UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOMENTA PHARMACEUTICALS, INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

Case IPR2015-01537
Patent 8,476,239

PATENT OWNER PRELIMINARY RESPONSE
PURSUANT TO 37 C.F.R. § 42.107

LIST OF EXHIBITS

Exhibit	Description
2001	Chen *et. al.* (2000) Plasma and Lymph Pharmacokinetics of Recombinant Human Interleukin-2 and Polyethylene Glycol-Modified Interleukin-2 in Pigs *J. Pharmacol. and Exp. Therapeutics*, 293(1):248–259
2002	McLennan *et al.* (2005) Subcutaneous drug delivery and the role of the lymphatics *Drug Discovery Today: Technologies*, 2(1):89–96
2003	Richter *et al.* (2012) Mechanistic Determinants of Biotherapeutics Absorption Following SC Administration *The AAPS Journal*, 14(3):559–570
2004	Nakashima *et al.* (2014) Drug delivery options to increase patient adherence and satisfaction in the management of rheumatoid arthritis – focus on subcutaneous tocilizumab *Drug Design, Development and Therapy*, 8:913–919
2005	Zhang *et al.* (2013) Pharmacokinetics and pharmacodynamics of tocilizumab after subcutaneous administration in patients with rheumatoid arthritis *Intl. J. Clin. Pharmacol. and Therapeutics*, 51(8):620–630
2006	Ohta *et al.* (2013) Mechanism-Based Approach Using a Biomarker Response to Evaluate Tocilizumab Subcutaneous Injection in Patients With Rheumatoid Arthritis With an Inadequate Response to Synthetic DMARDs (MATSURI Study) *J. Clin. Pharmacol*. 54(1):109–119
2007	CIMZIA® (certolizumab pegol) solution for subcutaneous use, Prefilled syringe – step by step instructions for use (2013)
2008	Besheer *et al.* (2013) Challenges for PEGylated Proteins and Alternative Half-Life Extension Technologies Based on Biodegradable Polymers; Chapter 13 in *Tailored Polymer Architectures for Pharmaceutical and Biomedical Applications*; Scholz, C. *et al.*; ACS Symposium Series; American Chemical Society: Washington, DC; pp. 215-233
2009	September 23, 2015 PRPS Screen Shot of Documents in IPR2015-01537

Exhibit	Description
2010	The International System of Units (SI) - Conversion Factors for General Use, NIST Special Publication 1038, May 2006

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I. Introduction

Patent Owner Bristol-Myers Squibb Company ("Patent Owner") provides the following preliminary response to the Petition filed by Momenta Pharmaceuticals, Inc. ("Petitioner"), on July 2, 2015, requesting *inter partes* review of claims 1–15 of U.S. Patent No. 8,476,239 ("the '239 Patent"). For at least the reasons set forth below, Patent Owner requests that the Board deny *inter partes* review as to the sole obviousness ground presented in the Petition.

From beginning to end, the Petition is nothing more than an impermissible hindsight reconstruction of the claimed formulations. The Petition begins by taking the '239 Patent's *solution*—"[t]he formulator's task is to develop a liquid, high concentration protein formulation that is stable and suitable for subcutaneous administration"—as the *starting place* for its obviousness analysis. Pet., p. 5. From there, rather than conduct a proper *Graham* analysis to address the differences between the cited references and the invention of the '239 Patent, the Petition instead identifies five so-called "known constraints" that a formulator might use to "empirically" develop a hypothetical CTLA4Ig formulation. *See, e.g.*, Pet., pp. 6–8, 11–12. It is this *hypothetical* "stable liquid formulation"—"optimized" based on the concepts claimed in the '239 Patent—that is asserted to meet the various limitations of the challenged claims. Yet, such an "analysis—which compares the challenged claims to a hypothetical [formulation] . . . —

obscures any comparison of the . . . references to the claim limitations, and leaves [the Board] unable to conduct a proper *Graham* analysis as required to determine whether the challenged claims are unpatentable." *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00441, Paper 11, p. 15 (PTAB July 13, 2015).

As in *ContentGuard*, the Petition's "known constraints"—including protein concentration, excipients, pH, viscosity—are impermissibly "plucked from" the claimed solution of the '239 Patent. In conclusory fashion, the Petition repeatedly asserts that applying the "known constraints" would be "logical" or "common sense." *See, e.g.*, Pet., pp. 33, 35, 41. Critically, the Petition fails to provide any articulated reasoning for selecting all of these "constraints" at the same time—and for ignoring other potential constraints identified in the cited references. The Petition merely identifies certain individualized teachings, failing to point to anything in the ***prior art*** to explain why a person of ordinary skill ***would have*** combined these particular "constraints" at the same time into one formulation. To the contrary, what the Petition *does* cite repeatedly in its obviousness analysis is the '239 Patent itself. *See, e.g.*, Pet., pp. 4, 7, 28–29, 39–40. Such circular reliance on the '239 Patent in arguing the obviousness of the challenged claims only underscores the Petition's hindsight-infected approach.

