Trials@uspto.gov
571.272.7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SWISS PHARMA INTERNATIONAL AG,
Petitioner,

v.

BIOGEN IDEC,
Patent Owner.

Case IPR2016-00912
Patent 8,815,236 B2

Before MICHAEL P. TIERNEY, LORA M. GREEN, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Swiss Pharma International AG ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–16, 21, and 22 of U.S. Patent No. 8,815,236 B2 (Ex. 1001, "the '236 patent"). Paper 1 ("Pet."). Biogen IDEC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has failed to demonstrate a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–16, 21, and 22. Accordingly, we decline to institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner states that it is "concurrently filing two additional petitions for *inter partes* review that will address certain claims of [U.S. Patent No. 8,349,321 ("the '321 patent") (IPR 2016-00915)] and U.S. Patent No. 8,900,577 ("the '577 patent") [IPR2016-00916]." Pet. 3. According to Petitioner, the "'236 and '577 patents are related to each other and to the '321 patent as continuations or divisionals." *Id.*

B. The '236 Patent (Ex. 1001)

The '236 patent issued on August 26, 2014, with David J. Burke, Shaun E. Buckley, Sherwood Russ Lehrman, Barbara Horsey O'Connor, James Callaway, and Christopher P. Phillips as the listed co-inventors.

Ex. 1001. It relates to "stable, concentrated formulations of proteins or antibodies, such as natalizumab, wherein the activity of the antibody is retained and also can be administered in a small volume and can be administered to a subject of variable weight in need thereof." *Id.* at 1:18–22.

According to the background of the '236 patent:

> Antibody and protein formulations are known in the art. However, preparing protein formulations, such as antibody formulations, which are chemically and biologically stable, are fraught with challenges. Preparing formulations which are also not only stable but can maintain a small volume (i.e., allowing for a small volume injection) even with an increased concentration of protein, such as antibody, also is problematic. The need for such formulations exist. For example, concentrated amounts of protein in a fixed volume that is also stable would be especially beneficial to patients of variable weight. Administration of fluids to patients of variable weights may, for example, have an adverse reaction. Development of such formulations has been hindered by the proteins or the antibodies themselves, which have a high tendency to aggregate and precipitate.

Id. at 1:26–40.

C. Challenged Claims

Petitioner challenges claims 1–16, 21, and 22 of the '236 patent. Claims 1, 9, 21, and 22 are independent. Claim 1 is illustrative and is reproduced below (emphasis added):

1. A method of treatment, comprising administering to a patient with multiple sclerosis a therapeutic amount of a stable, aqueous pharmaceutical formulation *comprising from about 20 mg/ml to about 150 mg/ml of natalizumab*, about 10 mM phosphate buffer, about 140 mM sodium chloride, and polysorbate 80 present in an amount of about 0.001% to 2% (w/v), wherein the multiple sclerosis is treated by administration of the stable, aqueous pharmaceutical formulation.

Ex. 1001, 17:62–18:2.

Note that independent claim 9 requires the limitation "comprising from about 20 mg/ml to about 150 mg/ml of natalizumab," and independent claims 21 and 22 specify that the natalizumab concentration is 20 mg/ml.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–16, 21, and 22 of the '236 patent on the following grounds (Pet. 7):

References	**Basis**	**Claims Challenged**
van Oosten[1] or Zenapax[2] and Sorbera[3]	§ 103(a)	1–16, 21, and 22
Gordon[4] and Orthoclone[5] or Aversano[6]	§ 103(a)	1–16, 21, and 22

[1] 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 1531–34 (1996) (Ex. 1014) ("van Oosten").

[2] Physicians' Desk Reference, Product Identification Guide and Product Information for Zenapax, 54th ed., 2696–97 (2000) (Ex. 1024) ("Zenapax").

[3] L.A. Sorbera, L. Martin, & X. Rabasseda, *Natalizumab*, 25 DRUGS OF THE FUTURE 917–21 (2000) (Ex. 1019) ("Sorbera").

[4] Gordon et al, *A Randomized Placebo-Controlled Trial of a Humanized Monoclonal Antibody to α4 Integrin in Active Crohn's Disease*, 121 GASTROENTEROLOGY 268–74 (2001) (Ex. 1017) ("Gordon").

[5] Physicians' Desk Reference, Product Identification Guide and Product Information for Zenapax, 50th ed., 1837–41 (1996) (Ex. 1022) ("Orthoclone").

