Trials@uspto.gov
571-272-7822

Paper No. 11
Entered: February 3, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SWISS PHARMA INTERNATIONAL AG,
Petitioner,

v.

BIOGEN IDEC,
Patent Owner.

Case IPR2016-00916
Patent 8,900,577 B2

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

GREEN, *Administrative Patent Judge*.

DECISION
Denying Petitioner's Request for Rehearing
37 C.F.R. § 42.71

Petitioner filed a Request for Rehearing (Paper 8, "Reh'g Req.") of our Decision denying institution of *inter partes* review (Paper 7, "Decision" or "Dec.") of claims 1, 3–7, and 9–12 of U.S. Patent No. 8,900,577 B2 (Ex. 1001, "the '577 patent"). We deny Petitioner's Request for Rehearing for the reasons set forth below.

STANDARD OF REVIEW

When reconsidering a decision on institution, the Board reviews the decision for an abuse of discretion. *See* 37 C.F.R § 42.71(c). An abuse of discretion occurs if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors. *See Star Fruits S.N.C. v. United States*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004); *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000). "The burden of showing that a decision should be modified lies with the party challenging the decision." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,768 (Aug. 14, 2012). In its request for rehearing, the dissatisfied party must, in relevant part, "specifically identify all matters the party believes the Board misapprehended or overlooked." 37 C.F.R. § 42.71(d); Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,768. We address Patent Owner's arguments with these principles in mind.

ANALYSIS

The challenged claims are directed "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." Ex. 1001, 18:41–45 (Claim 1) (emphasis added).

In our Decision, we determined that Petitioner had failed to establish sufficiently for purposes of institution that the combination of van Oosten or Zenapax and Sorbera rendered obvious a natalizumab formulation containing "about 20 mg/ml to about 150 mg/ml of natalizumab." Dec. 10–13.[1] In particular, we noted that the compositions taught by both van Oosten and Zenapax, which Petitioner characterized as having the "identical excipients" required by the challenged claims (Pet. 20), contain less than 20 mg/ml of an antibody that is not natalizumab. *Id.* at 11. Petitioner relied on Sorberra for its teaching of natalizumab, as well as its teaching that 3 mg of natalizumab per kg of body weight (3 mg/kg) is therapeutically effective. *Id.* at 12–13 (citing Pet. 27–28).

We reviewed also the additional multiple references relied upon by Petitioner in its attempt to establish that a formulation containing about 20 mg/ml to about 150 mg/ml of natalizumab would have been obvious to the ordinary artisan, as well as the analysis of Dr. Schöneich as to the volume of vials that were available for use to store therapeutics, including the small molecule drugs Xylocaine and Naropin. *Id.* at 11–13. Specifically, we determined that none of the references relied upon by Petitioner established a reasonable likelihood that the higher natalizumab concentration required by the challenged claims would have been rendered obvious by that prior art. *Id.* at 10–13.

[1] We also denied to institute on the obviousness challenge over Gordon and Orthoclone or Aversano, as Petitioner had incorporated by reference its arguments based on van Oosten or Zenapax and Sorbera. Dec. 15.

Petitioner contends in its Request for Rehearing that we erred by misapprehending or overlooking two issues raised by the Petition: 1) We overlooked "critical legal precedent that motivation is inherent when the doctrine of routine optimization applies to claimed variables, as it does here to concentration," and 2) "[E]ven if specific motivation to increase prior art concentrations of natalizumab is necessary, the Board misapprehended and overlooked Petitioner's evidence supporting such motivation as well as regulations requiring it to view evidence in the light most favorable to Petitioner." Reh'g Req. 1–2 (emphasis removed). We address each in turn below.

i. Doctrine of Routine Optimization

According to Petitioner, "the doctrine of routine optimization itself provides the requisite motivation to modify a prior art result effective variable, like concentration, in order to achieve a specifically claimed concentration. No additional and separate showing of motivation is necessary." *Id.* at 3. Petitioner argues that Gordon teaches a concentration of 5 mg/ml of natalizumab, and, thus, "the controlling law provides that a skilled artisan would naturally or inherently seek to routinely optimize that value." *Id.* at 1. Stated differently, Petitioner argues that "a motivation to zero in on a claimed concentration is unnecessary where, as here, the prior art already teaches one or more concentrations subject to routine optimization." *Id.* According to Petitioner, "the Board should have concluded as a matter of law that a skilled artisan would naturally or inherently vary prior art natalizumab concentrations to discover what is an optimum or workable range." *Id.* at 2.

Petitioner analyzes *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), arguing that the court, rather on focusing on whether there would be a reason to increase concentration of acid used in the reaction, "instead analyzed whether the claimed subject matter provided unexpected results differing in kind rather than degree, i.e., criticality." Reh'g Req. 4–5. Petitioner cites further a non-published case, *Gentiluomo v. Brunswick Bowling & Billiards Corp.*, 36 F. App'x 433, 435 (Fed. Cir. 2002), to support its contention that the Court of Appeals for the Federal Circuit continues to apply the reasoning set forth in *Aller*. Reh'g Req. 5–6.

