UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,

Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.,

Patent Owner

Case IPR2016-01018
Patent No. 9,114,166 B2

Coherus's Request for Rehearing Under 37 C.F.R. § 42.71(d)

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Pursuant to 37 C.F.R. § 42.71(d), Coherus Biosciences Inc. ("Petitioner") hereby requests rehearing of the Board's Decision denying institution of *Inter Partes* Review of U.S. Patent No. 9,114,166 ("the '166 patent"), assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner"), entered November 7, 2016 (Paper No. 10) ("Decision").

I. INTRODUCTION

Petitioner respectfully submits that the Board erroneously denied institution because it credited AbbVie's incorrect and unsupported attorney argument over specific sworn testimony from Petitioner's expert, Dr. Manning, essentially impeaching him without a trial and opportunity to respond. Dr. Manning's sworn testimony—and the teachings of Relton itself—demonstrate that a skilled artisan would have reasonably expected success in applying Relton's method for preparing stable, liquid formulations of IgG_1 antibodies at concentrations of 50 mg/ml and higher to the IgG_1 antibody D2E7.

AbbVie offered no expert testimony to the contrary. Instead, it directed the Board to out-of-context statements regarding the difficulties of developing *universal* formulation strategies for *all protein pharmaceuticals*, rather than the teachings of the prior art regarding formulation of the specific subclass of *IgG_1 antibodies*, including D2E7. In relying on AbbVie's cited quotations, the Board

misapprehended the state of the art and overlooked key evidence cited by Petitioner and Dr. Manning.

A fundamental point the Board overlooked or misapprehended in its decision not to institute the IPR is the critical difference between assessing a reasonable expectation of success across a nearly unrestricted genus of proteins, and doing so for a defined subclass of highly-conserved proteins. Specifically, the general prior art statements of Manning and Wang broadly encompass unrelated and structurally diverse categories of pharmaceutical proteins. Relton teaches stable formulations of antibodies in the defined IgG_1 subclass, which have a very high degree of structural similarity. This petition, and the sworn testimony of Dr. Manning on which it relies, are solely focused on the latter. Petitioner respectfully submits that the Board's rationale for assessing predictability, and specifically for deciding whether a POSA would have reasonably expected success in applying Relton to formulating D2E7—an IgG_1 antibody—should not have been grounded in the former.

Dr. Manning explained that *IgG_1 antibodies* are a "highly conserved" subclass with close structural similarities—unlike the vast genus of *protein pharmaceuticals as a whole*. Ex. 1002 ¶¶ 15, 165. Skilled artisans therefore would have had at least a reasonable expectation that the formulation strategies described by Relton would work for other IgG_1 antibodies, including D2E7. *Id.* ¶¶

127-129, 162, 165, 180. Indeed, Relton itself teaches that its method is useful for IgG_1 antibodies generally, and teaches how to optimize its formulations to specific antibodies within that subclass. *Id*. ¶¶ 130 (citing Ex. 1006 at 3:7-17), 158-162. These points were discussed in the Petition at 3-5, 27-32, and 35-38. The documentary evidence thus corroborates Dr. Manning's testimony that a POSA would have reasonably expected success in applying Relton's formulation procedures to the D2E7 antibody disclosed by van de Putte. Petitioner demonstrated a reasonable likelihood of success in proving the challenged claims unpatentable.

The Board's contrary conclusion is not supported by substantial evidence and represents an unreasonable weighing of AbbVie's attorney argument and generalized statements regarding formulation of *all proteins* over Dr. Manning's sworn testimony and evidence of successful formulation of stable, liquid, high-concentration IgG_1 formulations. *Inter Partes* Review should be instituted so that the Board can determine the POSA's reasonable expectation of success based on a full record, including cross-examination of AbbVie experts (if any) and Dr. Manning's responses to AbbVie's arguments.

II. LEGAL STANDARD

A request for reconsideration "must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each

matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d). The Board reviews a request for rehearing of a decision on a petition for an abuse of discretion. *Id.* § 42.71(c). An abuse of discretion may arise if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if an unreasonable judgment is made in weighing relevant factors. *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).