[6] Aversano et al, *A Chimeric IgG4 Monoclonal Antibody Directed Against CD18 Reduces Infarct Size in a Primate Model of Myocardial Ischemia and Reperfusion*, 25 JACC 781–8 (1995) (Ex. 1023) ("Aversano").

Petitioner relies also on the Declaration of Christian Schöneich, Ph.D. (Ex. 1002), as well as the Declaration of Staley Brod, M.D. (Ex. 1011).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the Specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–2145 (2016) (upholding the use of the broadest reasonable interpretation standard). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We determine that, for purposes of this Decision, none of the terms in the challenged claims require express construction at this time. *See, e.g. Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy).

B. Obviousness over Van Oosten or Zenapax and Sorbera

Petitioner asserts that claims 1–16, 21, and 22 are rendered obvious by van Oosten or Zenapax as combined with Sorbera. Pet. 19–43. Petitioner presents a claim chart for claim 1. *Id.* at 20–22. Patent Owner contends that Petitioner has not shown a reasonable likelihood that the claims are rendered obvious by van Oosten or Zenapax as combined with Sorbera. Prelim. Resp. 6–49.

i. Overview of van Oosten (Ex. 1014)

van Oosten "treated two rapidly progressive [multiple sclerosis ("MS")] patients with intravenous infusions of a humanized mouse monoclonal anti-TNF antibody (cA2)." Ex. 1014, Abstract. According to van Oosten:

> The cA2 antibody was supplied by Centecor, Inc. (Malvern, PA) as a sterile, vialed product. *Each vial contained 20 ml of a solution of 10.0 mg/ml cA2 in 0.15 M sodium chloride, 0.01 M sodium phosphate, 0.01% polysorbate 80, pH 7.2*. This murine-human chimeric monoclonal anti-TNF antibody was constructed by joining the antigen-binding variable regions of a murine monoclonal IgG antibody (A2), which is secreted by the murine hybridoma cell line C134A and binds with high affinity to natural and recombinant human TNF alpha, to the constant regions of a human IgG1 kappa immunoglobulin. This was done in order to lessen a potential human anti-mouse response. Also, the chimeric antibody might be expected to have better effector function and a longer serum half-life.

Id. at 1532[7] (emphasis added).

The authors concluded, bearing in mind the small sample size, that the study provided "evidence that intravenous treatment of MS patients with the anti-TNF antibody cA2 may lead to intrathecal immune activation and may . . . be harmful for MS patients. *Id.* at 1533.

ii. Overview of Zenapax (Ex. 1024)

Zenapax is an excerpt from the Physician's Desk reference ("PDR"), discussing a Zenapax ("Daclizumab") sterile concentrate for injection. Ex. 1024, 2696. According to the reference, Zenapax "is an immunosuppressive, humanized IgG1 monoclonal antibody produced by

[7] The page numbers used in this Decision refer to the page numbers of the original reference, unless otherwise indicated.

recombinant DNA technology that binds specifically to the alpha subunit . . . of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes." *Id.* The antibody "is supplied as a clear, sterile, colorless concentrate for further dilution and intravenous administration," wherein each milliliter "contains 5 mg of Daclizumab and 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, 0.2 mg polysorbate 80 and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9." *Id.*

iii. Overview of Sorbera (Ex. 1019)

Sorbera discusses natalizumab, and its use in the treatment of idiopathic inflammatory bowel disease ("IBD") and MS. Ex. 1019, 917. According to Sorbera, Natalizumab is an "[i]mmunoglobulin G 4 (human-mouse monoclonal AN100226 γ-chain anti-human integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer." *Id.* at Abstract. Sorbera discusses the safety and pharmacokinetics of a single-dose of natalizumab of 0.03, 0.1, 0.3, 1, or 3 mg/kg, intravenous. *Id.* at 918.

iv. Analysis

Petitioner relies on van Oosten and Zenapax for teaching "an IgG [monoclonal antibody ("mAb")] formulation comprising the identical excipients recited by the claims – phosphate buffer, sodium chloride and polysorbate 80." Pet. 19–20. Petitioner acknowledges that neither van Oosten nor Zenapax teach a formulation with natalizumab, asserting that Sorbera cures that deficiency, as it teaches that "natalizumab, like the infliximab of van Oosten, is an IgG mAb that is useful for treating [Crohn's

disease]." *Id.* at 20. According to Petitioner, the "actives qualify as simple substitutes under the case law." *Id.*