The Petition's arguments for the protein concentration limitations of independent claims 1 and 7 are especially problematic. The Petition cites no

references that teach the administration of CTLA4Ig in concentrations of "at least 100 mg/ml" or "about 125 mg/ml," as claimed. Rather, it proposes a complicated series of unwarranted assumptions and questionable calculations, based on repeatedly picking certain variables from the references while arbitrarily discarding others, wrongly assuming that certain bioavailability data for mice would apply to humans, and simply ignoring critical important factors that would need to be considered in developing an appropriate concentration. The only explanation behind these unprincipled twists and turns is that the Petitioner worked backwards, taking the claimed 125 mg/ml concentration as a starting point, and developing calculations to arrive at this value.

The Petition further fails to provide articulated reasoning supported by evidence for additional limitations in the independent and dependent claims in disregard of *KSR*'s mandate that obviousness cannot be sustained by "mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning . . . ," *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), and the regulatory requirement to specify where each element of the challenged claims is found in the ***evidence***, 37 C.F.R. § 42.104(b)(4).

In fact, the Petition fails to include any evidence for a number of claim limitations. Neither the Petition nor the Staples Declaration (Ex. 1006) provides evidence with articulated reasoning to support a finding that it would have been

obvious to one of ordinary skill in the art to select a viscosity ***within*** the range of from 9 to 20 cps recited in independent claim 1. Because the Petition fails to explain the protein concentration that results in the weight ratio (sugar:protein) recited in independent claim 1 (and dependent claims 14 and 15), the Petition fails to specify where the weight ratio element of these claims is found in the prior art. And the Petition provides no evidence of the surfactant concentration recited in claim 9, nor the temperature range recited in claim 11.

The Petitioner has the burden of proving unpatentability by a preponderance of the evidence, 35 U.S.C. § 316(e), and it has failed to show a reasonable likelihood of prevailing on any claim in the sole asserted obviousness ground. 35 U.S.C. § 314. The Petition should be denied.

II. Claim Construction Under "Broadest Reasonable Interpretation"

A claim subject to IPR is given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,764, 48,766 (Aug. 14, 2012); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1281 (Fed. Cir. 2015), *reh'g en banc denied*, 2015 WL 4100060 (Fed. Cir. July 8, 2015).

Under this governing standard, claim terms are given their ordinary and customary meaning as would be understood by a person of ordinary skill in the art at the time of the invention and in the context of the entire patent disclosure. *In re*

Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer and provides an explicit definition of a term, that explicit definition will control interpretation of that term in the claim, including under the broadest reasonable construction standard. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379 (Fed. Cir. 2007).

A. Stable Formulation

As the Petition expressly concedes:

> The'239 patent defines a "stable" formulation as follows: "one in which the CTLA4Ig molecule therein essentially retains its physical and chemical stability and integrity upon storage." '239 patent, col. 5, lines 29-31.

Pet., p. 19. The '239 Patent further explains that typically a stable formulation "may be one wherein the increase in aggregation, as measured by an increase in the percentage of high molecular weight species (% HMW), is less than about 5% and preferably less than about 3%, when the formulation is stored at 2–8 ºC." '239 Patent, 5:41–50. And claim 11 of the '239 Patent explicitly recites that the formulation "is stable when stored at 2 to 8 C for at least 12 months."

The Petition does not propose an alternative construction for "stable formulation," disagree with the explicit definition provided in the '239 Patent, or offer reasons why the explicit definition should not control. The Petition simply asserts that "the term 'stable' in claims 1 and 7 should be interpreted as being

satisfied where all other limitations of the claim are met," Pet., p. 19—and then, apparently on this basis, declines to address "stable formulation" in its obviousness analysis, *see id.* at 20–46. In any event, there are numerous reasons why the Petition's obviousness analysis are flawed (and why the Board should deny *inter partes* review) that do not turn on the construction of this or other claim terms, as explained in the following section.

III. Petitioner Has Not Shown a Reasonable Likelihood That at Least One Claim of the '239 Patent Is Unpatentable

For at least four independent reasons, the Petitioner has not shown a reasonable likelihood that any claim of the '239 Patent is unpatentable. First, while the Petition relies entirely on obviousness arguments, it fails to adhere to the framework required by *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). Rather than addressing the differences between the prior art and the invention of the '239 Patent, as *Graham* requires, the Petition relies upon a series of generalized teachings that it asserts *could* purportedly be used to generate a fully hypothetical formulation that would allegedly satisfy the claims. Second, the Petition's analysis is wrongly grounded in hindsight logic, using the '239 Patent itself as a roadmap to piece together the prior art to generate this hypothetical formulation. Third, the Petition fails to identify any references teaching the administration of CTLA4Ig in concentrations as specified in the two independent claims of the '239 Patent, relying on a complicated six-step analysis that is

technically flawed and again grounded in impermissible hindsight. Fourth, the Petition fails to provide articulated reasoning supported by evidence for several additional limitations appearing in the independent and dependent claims. For these reasons, the sole obviousness ground of the Petition is unsupported and the Petition should be denied.