III. THE BOARD MISAPPREHENDED THE STATE OF THE ART AND OVERLOOKED KEY EVIDENCE IN CONCLUDING PETITIONER DID NOT DEMONSTRATE A REASONABLE EXPECTATION OF SUCCESS IN COMBINING RELTON AND VAN DE PUTTE

A POSA would have looked to Relton for guidance on how to prepare a stable, liquid formulation of D2E7 for subcutaneous administration as taught by van de Putte. Pet'n at 3 & 35-38. D2E7 is an IgG_1 antibody, and Relton teaches a strategy for formulation of IgG_1 antibodies, including at concentrations of 50 mg/ml and higher. *Id.*; Ex. 1006 at 3:25-27. The Board's conclusion that a POSA would not have reasonably expected success in combining Relton and van de Putte (Decision at 10) was based on a misapprehension of the state of the art of IgG_1 antibody formulations. This misapprehension was compounded because the Board dismissed the sworn testimony of Dr. Manning in favor of AbbVie's misplaced attorney argument.

A. The Board Misapprehended the State of the Art by Relying on Out-of-Context Statements Regarding Formulation of Proteins *Generally* Over Specific Teachings Regarding IgG_1 Antibodies

AbbVie's Patent Owner Preliminary Response ("POPR") erroneously conflated difficulties in formulating *proteins generally* with the state of the art in formulating the specific subclass of antibodies to which D2E7 belongs: IgG_1. The Board overlooked several key points distinguishing IgG_1s from proteins in general. First, both parties agreed that "IgG_1 is a particular antibody subclass distinct in sequence, physical, and chemical properties from other IgG subclasses and other immunoglobulin classes." POPR at 11. Second, IgG_1 antibodies share a high degree of structural similarity and are "highly conserved as a subclass." Ex. 1002 ¶ 165; *see also* ¶ 15 ("All immunoglobulins of the G subclass, especially IgG_1s[,] exhibit similar tertiary structure …."). Indeed, human IgG_1 antibody sequences are approximately *95% identical* to one another. Ex. 2007 at 5-6 ("[T]he conserved sequences in human IgG_1 antibodies are approximately 95% and the remaining 5% is variable and creates their antigen-binding specificity.").

As Dr. Manning explained, before 2002, other IgG_1 antibodies had been successfully formulated as stable liquid formulations. Ex. 1002 ¶¶ 85, 134-147; Pet'n at 12. Dr. Manning pointed out that "*these different IgG_1 products all have similar formulations* exemplified by acidic pH and similar buffer composition. This would suggest to the skilled artisan that IgG_1 antibodies, in general, could be

stabilized by a common formulation containing a buffer, NaCl as a tonicity modifier, and a polysorbate surfactant." *Id.* ¶ 146 (emphasis added).

The various stable formulations of IgG_1 antibodies, which were achieved using similar formulations, would have given the POSA a reasonable expectation of success in formulating D2E7 using techniques that Relton teaches are useful for IgG_1 antibodies as a subclass. *Id.* ¶ 165 ("[T]he formulations of the marketed liquid monoclonal antibody products in 2002 would have supported the view that *IgG_1 antibodies* could be formulated similarly and validated the teaching of Relton, especially when a POSA considered that IgG_1 antibodies are *highly conserved as a subclass*.") (emphasis added). Dr. Manning recounted how Relton demonstrated the applicability of his technique for preparing high-concentration formulations for different IgG_1 antibodies. *See id.* ¶¶ 120-128. He concluded:

> [A] POSA would have had every reason to believe that Relton's teachings would lead to success in making the claimed formulations. Relton had shown that its formulations worked for multiple IgG_1 antibodies and disclosed that its teachings worked for IgG_1 antibodies in general.

Id. ¶ 162; *see also* Pet'n at 12-13, 35-37.

The Board dismissed Dr. Manning's testimony that there was a reasonable expectation of success in formulating the IgG_1 antibody D2E7 according to Relton, because it misapprehended the state of the art. The Board mistakenly found Dr.

Manning's testimony to be inconsistent with various statements in Dr. Manning's textbook (Ex. 1025) and a review article by Wang (Ex. 1030). *See* Decision at 10-13. These statements from Manning and Wang, however, broadly encompass *unrelated and structurally diverse pharmaceutical proteins*—a genus that is vastly more varied than the IgG_1 subclass of antibodies. The general statements in the prior art on which the Board placed such great reliance are *not* inconsistent with Dr. Manning's testimony; they are inapposite.