As to the claim limitation that the pharmaceutical formulation comprises "from about 20 mg/ml to about 150 mg/ml of natalizumab," Petitioner relies on the teaching of van Oosten that the vial contain 10 mg/ml of antibody, the teaching of Zenapax that each milliliter contains 5 mg of antibody (i.e., 5 mg/ml), and the teaching of Sorbera of intravenous infusions of 3mg/kg of antibody. *Id*. at 21. In order to reach the concentration of antibody required by the claim of at least 20 mg/ml, Petitioner asserts that "that is nothing more than routine optimization of a result effective variable." *Id.* at 27. Specifically, according to Petitioner:

> While van Oosten and Zenapax include IgG mAb concentrations of 10 mg/ml and 5 mg/ml, respectively (Ex. 1014 at 5[8]; Ex. 1024 at 2), 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 ¶ 109; Ex. 1011 at ¶ 27.)

Id. at 28 (footnote added).

In particular, Petitioner contends:

> 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 ¶ 110 (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,

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[8] The page number referenced by Petitioner refer to the numbering of the pages of the exhibit added by Petitioner in the lower right hand corner of the pages of the exhibit.

> 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 ¶ 111.) 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 ¶¶ 26–27.)

Id.

Patent Owner responds "there was overwhelming scientific evidence in 2003, and still today, that achieving a stable liquid formulation of a monoclonal antibody was an unpredictable and highly antibody-specific challenge." PO Resp. 6. In particular, Patent Owner argues that "the art taught that stable, high-concentration (*e.g.*, 20 mg/mL) liquid antibody formulations, like the formulations recited in the '236 patent, were particularly difficult to achieve." *Id.* at 6–7 (citing Ex. 2004, 1394 (noting that therapeutic formulations having greater than10 mg/mL protein are considered highly concentrated)). In fact, Patent Owner contends, Petitioner fails "to identify *any* stable, high concentration antibody formulation in the prior art." *Id.* at 7 (quoting Pet. 15, Table 1, which shows the claims require from about 20 mg/ml to 150 mg/ml, whereas the closest prior art, van Oosten, teaches 10 mg/ml).

Patent Owner argues further that Petitioner has failed to demonstrate that it would be only a matter of routine optimization to formulate natalizumab at a concentration of about 20 mg/ml to about 150 mg/ml. *Id.* at 26–30. Specifically, Patent Owner argues that "Petitioner fails to cite *any* prior art reference that discloses a range of natalizumab concentrations that includes or overlaps with the claimed range of 'about 20 mg/ml to about 150 mg/ml.'" *Id.* at 29. Moreover, Patent Owner contends, "Gordon

(Ex. 1017 at 7), which discloses a natalizumab formulation, is four times *less* concentrated than the lowest claimed level of 20 mg/mL." *Id.*

Patent Owner asserts that Petitioner's declarant, Dr. Schöneich, relies on Gordon (Ex. 1017) and Cummins (Ex. 1021) to support his contention that IgG formulations between 5 and 50 mg/ml were known. *Id.* at 34 (citing Ex. 1002 ¶ 106). According to Patent Owner, however, Gordon does not disclose a high concentration natalizumab formulation, and Cummins discloses a mixture of IgG antibodies against HIV1. *Id.* Cummins, Patent Owner argues, "does not provide any information about natalizumab, a buffer, pH, or the need for polysorbate 80, let alone the amount, or concentration of a particular component claimed by the '236 patent." *Id.* Moreover, the one formulation of Cummins that has 50 mg/ml is in saline for in vitro testing, and Petitioner presents no evidence as to its stability. *Id.* Thus, Patent Owner argues, Cummins and White (Ex. 1020), which was also cited by Petitioner, are directed to different antibodies, and Petitioner does not explain why the ordinary artisan would use those formulation concentrations for a natalizumab formulation. *Id.* at 45.

As to Petitioner's calculations based in Sorbera, Patent Owner argues that Dr. Brod, one of Petitioner's declarants, states that "the concentration of natalizumab is not important from the stand-point of administration as partial, single or multiple vials can be added to an intravenous bag in order to provide the proper dose." *Id.* at 40 (quoting Ex. 1011 ¶ 27). Thus, Patent Owner contends, Dr. Brod in fact supports that a desired dosing would not have taught or suggested a particular formulation concentration to the ordinary artisan. *Id.*

After considering the Petition, Preliminary Response, and evidence of record, we conclude that Petitioner has failed to demonstrate a reasonable likelihood that the challenged claims are rendered obvious by van Oosten or Zenapax as combined with Sorbera. Petitioner has failed to provide sufficient and credible evidence that the combination renders obvious a natalizumab formulation containing about 20 mg/ml to about 150 mg/ml of natalizumab.