A. The Petition Fails to Perform a Proper *Graham* Analysis

The Petition's obviousness analysis is unorthodox and legally flawed. Rather than follow the *Graham* framework, it centers on an array of generalized teachings that a "highly skilled protein formulator" supposedly could apply—along with sufficient experimentation or optimization—to develop a hypothetical CTLA4Ig formulation that appears nowhere in the prior art. *See, e.g.*, Pet., p. 5 ("[T]here were a limited number of parameters that ***could*** be varied in order to achieve a stable, high concentration, liquid formulation." (emphasis added)). The Petition never explains why a person of ordinary skill in the art ***would*** vary these particular parameters at the same time in the precise manner that results in the formulations as claimed.

The Petition thus fails to address the differences between the prior art and the invention of the '239 Patent, as required by *Graham* step 2. *See Graham*, 383 U.S. at 17–18 ("Under § 103, [(1)] the scope and content of the prior art are to be determined; [(2)] differences between the prior art and the claims at issue are to be

ascertained; and [(3)] the level of ordinary skill in the pertinent art resolved."); *see also KSR*, 550 U.S. at 407 ("[These] factors continue to define the inquiry that controls.").

This is not a case where Petitioner is taking a primary prior art reference and modifying it (*e.g.*, based on one or two secondary references) to overcome differences between the prior art and the claimed invention. Instead, the Petition identifies five different so-called "known constraints," Pet., pp. 6–8,[1] that a highly skilled formulator might use to "empirically" develop a hypothetical CTLA4Ig formulation that would satisfy the '239 Patent's claims. *See, e.g.*, Pet., pp. 11–12 ("Accordingly, formulators would empirically determine the optimized amount of sugar, taking into account tonicity and viscosity issues, and consider augmenting the sugar stabilizer with other known excipients in the formulator's toolbox such as surfactants to prepare a stable, liquid formulation.").

In other words, the Petition invites the Board to assume a successful multi-parameter experiment, performed by a hypothetical skilled formulator, to arrive at the claimed invention. This is precisely the approach that the Board rejected in

[1] These constraints are: (1) volume and protein concentration; (2) the "list of possible excipients"; (3) tonicity; (4) pH; and (5) viscosity. Pet., pp. 6–8.

denying institution in *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00441, Paper 11 (PTAB July 13, 2015):

> [T]he Petition fails to identify sufficiently the differences between any challenged claim of the '859 patent and the asserted prior art references, Kahn and Linn. *See* Pet., 22–57; Prelim. Resp. 6–7, 41. Rather than address these differences, ***the Petition creates a hypothetical Kahn-Linn system—based on how a person of ordinary skill in the art allegedly "would" or "could" combine the two references into an integrated system***—in an analysis that is divorced from the language of the challenged claims of the '859 patent. * * * ***The Petition plucks out certain claim terms*** "usage rights" and "repositories" ***and argues that Kahn and Linn teach these concepts.*** *See id.* at 41–48 (§ IV.D). The Petition then argues, in conclusory fashion, that this hypothetical system "would" meet each of the limitations of the challenged claims. *See id.* at 48–57 (§ IV.E). . . . Therefore, the Petition fails to perform an adequate *Graham* analysis, and leaves us unable to conduct a proper *Graham* analysis as required to determine whether the challenged claims are unpatentable.

IPR2015-00441, Paper 11, at 14–15 (emphasis added). As in *ContentGuard*, the Petition here asserts that the prior art teaches *concepts* plucked from the patent claims (*e.g.*, protein concentration, excipient selection, tonicity, pH, viscosity

requirements), and declares that (1) "by using a limited set of possible excipients a skilled artisan could be 'quite confident' in achieving a stable liquid formulation of the [CTLA4Ig] protein," and (2) that various other claim elements could be satisfied by "a highly trained person . . . following well-known formulation principles . . . to optimize known variables." Pet., p. 26.

Critically, it is this *hypothetical* "stable liquid formulation"—which has been "optimized" based on the concepts claimed in the '239 Patent—that is asserted to meet the various limitations of that patent. As the Board explained in *ContentGuard*, "[t]his analysis—which compares the challenged claims to a hypothetical integrated system . . . —obscures any comparison of the individual prior art references to the claim limitations." IPR2015-00441, Paper 11, at 15. Thus, the Petition "leaves [the Board] unable to conduct a proper *Graham* analysis as required to determine whether the challenged claims are unpatentable" and "does not show a reasonable likelihood that Petitioner would prevail" in showing obviousness of the challenged claims. *Id.*

B. The Petition Improperly Uses the '239 Patent as a "Roadmap" to Challenge the Claims

Likewise, in seeking to build an obviousness case on an array of "known constraints" plucked straight from the '239 Patent's claims, the Petition is a classic example of wrongly using the '239 Patent as a roadmap to piece together the prior art.

