided in a container, either a vial or ampule, prior to dilution. (Ex. 1002 at ¶ 162.) Similarly, the sterile, non-pyrogenic solution of the CLB54 monoclonal antibody disclosed in Aversano necessarily resided in a container. (Ex. 1023 at 5.) Orthoclone states that the IgG mAb muromonab-CD3 resides in an "ampule." (Ex. 1022 at 3.) Thus, Gordon,

Aversano and Orthoclone teach a container for holding their stable formulations, which renders claims 7 and 9-12 invalid as obvious.

To the extent Gordon does not inherently disclose a container, the prior art would have motivated one of ordinary skill to incorporate the formulation into a container for practical reasons, i.e., ease of storage, handling, shipping or delivery. The prior art, for example, discloses the use of ampules for storing Orthoclone. And as Dr. Schöneich explains, it was vital that an injectable liquid formulation reside in a container for shipping, delivery and storage. (Ex. 1002 at ¶ 129.)

**6. Reasonable Expectation of Success**

The person of ordinary skill in the art would also have had a reasonable expectation that the combination of Gordon (Ex. 1017) and Orthoclone (Ex. 1022) or Aversano (Ex. 1023) would successfully result in the claimed stable natalizumab formulation. See Pfizer, 480 F.3d at 1364. As discussed in great detail in Section VII.B.7, above, those of ordinary skill recognized that the claimed formulation could be made and would work for its intended purpose. (Ex. 1002 at ¶ 163.) Once again, the prior art reports several stable IgG mAb formulations with excipients identical to those recited by the Challenged Claims. And the IgG mAb actives in these formulations share key structural characteristics leading to comparable behavior in comparable formulations.

### D. Statement of No Redundancy

Neither vertical nor horizontal redundancy is present here. With respect to Ground 1, the rationale for modifying van Oosten with Sorbera (simple substitution) is different than the motivation to modify Zenapax with Sorbera (combining known elements). The alternate combinations of Ground 2 are also distinct because the secondary references, Orthoclone and Aversano, each present different concentrations of excipients, making routine optimization necessary in some cases but not others. Finally, Grounds 1 and 2 themselves are not redundant because each presents entirely different primary references leading to distinct substitutions and rationales. Ground 1 starts with a formulation satisfying all formulation components and replaces the active IgG mAb with natalizumab. Ground 2 starts with a known natalizumab formulation and substitutes one of the formulation excipients, i.e., a buffer. The Grounds thus do not qualify as vertically or horizontally redundant.

### E. Secondary Considerations of Nonobviousness Fail to Overcome the Strong *Prima Facie* Showing of Obviousness

Petitioners are not aware of any evidence of secondary considerations of nonobviousness sufficient to rescue the Challenged Claims from the strong case for *prima facie* obviousness discussed herein. See, e.g., Q.I. Press Controls, B.V. v. Lee, 752 F.3d 1371, 1379-80 (Fed. Cir. 2014); Ohio Willow Wood Co. v. Alps S., LLC, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

During prosecution of the ‘577 patent, Applicants alleged unexpected results, but the Preformulation Study they relied upon was “based on preliminary data which was not accurate . . . [and] could not be reproduced” by their own admission. (Ex. 1040 at 1.) Furthermore, as Dr. Schöneich explains in his declaration, even if the Preformulation Study data were accurate and reproducible, such data does not support unexpected results. (Ex. 1002 at ¶ 173.) For example, the protein concentration for the only formulation using polysorbate 80 (which also contained NaCl) purportedly increased, rather than decreased as would have been expected if the protein was degrading. (Id. at ¶ 174; Ex. 1038 at 20, Table 2.) In addition, that same formulation was able to maintain a stable pH over 8 weeks – the same pH as in a similar formulation without the polysorbate 80. (Ex. 1038 at 19, Table 1.) And a different formulation using phosphate buffer maintains the exact same pH over time both with and without NaCl. (Ex. 1038 at 19, Table 1.) According to Dr. Schöneich, these results do not support the Patent Owner’s assertions in support of the alleged unexpected results that “the inclusion of NaCl or polysorbate 80 was found to accelerate the degradation process.” (Ex. 1002 at ¶ 184; see also Ex. 1045 at 9.)

Commercial success also cannot rescue the ‘577 patent. To the extent commercial success, if any, exists, it can only trace back to the natalizumab active, which was well-known in the prior art before the ‘577 patent. (Ex. 1011 at ¶ 17.)

And as the Federal Circuit has explained, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." Ormco Corp. v. Align Technology, Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006).

### F. The Examiner Relied On Incorrect and Incomplete Information

Finally, the prosecution history of the '577 patent reveals that the Examiner premised allowance on incorrect and incomplete information.

*First*, the Examiner was not aware of the extensive prior art disclosing IgG mAb formulations comprising the same three excipients recited by the Challenged Claims. The existence of these formulations refutes Applicants' contentions that the prior art did not evidence any reasonable expectation of success.

*Second*, the Examiner was not aware that the prior art, namely Subramanian (Ex. 1026 at 4), discloses accelerated potency loss of IgG mAb actives attributable to histidine buffers in the presence of polysorbate 80. Subramanian would have led one of ordinary skill to identify the problem with Gordon, thereby refuting the Applicants' suggestion during prosecution that testing Gordon would lead one of ordinary skill away from its formulation. (Ex. 1045 at 7-8.)

*Third*, the Examiner relied heavily upon Applicants' representations concerning the Preformulation Study in support of allegedly unexpected results. What Applicants neglected to provide, however, was their public admission in another forum that this study was inaccurate and non-reproducible. On February 3,

2016, the Applicants' representative told the EPO that the results of the Preformulation Study "showed that the natalizumab antibody was relatively stable in *all* of the formulations evaluated," (Ex. 1041 at 10) (emphasis added), which contradicts their assertion to the Patent Office regarding degradation problems with either sodium chloride or polysorbate 80. (Ex. 1045 at 9.)

## VIII. CONCLUSION

Given the foregoing, Petitioner respectfully submits that it has shown a reasonable likelihood that Challenged Claims 1, 3-7 and 9-12 of the '577 patent are obvious. Petitioner requests, therefore, that the Board institute *inter partes* review for each of these claims.

Respectfully submitted,

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## CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,900,577 PURSUANT TO 35 U.S.C. § 312 AND 37 C.F.R. § 42.108** was served on April 18, 2016 via *FedEx Priority Overnight* service to the corresponding address for the subject patent pursuant to 37 C.F.R § 42.105:

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