Specifically, both van Oosten and Zenapax, which Petitioner characterizes as having the "identical excipients" required by the challenged claims (Pet. 20), contain less than 20 mg/ml of the antibody. The concentration of antibody in van Oosten in 10 mg/ml (Ex. 1014, 1532), and the concentration in Zenapax is 5 mg/ml (Ex. 1024, 2696).

Petitioner also cites to several references, not specifically relied upon in the instant challenge, to demonstrate that "IgG formulations containing between 5 and 50 mg/ml were known in the art." Pet. 28 (citing Ex. 1017, 7; Ex. 1020, 16; Ex. 1021, 6; Ex. 1002 ¶ 109; Ex. 1011 ¶ 27). Petitioner has not demonstrated sufficiently that the adjustment of natalizumab concentration to 20 mg/ml would have been a matter of routine optimization based on any of these other references.

Gordon (Ex. 1017), which Petitioner relies upon in the challenge discussed below, teaches a 5 mg/ml formulation, which is then used to deliver a 3 mg/kg infusion. Ex. 1017, 269. Gordon does not suggest the desirability or need for a higher IgG concentration.

Although White includes entries for Sigma F 7381, Sigma F 9636, and Sigma F 7256, wherein each antibody solution contains approximately 20 mg/ml of protein, White also teaches that each of those antibodies are

conjugated to FITC, and that each antibody is in a solution of phosphate buffered saline at a pH of 7.4, containing sodium azide as a preservative. Ex. 1020,110. Neither Petitioner nor its declarants explain sufficiently how the concentration of an unrelated FITC-conjugated antibody in a solution containing sodium azide as a preservative may be extrapolated to the concentration of the natalizumab antibody, which is not conjugated to FITC, in the claimed formulation.

Cummins (Ex. 1021), as noted by Patent Owner (Prelim. Resp. 34), discloses a mixture of IgG antibodies against HIV1. Ex. 1021, 1111. Cummins teaches a "5% protein solution in normal saline as a sterile, nonpyrogenic solution." *Id.* Again, neither Petitioner nor its declarants provide a sufficient explanation as to how a mixture of IgG antibodies against HIV1 in a normal saline may be extrapolated to the concentration of the natalizumab antibody required in the claimed formulation.

Petitioner also relies on the Declaration of Dr. Schöneich, who testifies:

> Cummins discloses a 5% (50 mg/mL) IgG solution in "normal saline." (Id. at 6.) Cummins states "[t]he purity and integrity of the product in the absence of stabilizing agents was supported by a minimum of 12 months stability (0° to 8°C storage) with no changes detected in pH, [or] percentage of monomeric IgG." (Id. at 8.)

Ex. 1002 ¶ 79. As discussed above, however, Dr. Schöneich does not explain how a mixture of IgG antibodies against HIV1 in a normal saline may be extrapolated to the natalizumab antibody in the claimed formulation.

As to Petitioner's arguments based on the teaching of Sorbera that 3 mg of natalizumab per kg of body weight (3 mg/kg) is therapeutically effective (Pet. 27–28), Gordon also teaches a 3 mg/kg infusion, but uses a

5 mg/ml formulation. Ex. 1017, 269. Petitioner again relies on the Declaration of Dr. Schöneich, who testifies:

> Sorbera discloses that 3 mg of natalizumab per kg of body weight (3 mg/kg) is therapeutically effective. (Sorbera, Ex. 1019 at 3.) Because the average adult male weighs 78.5 kg (SD = ± 11.8 kg), 235.5 mg (3 mg/kg * 78.5 kg) of natalizumab would have been considered necessary for a single treatment. (Mikulandra, Ex. 1037 at 6, Table 1.) In my review of the 54th edition of the Physician's Desk Reference, focusing on aqueous pharmaceuticals approved by FDA prior to February 10, 2003 I found that the formulations were available in stoppered vials in a number of different volumes including, for example, 5, 10, 20, 25 and 50 mls. (Zenapax, Ex. 1024; Xylocaine, Ex. 1027; Naropin, Ex. 1028.)

Ex. 1002 ¶ 110.

Zenapax (Ex. 1024), the only antibody solution referenced by Dr. Schöneich, contains 25 mg/ 5 ml (5 mg/ml) of antibody. Xylocaine (Ex. 1027) and Naropin are both small molecule drugs, and Dr. Schöneich does not explain why the ordinary artisan would look to those teaching in formulating the claimed antibody solution. Moreover, other than stating that vials for aqueous protein formulations come in a range of different volumes, including, for example, 5, 10 and 50 ml, Petitioner does not point to any evidence that sufficiently demonstrates that the ordinary artisan would have quadrupled the amount of natalizumab in the formulation taught by Gordon, or the daclizumab antibody in the formulation of Zenapax, to achieve at least about 20 mg/ml of natalizumab as required by the challenged claims.