As the Board and the Federal Circuit have repeatedly cautioned, "[t]o the extent Petitioner uses the [challenged patent], rather than the cited references, as a roadmap to evaluate the obviousness of the challenged claims, Petitioner relies on improper hindsight." *S.S. Steiner, Inc. v. John I. Haas, Inc.*, IPR2014-01491, Paper 7, at 16 (PTAB March 16, 2015) (citing *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008)); *see also, e.g.*, *ContentGuard*, IPR2015-00441, Paper 11, at 14 ("[C]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." (quoting *Grain Processing Corp. v. Am.–Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988)) (further citations and internal quotation marks omitted)); *InTouch Techs., Inc. v. VGo Commc'ns*, 751 F. 3d 1327, 1351 (Fed. Cir. 2014) (admonishing against use of challenged patent as "roadmap for putting . . . pieces of a 'jigsaw puzzle' together"); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art . . . .").

Once again, it is instructive to consider the denial of institution in *ContentGuard*, where—as here—the Petitioner "pluck[ed] out certain claim terms . . . argue[d] that [prior art references] teach these concepts, [and] compare[d] the challenged claims to a hypothetical integrated system." IPR2015-00441, Paper 11,

at 15. There, the Board concluded "that Petitioner is simply using Patent Owner's claims as a guide in constructing a system loosely based on [prior art references] that resembles the claimed invention." IPR2015-00441, Paper 11, at 22. The present petition suffers the same defects.

First, while the Petition's five "known constraints" are offered as a starting place for the analysis, they in fact are "plucked from" the claimed solution of the '239 Patent, as in *ContentGuard:*

- The "constraint on volume defin[ing] the protein concentration," *i.e.*, that "concentrations exceeding 100 mg/mL," Pet., p. 6, is simply a recitation of the claimed requirement of "at least 100 mg/ml CTLA4IG molecule," '239 Patent claim 1; *see also* claim 7 ("CTLA4Ig molecule . . . in an amount of about 125 mg/ml");
- The constraint that "[t]he list of possible excipients is restricted," Pet., p. 6, with "sucrose and trehalose [being] the logical choices and starting place," *id.* at 36, is likewise plucked from '239 Patent claim 1 (specifying "sugar selected from the group consisting of ***sucrose***, lactose, maltose, mannitol and ***trehalose*** and mixtures thereof" (emphasis added));
- The proffered "goal . . . to achieve a pH as close to physiological pH as possible," Pet., p. 8, where a "pH range of 6 to 8 . . . corresponds to

physiological pH," *id.* at 41, is a restatement of '239 Patent claims 1 and 10 (specifying "pH range from 6 to 8"); and

- The constraint on the "viscosity of the formulation," Pet., p. 8, again is pulled from the limitations of claim 1 (specifying "viscosity of from 9 to 20 cps").

This backwards logic is the essence of hindsight reconstruction.

Second, the Petition does not provide any articulated reasoning for selecting these five "constraints" at the same time—and for ignoring other potential constraints identified in the cited references.[2] *Cf. ContentGuard*, IPR2015-00441, Paper 11, at 21 ("[N]owhere in its analysis in the Petition does Petitioner provide any articulated reasoning for making all of these changes at the same time. . . . The mere fact that individual changes might have been minor or even obvious does not make doing all of the changes at once obvious."). That is, the Petition identifies certain individualized teachings, but does not point to anything in the ***prior art*** to

[2] For example, neither the Petition nor Dr. Staples considers deamidation, a protein characteristic upon which stability depends, *see, e.g.,* Ex. 1004, p. 13; Ex. 1005, p. 1393, much less the effect of pH—the "most powerful" formulation variable—on deamidation or aggregation, the primary degradation pathway in high concentration protein formulations. Ex. 1004, p. 13; Ex. 1005, p. 1393.

explain why a person of ordinary skill ***would have*** combined all the selected "constraints" (and only those constraints) at the same time into one formulation. To the contrary, what the Petition *does* cite repeatedly in its obviousness analysis, is the '239 Patent itself. *See, e.g.*, Pet., pp. 4, 7, 28–29, 39–40. Of course, such circular reliance on the '239 Patent in arguing the obviousness of its claims only underscores the Petition's hindsight-driven approach.