The Board overlooked that Chapter 8 of Dr. Manning's textbook (cited heavily in the Decision) is directed to formulation of a "new wave of protein drugs [which] will include compounds that can function as growth factors, act as specific stimulators or suppressors of certain functions or exhibit activities that have not been observed before." Ex. 1025 at 178. Similarly, Wang covers a wide variety of proteins, including "functional regulators and supplements, enzyme activators and inhibitors, poly- and monoclonal antibodies, and various vaccines." Ex. 1030 at 130. The vast class of protein pharmaceuticals addressed by Wang and Manning's textbook is far more diverse than the highly conserved IgG_1 subclass of antibodies discussed in Dr. Manning's Declaration. There is no evidentiary basis for AbbVie's argument, adopted by the Board, that general statements regarding the difficulty of stabilizing a liquid formulation for "most proteins" can be extrapolated to *IgG_1 antibodies* specifically. *See* Decision at 11 (citing Ex. 1025 at

10-11, 184, 188). To the contrary, an article cited by AbbVie explains that "antibodies, on the average, seem to be more stable than other proteins." Ex. 2007 at 8.

The Board mistakenly relied on statements from both Wang and Manning's textbook regarding the difficulty of identifying "universal stabilization strategies" for *proteins as a general class*. Decision at 13 (quoting Ex. 1030 at 130); *see also id.* at 12 (quoting Ex. 1025 at 185). These general statements shed no light on the reasonable expectation of success a POSA would have had in formulating antibodies, like D2E7, in the highly conserved IgG_1 subclass. Neither Manning's textbook nor Wang suggests there was uncertainty regarding formulation requirements *for the IgG_1 subclass of antibodies*. To the contrary, when describing protein stability characteristics, Wang refers to IgGs as a single class of proteins, suggesting that all IgGs have similar stability characteristics. Ex. 1030 at 135.

Tellingly, AbbVie's POPR never directly addresses or contradicts the teachings of Relton by addressing variability of stability within the IgG_1 subclass specifically. AbbVie only cited art discussing more general classes of proteins or antibodies. *See, e.g.*, POPR at 34-35.

The Board cited the statement in Dr. Manning's textbook chapter that "[e]ven for closely related proteins, the relative stability and major pathways for degradation might be quite different." Decision at 12 (quoting Ex. 1025 at 185-86). This statement does not contradict Dr. Manning's sworn testimony. First, the

"closely related" proteins referenced in the statement are not proteins in the highly conserved IgG_1 subclass. Moreover, the Board overlooked that the next sentences of Dr. Manning's text explain that any such stability and degradation differences are addressed through preformulation studies of, for example, "pH, protein concentration, ionic strength, buffer composition and temperature." Ex. 1025 at 186. The Manning textbook conveys that these are routine studies that can be leveraged for "speedy formulation development." *Id.* This is consistent with the teachings of Relton and Dr. Manning's Declaration to perform routine studies to optimize the formulation pH for the specific antibody. Ex. 1002 ¶ 91, 128-129; Ex. 1006 at 4:24-34; Pet'n at 28-31, 36, 45. Moreover, because the sequence and isoelectric point (pI) for D2E7 were known, a POSA could have predicted the appropriate pH to avoid degradation and instability of D2E7. Ex. 1002 ¶¶ 95-101; Pet'n at 41-44.

AbbVie argued that the D2E7 antibody differs in amino acid sequence and binding properties from the antibodies formulated by Relton. POPR at 33-34. While Petitioner and Dr. Manning never disputed that some such differences exist, AbbVie failed to explain that the sequence differences between IgG_1 antibodies occur almost exclusively in the "complementarity determining regions (CDRs)" responsible for recognizing antigen. *See* Ex. 1002 ¶¶ 15-16. These represent a very small fraction of the overall protein sequence. *Id.*; *see also* Ex. 2007 at 6

(indicating that human IgG_1 antibody sequences are 95% conserved). For this reason, a POSA would have reasonably expected a formulation and stabilization strategy that was shown to be successful for multiple antibodies in the IgG_1 subclass also to be successful for another antibody in that subclass. *See*, *e.g.*, Ex. 1002 ¶¶ 162, 165; Pet'n at 35, 37. There is no reason to believe that a D2E7 IgG_1 antibody differs structurally from the CD4 and CD23 IgG_1 antibodies described by Relton any more than those antibodies differ structurally from each other; the differences in all of them occur principally in the CDR regions that make up only a small percentage of the overall protein structure. *See* Ex. 1002 ¶¶ 15-17.