According to Petitioner, our Decision does not mention either *Aller* or *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003), nor does it state that the concentration yielded unexpected results, but denies institution "on the absence of a motivation to modify the known 5 mg/ml natalizumab concentration of Gordon by increasing it to 20 mg/ml." *Id.* at 6. Moreover, Petitioner asserts, our reasoning that "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" has been rejected by the Federal Circuit in *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 734, 737 (Fed. Cir. 2013). Reh'g Req. 7–8 (quoting Dec. 13). In particular, Petitioner asserts that "the Federal Circuit refused to burden the routine optimization inquiry with the need to show a specific motivation to triple a known prior art concentration." *Id.* at 7.

We have reconsidered our Decision in light of Petitioner's argument, but conclude that Petitioner has not established that we abused our discretion in denying the Petition. In the claim chart addressing the limitation "from

about 20 mg/ml to about 150 mg/ml of natalizumab," Petitioner pointed to the following:

> **van Oosten:** "Each vial contained . . . 10.0 mg/ml cA2. . . ." (Ex. 1014 at 5.)
> **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.)

Pet. 21–22.

Addressing that limitation in the Petition, Petitioner stated:

> With respect to the "from about 20 mg/ml to about 150 mg/ml" limitation – that 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 pharmaceuticals 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.)

Id. at 27–28 (emphasis added).

As noted in our Decision, however, Petitioner failed to demonstrate that the adjustment of the concentration of natalizumab would have been only routine optimization. Dec. 11. Gordon teaches a 5 mg/ml formulation of natalizumab. *Id.* The other references relied upon by Petitioner to establish that "IgG formulations containing between 5 and 50 mg/ml were known in the art" do not relate to natalizumab, nor are they limited to the claimed excipient, and Petitioner does not address our concern as to how the concentrations of those antibodies could be extrapolated to natalizumab in the claimed excipient. *Id.* at 11–12 (quoting Pet. 27–28). In fact, the references relied upon by Petitioner to teach the claimed excipient, contained 10 mg/ml (van Oosten) or 5 mg/ml (Zenepax) of antibody. *Id.* at 11. Moreover, Petitioner does not address our concern that two of the three references relied upon by Dr. Schöneich to establish that stoppered vials in different sizes were known related to small molecule drugs, and the one that related to antibodies, Zenepax, contained 5 mg/ml of antibody. *See* Dec. 13.

Neither *Aller* nor *Peterson* help Petitioner's analysis. In *Aller*, the claims were drawn to the treatment of isopropyl benzene hydroperoxide with sulfuric acid, with the hydroperoxide decomposing into phenol or acetone. 220 F.2d at 455. The process of the rejected claims was identical to that of the prior art, except that the claims specified lower temperatures and higher sulfuric acid concentrations. *Id.*

The court held that "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." *Id.* at 456. The court noted, however, that "changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Id.* In concluding that the patentability of the claims was not demonstrated, the court noted that "[a]ny chemist reading the article could logically assume that higher yields might be obtainable, and by experimentally varying the conditions of temperature and acidity could find the most productive conditions." *Id.* at 458.

In *In re Antonie*, 559 F.2d 618 (CCPA 1977), the court noted, however, that the variable to be optimized had to be recognized as a result effective variable. *Id.* at 620. In the instant case, Petitioner only suggests changing the concentration of the antibody to allow it to be stored in known vials. Petitioner does not explain, however, how merely adding a sufficient concentration of natalizumab to a known vial is a result effective variable. As noted by Patent Owner (Prelim. Resp. 40), Dr. Brod testified 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 administer an efficacious dose." Ex. 1011 ¶ 20. Thus, although the testimony may be read as demonstrating that the concentration is not critical, it also demonstrates that the concentration of the antibody in terms of its storage was not recognized as a result effective variable.

In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003), dealt with ranges. In particular, the court noted that "[a] *prima facie* case of obviousness typically exits when the ranges of a claimed composition

overlap the ranges disclosed in the prior art." *Id.* The only range offered by Petitioner in the instant proceeding is "IgG formulations containing between 5 and 50 mg/ml were known in the art," but, as discussed above, the formulations at the higher end do not relate to natalizumab, nor are they limited to the claimed excipient, and Petitioner does not address our concern as to how the concentrations of those antibodies could be extrapolated to natalizumab in the claimed excipient.

Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731 (Fed. Cir. 2013), does not persuade us otherwise. In that case, the district court's determination that Tolmar had failed to provide motivation to triple the concentration of the active ingredient from 0.1% to 0.3% was determined to be in error because the Federal Circuit determined that there was no requirement to start from the commercial embodiment containing 0.1%, and the prior art "teaches a range that encompasses both the prior art commercial embodiment and the claimed invention." *Id.* at 737. As discussed above, Petitioner has not demonstrated that the ordinary artisan would have understood that the range of IgG formulations containing between 5 and 50 mg/ml to be applicable to formulations of natalizumab in the claimed excipient.