Third, in another similarity to *ContentGuard*, the Petition repeatedly asserts that applying the "known constraints" would be "logical" or "common sense." *See, e.g.*, Pet., p. 33 ("the CTLA4Ig concentrations claimed are merely the logical result of incorporating the needed amount of CTLA4Ig . . . into the limited volume of a subcutaneous formulation"); p. 35 ("sucrose and trehalose were the logical choices"); p. 41 ("the viscosity range recited in the claims was merely the logical choice"); p. 41 ("claimed pH was the logical choice").[3] Such conclusory assertions cannot substitute for articulated reasoning with rational underpinning, and they cannot sustain an obviousness conclusion. *See ContentGuard,* IPR2015-00441, Paper 11, at 21 ("We see no difference between conclusory statements that these

[3] The Staples Declaration relies on similar conclusory assertions. *See, e.g.*, Ex. 1006, ¶ 27 (use of excipients as "common sense"); ¶ 53 (pH from 6 to 8 as "logical starting point"); ¶ 55 (use of phosphate buffer "would have been a logical choice").

changes are 'logical and routine' and saying that these changes are 'common sense,' which alone is insufficient to support an obviousness analysis."). For these reasons, the Board's conclusion in *ContentGuard* is fully applicable here:

> Without some reason why a person of ordinary skill would engage in, what appears to us to be, a nearly wholesale reconstruction of [prior art references], the only conclusion that [the Board] can draw is that Petitioner is simply using Patent Owner's claims as a guide in constructing a system loosely based on [the references] that resembles the claimed invention.

Id. at 22.

Moreover, in seeking to establish a rationale for achieving the claimed invention, the Petition wrongly "defin[es] the problem in terms of its solution" and thus further "reveals improper hindsight." *Purdue Pharma L.P. v. Depomed, Inc.*, IPR2014-00379, Paper 72, at 28 (PTAB July 8, 2015) (quoting *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015)). That is, with the Petition beginning by asserting, "[t]he formulator's task is to develop a liquid, high concentration protein formulation that is stable and suitable for subcutaneous administration," Pet., p. 5, it takes the '239 Patent's *solution* as the *starting place* for its obviousness analysis—and assumes that it is achievable, without any recognition or assessment of the technical challenges that it would entail. Indeed, the very documents relied upon by Petitioner explain these challenges, stressing

that "[p]rotein properties such as self-association/aggregation, solubility, and viscosity pose challenges to developing pharmaceutically and economically acceptable formulations at high concentration." Ex. 1005, p. 1399. Critically, the Petition ignores the conclusion reached in the Shire article (Ex. 1005), a document cited repeatedly throughout the Petition:

> ***Very little work has been published on high concentration protein formulation development*** and this review has touched on the key issues with examples of the potential solutions to the issues. ***Achieving a suitable formulation requires an integrated approach*** whereby a stable formulation is developed that can also be successfully administered and economically manufactured.

Id. (emphasis added). Thus, objective evidence of record underscores the problems with the Petitioner's hindsight-driven approach.

The Petition further ignores the integrated approach necessary to achieve a successful stable formulation, merely treating the problem as a series of single-factor experiments. For example, the Petition proclaims that the "claimed pH was the logical choice for avoiding injection site irritation." Pet., p. 41. Although Dr. Staples recognizes that aggregation increases at higher protein concentrations, Ex. 1006, ¶ 41, Dr. Staples never considers the effect of pH on aggregation, despite the fact that aggregation is "expected to be the primary degradation pathway in high

concentration protein formulations," Ex. 1005, p. 1393, and pH is the "most powerful" formulation variable, Ex. 1004, p. 13. And Dr. Staples ignores deamidation completely, another protein characteristic upon which stability depends. *See, e.g.,* Ex. 1004, p. 13; Ex. 1005, p. 1393.

Dr. Staples' failure to consider the effect of pH on aggregation and deamidation is a direct consequence of the hindsight analysis that is the foundation of the Petition and his declaration. Starting with the '239 Patent's solution of "a liquid, high concentration protein formulation that is stable and suitable for subcutaneous administration," Pet., p. 5, the Petition then assumes that the term "stable" is "satisfied where all other limitations of the claim are met," Pet., p. 19. Dr. Staples declares that "stable" "gives no additional meaning to the claims," Ex. 1006, ¶ 23, and then proceeds to ignore what the very documents he cites discuss about solving stability problems such as aggregation and deamidation: "The optimization of formulation variables for product stability is the most critical part of protein formulation development. . . . Among the listed formulation variables, the most powerful one is pH." Ex. 1004, p. 13.

Neither the Petition nor Dr. Staples explains how a person of ordinary skill in the art, without the benefit of the '239 Patent claims as a starting point, arrives at a "stable" protein formulation without considering the effect of pH—the "most powerful" formulation variable, Ex. 1004, p. 13, on aggregation, which in turn is

"the primary degradation pathway," Ex. 1005, p. 1393. Relying only on injection site discomfort, Dr. Staples' conclusion that "the claimed pH range of from 6 to 8 . . . would have been the obvious starting point," Ex. 1006, ¶ 44, is not only overly simplistic, but also the result of nothing more than hindsight.