Thus, for the reasons set forth above, we conclude that Petitioner has failed to demonstrate a reasonable likelihood that claims 1–16, 21, and 22 are rendered obvious by the combination of van Oosten or Zenapax as combined with Sorbera.

C. Obviousness over Gordon and Orthoclone or Aversano

Petitioner asserts that claims 1–16, 21, and 22 are rendered obvious by Gordon as combined with Orthoclone or Aversano. Pet. 43–58. Petitioner presents a claim chart for claim 1. *Id.* at 44–46. Patent Owner contends that Petitioner has not shown a reasonable likelihood that the claims are rendered obvious by Gordon as combined with Orthoclone or Aversano.
Prelim. Resp. 49–63.

i. Overview of Gordon (Ex. 1017)

Gordon discusses a trial in which thirty patients with Crohn's disease received a 3 mg/ml infusion of natalizumab. Ex. 1017, Abstract. Gordon teaches that natalizumab at a concentration of 5 mg/ml "was formulated in a solution of 50 mmol/L histidine buffer and 0.02% polysorbate 80 adjusted to pH 6 with hydrochloric acid and diluted to 100 mL in 0.9% saline for administration." *Id.* at 269.

ii. Overview of Orthoclone (Ex. 1022)

Orthoclone is an excerpt from the PDR, and teaches that Orthoclone sterile solution "is a murine monoclonal antibody to the CD3 antigen of human T cells which functions as an immunosuppressant." Ex. 1022, 1837. According to Orthoclone, "[e]ach 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution" in a "buffered solution (pH 7.0 $\pm$0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg), sodium chloride (43 mg), and polysorbate 80 (1.0 mg) in water for injection." *Id.*

iii. Overview of Aversano (Ex. 1023)

Aversano teaches administration of a chimeric monoclonal antibody directed against CD18 to primates that are a model for myocardial ischemia and reperfusion. Ex. 1023, Abstract. The antibody "was supplied as a

sterile, nonpyrogenic solution of 5 mg of monoclonal IgG4 per milliliter of buffer solution containing 0.15 mol/liter of sodium chloride, 0.01 mol/liter of sodium phosphate and 0.01% of polysorbate 80 at pH 6.5." *Id.* at 782.

iv. Analysis

Petitioner relies on Gordon for its teaching of a "natalizumab formulation containing all of the claimed excipients, with the exception of histidine buffer in place of phosphate buffer." Pet. 43. Petitioner then relies on Orthoclone and Aversano for teaching the excipients required by the challenged claims. *Id.* at 43–44. According to Petitioner, "[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[9] reported that formulations containing histidine buffer combined with polysorbate 80 impair the biological activity of an IgG mAb." *Id.* at 44 (footnote added).

As to the claim limitation that the pharmaceutical formulation comprises "from about 20 mg/ml to about 150 mg/ml of natalizumab," Petitioner contends that "[a]lthough 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." *Id.* at 48. Petitioner incorporates by reference its discussion of this limitation from the challenge over van Oosten or Zenapax as combined with Sorbera. *Id.* Thus, for the reasons set forth with respect to that challenge, discussed above, we determine that Petitioner has failed to

[9] Subramanian et al., *Effect of Histidine Oxidation on the Loss of Potency of a Humanized Monoclonal Antibody*, 3 AAPS PHARMSCI SUPP. S-29, Abstract M2154 (2001) (Ex. 1026) ("Subramanian").

demonstrate a reasonable likelihood that the challenged claims are rendered obvious by Gordon as combined with Orthoclone or Aversano.

Thus, for the reasons set forth above, we conclude that Petitioner has failed to demonstrate a reasonable likelihood that claims 1–16, 21, and 22 are rendered obvious by Gordon as combined with Orthoclone or Aversano.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–16, 21, and 22 of the ’236 patent are unpatentable under 35 U.S.C. §103(a).

IV. ORDER

In consideration of the foregoing, it is

ORDERED that the Petition is DENIED and no trial is instituted.

PETITIONER:

Jeremy Lowe
jlowe@axinn.com

PATENT OWNER:

Andrea Reister
areister@cov.com

Jennifer Robbins
jrobbins@cov.com