Moreover, absolute certainty of success is not the standard. "[C]ase law is clear that obviousness 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).

B. The Board Erred in Misapprehending or Overlooking Dr. Manning's Sworn Testimony in Favor of AbbVie's Incorrect Attorney Argument

AbbVie could have filed an expert declaration with its POPR, but elected not to do so. *See* 37 C.F.R. § 42.107(a) (effective May 2, 2016). Instead, AbbVie relied on incorrect attorney argument to contradict Dr. Manning's sworn testimony. The only attempt at factual corroboration of AbbVie's attorney argument was its misplaced reliance on generalizations in the prior art about

formulation approaches across widely differing classes of proteins. Dr. Manning's sworn testimony, by contrast, explains the state of the art specific to IgG_1 antibodies and demonstrates that a POSA would have had a reasonable expectation of success in formulating D2E7. The following chart illustrates how Dr. Manning's testimony specifically contradicts the generalizations relied upon in the Board's decision at AbbVie's urging. All emphasis in the chart is added.

Broad Generalizations Cited in Decision	***Contrary Evidence Specific to IgG_1 Formulations***
"*protein drugs may not* be stable enough to be handled as a liquid formulation" (Decision at 11, quoting Ex. 1025 at 10.) "[i]t can be assumed that *most proteins* will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed" (Decision at 11, quoting Ex. 1025 at 188.)	"the formulations of the *marketed liquid monoclonal antibody products* in 2002 would have supported the view that *IgG_1 antibodies* could be formulated similarly and validated the teaching of Relton, especially when a POSA considered that IgG_1 antibodies are *highly conserved* as a subclass" (Ex. 1002 ¶ 165; Pet'n at 12.) "[T]he literature revealed both a rational approach to follow and *specific example formulations of IgG_1 antibodies*. (D2E7 belongs to the IgG_1 subclass.)" (Ex. 1002 ¶ 85, *see* ¶¶ 134-147; Pet'n at 35-36, 42.)
"[t]he exquisite sensitivity of protein structure, function, and stability to the primary sequence does not readily lend itself to *a generic approach for protein formulation*" (Decision at 12, quoting Ex. 1025 at 185.) "the most formidable challenge in formulating a liquid *protein pharmaceutical* is to preserve the biological activity of the protein for an acceptable shelf life. Unfortunately,	"these different [commercially-available] IgG_1 products all have similar formulations exemplified by acidic pH and similar buffer composition. This would suggest to a skilled artisan that *IgG_1 antibodies, in general, could be stabilized by a common formulation* containing a buffer, NaCl as a tonicity modifier, and a polysorbate surfactant" (Ex. 1002 ¶ 146; *see* Pet'n at 30, 38.) "[A] POSA would have had every reason

there is no *single pathway* to follow in formulating such a product. *Usually, proteins* have to be evaluated on a case-by-case basis." (Decision at 13, quoting Ex. 1030 at 178.)	to believe that Relton's teachings would lead to success in making the claimed formulations. Relton had shown that its formulations *worked for multiple IgG_1 antibodies* and disclosed that its teachings *worked for IgG_1 antibodies in general*." (Ex. 1002 ¶ 162; *see also* ¶¶ 128-129; Pet'n at 37.)
"the *structural differences* among *different proteins* are so significant that generalization of *universal stabilization strategies* has not been successful" (Decision at 13, quoting Ex. 1030 at 130.)	"All immunoglobulins of the G subclass, especially *IgG_1s exhibit similar tertiary structure* …" (Ex. 1002 ¶ 15; Pet'n at 35.) "IgG_1 antibodies are *highly conserved* as a subclass." (Ex. 1002 ¶ 165; Pet'n at 38.)