Given the complexities that are attendant to a stable protein formulation that is suitable for subcutaneous administration, the Petition's repeated assertions that a formulator could be "quite confident" in achieving the claimed invention ring hollow. *See, e.g.*, Pet., p. 26. As the Board explained in *ContentGuard:*

> ***Particularly when the many proposed changes are considered together***, the Petition lacks adequate reasoning, with rational underpinning, to show sufficiently that a person of ordinary skill would have combined the teachings of [the prior art] and the knowledge in the art to reach the hypothetical [result] . . . . ***The mere fact that individual changes might have been minor or even obvious does not make doing all of the changes at once obvious.*** . . . Petitioner is simply using Patent Owner's claims as a guide . . . .

IPR2015-00441, Paper 11, at 21-22 (emphasis added). The Petition's fundamental deficiency is underscored by its attempt to analogize to the markedly different facts of *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship.*, IPR2013-00534, Paper No. 81 (PTAB Feb. 23, 2015). Critically, in *Biomarin*, "[t]he *only*

limitation . . . not expressly disclosed in [the prior art]" in a claim for a drug treatment method, "was the 'biweekly' limitation" specifying the frequency of treatment. *Id.* at 11 (emphasis added). The Board found this biweekly dosing schedule to be "routine optimization." IPR2013-00534, Paper No. 81, at 14. Here, in contrast, the Petition is grounded not in changing one variable from a prior art therapy, but in developing a hypothetical CTLA4Ig formulation out of whole cloth, based on five generalized principles.

Indeed, the Board in *Biomarin* stressed that "this is not a case where the prior art teaches merely to *pursue a general approach* . . . or gave only *general guidance* as to the particular form of the claimed invention or how to achieve it." IPR2013-00534, Paper No. 81, at 15 (emphasis added) (internal quotations and citations omitted). Here, of course, the Petition's entire theory is grounded on applying *general principles*—along with significant trial-and-error—to achieve the claimed invention. Likewise, the Board in *Biomarin* stressed that "this is also not a case where there were 'numerous parameters' to try." *Id.* at 17 (distinguishing *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 1364 (Fed. Cir. 2007)). Here, of course, the Petition asks the Board to assume that a highly skilled formulator would try and optimize among *at least five* different parameters. Thus, what the Petition euphemistically calls "routine trial and error, to optimize known variables," Pet., p. 26, is plainly a hindsight-driven reconstruction of the invention of the '239 Patent.

The Petition is premised on impermissibly using the '239 Patent as a roadmap to challenge its claims. It fails to demonstrate a reasonable likelihood that any claim of the '239 Patent is unpatentable.

C. The Petition's Argument That the Prior Art "Dictated the Claimed CTLA4Ig Concentrations" in Independent Claims 1 and 7 Is Scientifically Flawed and Impermissibly Grounded in Hindsight

The Petition asserts that the amount of CTLA4Ig needed to treat rheumatoid arthritis was "known in the art," Pet., p. 26, and that the art "dictated the claimed CTLA4Ig concentrations," *id.* at 29. Yet it cites no references that teach the administration of CTLA4Ig in concentrations of "at least 100 mg/ml" or "about 125 mg/ml," as specified in the two independent claims of the '239 Patent, claims 1 and 7. Instead, it invites the Board to follow it through eight pages of unwarranted assumptions and questionable calculations, which conveniently result in a concentration of 125.0 mg/ml—precisely the amount specified in claim 7, down to the one-tenths digit. *See* Pet., pp. 26–33. This again is impermissible hindsight. While the Petition claims that its "math . . . is straightforward," *id.* at 32, basic scrutiny reveals that it is anything but:

- First, the Petition begins with a study in Cohen of ***intravenously administered*** CTLA4Ig or L104EA29YIg, which purportedly showed that groups treated with either 2 or ***10 mg*** per kg of body weight of CTLA4Ig ***or***

L104EA29YIg experienced greater relief from the symptoms of rheumatoid arthritis. Pet., pp. 26–28.

- Second, the Petition inexplicably casts aside Cohen's 10 mg/kg dosage in favor of the lower 2 mg/kg figure, *see* Pet., pp. 29–30, even though Cohen expresses no preference for 2 mg/kg but rather identifies a "clear significant response at 10 mg/kg per body weight of the patient." Ex. 1003 at [0267].
- Third, the Petition proposes multiplying this number by 79.7 kg, citing the "average adult weight." Pet., p. 30.
- Fourth, the Petition cites disclosures that a subcutaneous injection has a maximal volume of ***either*** "~1mL" ***or*** "1.5ml," inexplicably using the latter figure and discarding the former. *See* Pet., p. 32.
- Fifth, the Petition turns to data on subcutaneous bioavailability ***in mice*** at 85% and uses that in calculating the correct subcutaneous dosage ***in humans***, without any evidence that the bioavailability would be similar. *See* Pet., p. 31–32.
- Sixth, the Petition then applies the "straightforward" calculation of ***2 mg/kg × 79.7 kg ÷ 1.5ml ÷ 85%*** to determine the CTLA4Ig concentration of its hypothetical subcutaneous formulation. Pet., p. 32.