We determine, therefore, that we did not overlook the "critical legal precedent that motivation is inherent when the doctrine of routine optimization applies to claimed variables, as it does here to concentration;" as asserted by Petitioner in its Rehearing Request. Reh'g Req. 1.

ii. Board Overlooked Evidence and Violated Its Own Regulations

Petitioner also contends that we "overlooked or misapprehended Petitioner's reliance on the high concentration of natalizumab required for

therapeutic efficacy, i.e., 235 mg, which would have motivated a person of ordinary skill to explore increasing prior art concentrations of 5 mg/ml to higher levels." Reh'g Req. 2. According to Petitioner, Dr. Schöneich testified that vials come in a range of different sizes, and, thus, "the person of ordinary skill would explore a range of higher concentrations for these different vials, including but not limited to the claimed concentration." *Id.* at 9 (citing Pet. 27–28, Ex. 1002 ¶ 108). According to Petitioner, we failed to address those arguments in our analysis. *Id.* at 9–10.

Petitioner contends that if we had taken the testimonial evidence of Dr. Brod and Dr. Schöneich, which demonstrates that the ordinary artisan "would have been motivated to seek a higher concentration of natalizumab because of well-known dosages and the need to store natalizumab concentration in available vials," in the light most favorable to Petitioner, we would have found that their statements demonstrate that the claimed concentration ranges are not critical given the storage and administration practices. *Id.* at 11–12. By not doing so, Petitioner asserts we abused our discretion in denying the Petition. *Id.* at 12.

Petitioner asserts moreover that to the extent we considered Dr. Brod's testimony, we viewed his evidence of no criticality as evidence of no motivation to achieve a specific concentration. *Id.* at 11. That statement, Petitioner asserts, "turns the doctrine of routine optimization on its head." *Id.* That is, Petitioner contends, "[t]o the extent routine optimization requires the absence of criticality, such evidence cannot also be proof of no motivation. Otherwise, no case for routine optimization could ever succeed because every time a petitioner presented evidence of no criticality, there would also be no motivation." *Id.*

We disagree. We noted in our decision that similarly to Soberra, Gordon also taught a 3 mg/ml infusion, and used a 5 mg/ml formulation. Dec. 12. We then looked at the references relied upon by Dr. Schöneich in establishing that formulations were available in stoppered vials in a number of different volumes. *Id.* at 12–13. We noted that only one antibody solution was referenced by Dr. Schöneich, and that antibody solution contained 5 mg/ml of antibody. *Id.* at 13. The other references were directed to small molecule drugs, and we noted that Dr. Schöneich did not explain why the ordinary artisan would look to those references when formulating an antibody solution. *Id.* The fact that Petitioner may not agree with our consideration of the evidence does not mean that we overlooked that evidence, or that we misapprehended it.

Petitioner argues moreover that we "viewed Dr. Brod's testimony in a light most favorable to Patent Owner, contrary to the requirements of 37 C.F.R. § 42.108(c)." Reh'g Req. 2. Contrary to our apparent understanding of Dr. Brod's testimony, Petitioner argues that "Dr. Brod was not speaking about the absence of a motivation to explore different concentrations for storage, but rather about the absence of a critical concentration of natalizumab." *Id.* at 10.

Again, Petitioner's arguments in its Rehearing Request do not convince us that we misapprehended or overlooked any evidence, such that we abused our discretion in denying institution.

37 C.F.R. § 42.108 relates to institution of *inter partes* review. 37 C.F.R. § 42.108(c) states:

> *Sufficient grounds. Inter partes* review shall not be instituted for a ground of unpatentability unless the Board decides that the petition supporting the ground would demonstrate that there is a

> reasonable likelihood that at least one of the claims challenged in the petition is unpatentable. The Board's decision will take into account a patent owner preliminary response where such a response is filed, including any testimonial evidence, but a genuine issue of material fact created by such testimonial evidence will be viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an *inter partes* review. A petitioner may seek leave to file a reply to the preliminary response in accordance with §§ 42.23 and 42.24(c). Any such request must make a showing of good cause.

37 C.F.R. § 42.108(c), therefore, applies to those situation in which patent owner submits testimonial evidence to support its preliminary response. In those situations where that testimonial evidence creates an issue of material fact, the evidence will be considered in the light most favorable to the petitioner. Patent Owner did not submit any such testimonial evidence in support of its Preliminary Response in the instant proceeding.

Moreover, the rule does not relieve Petitioner of its burden of demonstrating in its Petition a reasonable likelihood that at least one of the challenged claims is unpatentable, such that *inter partes* review may be instituted. In the instant proceeding, for the reasons discussed in the Decision, we determined that the Petition failed to make such a showing.

CONCLUSION

We have considered Petitioner's request for rehearing, but are not persuaded that we abused our discretion in declining to institute an *inter partes* review.

ORDER

It is

ORDERED that Petitioner's request for rehearing of the Decision instituting an *inter partes* review of claim 1, 3–7, and 9–12 of U.S. Patent No. 8,900,577 B2 is *denied*.

FOR PETITIONER:

Jeremy Lowe
AXINN, VELTROP & HARKRIDER LLP
jlowe@axinn.com

FOR PATENT OWNER:

Andrea Reister
Jennifer Robbins
COVINGTON & BURLING LLP
areister@cov.com
jrobbins@cov.com