Dr. Manning was well aware of the teachings in Wang (Ex. 1030) and his textbook (Ex. 1025), as cited in the Decision, at the time that he prepared his Declaration. Both references are cited in his Declaration. *See, e.g.*, Ex. 1002 ¶¶ 7, 69, 80, 85-88, 91-92, 106, 111, 153, 188. It is evident that Dr. Manning did not believe that these references highlighted any uncertainty with regard to formulating antibodies of the IgG_1 subclass, including D2E7. Dr. Manning's opinion took these references into account. Yet, despite the lack of guidance of any expert testimony from AbbVie, and without any opportunity for Dr. Manning to respond or put the inapposite statements from his textbook into context, the Board decided that the references' statements regarding formulation strategies across broad protein classes contradicted Dr. Manning's sworn testimony. *See* Decision at 10-13. Such a conclusion was not warranted.

The most that could possibly be said about the passages quoted in the Decision is that they might raise a factual issue regarding the POSA's reasonable expectation of success. But if any such factual issue exists, it should be resolved based on a complete record, including cross-examination of both Dr. Manning and any experts for AbbVie. *See, e.g.*, *Colas Solutions, Inc. v. Blacklidge Emulsions, Inc.*, IPR2016-01032, Paper No. 9 at 16 (PTAB Nov. 9, 2016) ("At this stage of the proceeding, Patent Owner's documentary evidence and argument raise genuine issues of material fact relating to what Bardesi would have taught and suggested to an ordinary artisan at the time. When determining whether Patent Owner's argument is ultimately persuasive, we prefer to have a full record including any further testimony from Dr. King elicited during the trial."); *Shell Oil Co. v. ExxonMobil Research & Eng'g Co.*, IPR2016-00009, Paper No. 10 at 14 (PTAB Apr. 5, 2016) ("Although Patent Owner raises substantial questions regarding the interpretation of Petitioner's XRD evidence, on this record, *we cannot reject the testimony of Dr. Lobo based upon attorney argument interpreting highly technical evidence*.") (emphasis added).

Notably, if AbbVie had presented its arguments through expert testimony, it would have triggered the rule requiring the factual disputes to be resolved in the light most favorable to Petitioner at the institution stage. 37 C.F.R. § 42.108(c) ("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."); *see also WhatsApp Inc. v. TriPlay, Inc.*, IPR2016-00718, Paper No. 17 at 16 (PTAB Sept. 8, 2016) ("[I]t would be premature for us to weigh the declarants' testimony before either declarant is deposed….").

AbbVie's attorney argument should not have been given *greater* weight than expert testimony submitted by a Patent Owner at the pre-institution stage. The sound reasons that led the Office to adopt a presumption favoring the Petitioner in the event of factual disputes involving testimonial evidence are equally applicable here. Denial of a petition is "final and nonappealable." 35 U.S.C. § 314(d). As the Office has stated, "[a] presumption in favor of petitioner for disputed facts, which may be fully vetted during a trial when cross-examination of declarants is available, is appropriate given the effect of denial of a petition." 81 Fed. Reg. 18750, 18756 (Apr. 1, 2016), Resp. to Comment 4.

C. The Board Overlooked that Relton is Presumed Enabling

Neither AbbVie nor the Board addressed Petitioner's argument that there is a presumption that Relton is enabled for both "claimed and unclaimed" disclosures. Pet'n at 36-37 (quoting *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d

1313, 1354-56 (Fed. Cir. 2003)). This is a key point that the Board overlooked.

Relton discloses a method for formulating the subclass of IgG_1 antibodies at concentrations including 50 mg/ml. The '166 patent claims a *species* of that subclass: D2E7. Because D2E7 is within the subclass taught by Relton, Relton must be presumed enabling for the D2E7 formulation. The burden was on AbbVie to show that a POSA would not have been able to formulate D2E7 as disclosed by Relton. AbbVie failed to do so. This illustrates that the state of the art included an enabling disclosure of a method for preparing stable, liquid, high-concentration formulations of IgG_1 antibodies. A POSA therefore would have expected success in applying Relton's formulation to D2E7. The Board misapprehended or overlooked this point.

IV. CONCLUSION

For all of the foregoing reasons, Petitioner respectfully requests that the Board grant rehearing and institute trial on the Petition.

Respectfully submitted,

Dated: December 2, 2016

/s/ Louis E. Fogel

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), the undersigned certifies that on December 2, 2016, a complete and entire copy of this COHERUS'S REQUEST FOR REHEARING UNDER 37 C.F.R. § 42.71(d) was provided via email, to the Patent Owner by serving the email correspondence address of record as follows:

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