This calculation—which conveniently results in a CTLA4Ig concentration of precisely 125.0 mg/ml—can only be the result of impermissible hindsight. The

Petition provides no articulated reasoning with rational underpinning for starting where it does, or for taking various forks along the way, in each case discarding alternative approaches suggested in the references that would yield far different results. For example, simply using an injection volume of 1 ml yields a concentration 50% higher (187.5 mg/ml) under Petitioner's own logic—a calculation actually made by Dr. Staples. Moreover, the Petition is premised on the scientifically baseless assumption—made without any supporting evidence—that a person of ordinary skill could reliably apply the bioavailability of a protein administered subcutaneously to sixteen mice to an intravenous dosage for humans. The Staples declaration does not remedy any of these deficiencies.

The only explanation behind these unprincipled twists and turns is that the Petitioner worked backwards, taking the claimed "about 125 mg/ml" concentration as a starting point, and thus wrongly "using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *ContentGuard*, IPR2015-00441, Paper 11, at 14 (quoting *Grain Processing Corp.*, 840 F.2d at 907) (further citations and internal quotation marks omitted). This is especially so given that the Petition fails to explain why a person of ordinary skill would have made all of these assumptions and decisions at the same time. *See id.* at 21 ("The mere fact that individual changes might have been minor or even obvious does not make doing all of the

changes at once obvious."). This backwards approach is contrary to decades of Federal Circuit precedent barring hindsight reconstruction of claim terms (*see* Section III.B., *supra*).

Furthermore, the Petition does not account for other important factors that would need to be considered in developing an appropriate concentration for subcutaneous formulation, including dosing schedules, efficacy, safety, serum concentration, and immunogenicity.

Given these fatal flaws, the Petition fails to provide articulated reasoning that any particular protein concentration is "dictated" by the prior art, let alone the concentrations recited in either independent claims 1 ("at least 100 mg/ml") or 7 ("about 125 mg/ml"). Therefore, the Petition fails to establish a reasonable likelihood that any claim of the '239 Patent is unpatentable, as explained further in the following subsections.

1. The Petition uses the required protein concentration of "about 125 mg/ml" as a roadmap to pluck the desired starting point from the prior art

Plainly starting with "about 125 mg/ml" as the goal, the Petition relies on the disclosure in Cohen (Ex. 1003) of an intravenous formulation of the CTLA4Ig molecule as a spring board to show how a person having ordinary skill in the art ***could have*** calculated this protein concentration. Pet., p. 26–33. Thus, the Petition uses the claimed 125 mg/ml as a roadmap for "incorporating the needed amount of

CTLA4Ig" "into the limited volume of a subcutaneous formulation," pronouncing that the claimed concentrations are "merely the ***logical result***." Pet., p. 33 (emphasis added). Such a hindsight-driven calculation cannot support a finding of obviousness, particularly where, as here, it is based on flawed scientific reasoning.

Critically, nowhere does Cohen disclose a stable formulation comprising a CTLA4Ig protein concentration of "about 125 mg/ml" as required by claims 7–13 of the '239 Patent. Rather, Cohen discloses a phase II clinical study involving 214 patients who were administered an *intravenous* formulation of the CTLA4Ig protein having a concentration of 25 mg/ml at a dosage of 0.5, 2.0, or 10 mg/kg. Ex. 1003 at [0240], [0243]. The purpose of the study was to evaluate relief of at least one symptom associated with rheumatoid arthritis, including reducing joint swelling, joint tenderness, inflammation, morning stiffness and pain. *Id*. at [0237]. The patients who followed protocol guidelines and did not discontinue before day 57 of the study received a total of 4 intravenous infusions, one infusion each on days 1, 15, 29, and 57. *Id*. at [0240]. Cohen reports that "[t]he responses appear to be dose-dependent with a *clear significant response at 10 mg/kg per body weight of the patient.*" *Id*. at [0267] (emphasis added). Cohen also states that "[a] larger percentage of patients show improvement of 20, 50, 70 and even 100% in the *2 and 10 mg/kg* groups . . . ." *Id*. at [0268] (emphasis added). Indeed, the Petition acknowledges Cohen's *two different* effective doses (2 and 10 mg/kg):

> The results of [Cohen's] clinical study demonstrated that the groups treated with 2 or 10 mg/ml [sic[4]] of CTLA4Ig or its variant experienced greater relief from the symptoms of rheumatoid arthritis than those groups treated with placebo or 0.5 mg/ml [sic].

Pet., p. 27.

Cohen also reports that (a) the median and mean tender joint counts; (b) swollen joint counts; (c) pain assessment scores over time; and (d) disease activity assessment scores in patients treated with CTLA4Ig "*appears to be more important in the 2 and 10 mg/kg groups than placebo or 0.5 mg/kg groups*." *Id*. at [0274]-[0277] (emphasis added). In fact, the only distinction Cohen makes between the 2 and 10 mg/kg doses is to state that there was "a clear significant response at 10 mg/kg per body weight of the patient." *Id*. at [0267]. In other words, Cohen expresses no preference between the 2 and 10 mg/kg doses except to state that the 10 mg/kg dosage exhibited "a clear significant response." *Id.*

The Petition—citing only Paragraphs 39–41 of the Staples Declaration—seizes upon Cohen's 2 mg/kg dosage, and discards Cohen's 10 mg/kg dosage, to begin a series of calculations that allegedly would have led a person having

[4] The mg/***ml*** language in this quotation appears to be referring to the mg/***kg*** concentrations discussed in Cohen.

ordinary skill in the art to the CTLA4Ig concentration of "about 125 mg/ml" recited in claims 7–13 of the '239 Patent. Pet., pp. 28–30.

Critically, the Petition does not establish why a person having ordinary skill in the art would have chosen Cohen's 2 mg/kg dosage over Cohen's 10 mg/kg dosage as a starting point for these calculations, even though Cohen expressed no preference for the 2 mg/kg dosage. If anything, Cohen points a person of ordinary skill in the art to start from 10 mg/kg because this dosage exhibited "a clear significant response." Ex. 1003 at [0267]. The Petition asserts that "[w]hen developing a subcutaneous formulation, a formulator would start with the minimum dosage known to be effective intravenously and shrink the formulation's volume down to that allowed for subcutaneous administration." Pet., p. 30. The Petition adduces no actual evidence for this assertion (*e.g.*, facts, data, or supporting documents), citing only to Paragraphs 39–41 of the Staples Declaration. Dr. Staples, in turn, simply asserts that "[w]hen trying to develop a subcutaneous formulation of a protein with a known effective amount when delivered intravenously, a person of ordinary skill would start with a subcutaneous formulation having the minimum amount of protein known to be effective when administered intravenously." Ex. 1006, ¶ 40. But with no underlying facts, supporting data or evidentiary support for his assertion, Dr. Staples' conclusory assertion cannot sustain Petitioner's argument. *See* 37 C.F.R. § 42.65(a) ("Expert

testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

The Petition's true reason for choosing Cohen's 2 mg/kg dosage instead of Cohen's 10 mg/kg dosage as a starting point for its calculations is transparent: that is the value that happens to lead to the '239 Patent's concentration. Instead of beginning its *Graham* analysis with the prior art as it must, the Petition impermissibly *starts* with the protein concentration of "about 125 mg/ml" recited in claims 7–13 *and works backwards* to identify the dosage from Cohen that works best for the calculation, *i.e.*, 2 mg/kg instead of 10 mg/kg—even though Cohen expresses no preference for the lower concentration. The only reasonable inference to draw is that the Petitioner is using the claims as a guide to "pick and choose" elements from Cohen, as the Federal Circuit has warned against. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Indeed, [i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art . . . ." *Fritch*, 972 F.2d at 1266. The Board can, and should, decline to institute trial for this reason alone.

2. The calculations using Cohen's 2 mg/kg dosage rely on impermissible hindsight and flawed scientific reasoning

After plucking the 2 mg/kg dosage from Cohen with no supported explanation for discarding Cohen's 10 mg/kg dosage, the Petition then takes the reader through a series of calculations purporting to show how a person having

ordinary skill in the art would have reached the 125 mg/ml CTLA4Ig protein concentration recited in claims 7–13 of the '239 Patent. These calculations are premised not only on the hindsight analysis that led to choosing Cohen's 2 mg/kg dosage as a starting point, but also on choosing a final volume of 1.5 ml for the formulation, instead of 1.0 ml. This is in spite of the fact that Petitioner's own exhibit, the Carpenter Handbook, cautions that "in the case of subcutaneous injection, there is a maximal volume (~1 ml) that can be given to a patient without discomfort." Ex. 1004, p. 182. The Petition provides no explanation, much less articulated reasoning with rational underpinning, why a person having ordinary skill in the art would pick a volume of 1.5 ml for the formulation instead of 1.0 ml. Pet., pp. 32–33. Indeed, the Petition explicitly acknowledges that both volumes were possible choices:

> Likewise, it was known that the volume of a liquid formulation for subcutaneous [sic] could be no more than 1-1.5 ml.

Pet., p. 30.

The Petition's first calculation is to multiply Cohen's 2 mg/kg dosage by the average weight of an adult human, which the Petition alleges is 79.7 kg. Pet., p. 30. The result—something the Petition calls "the average minimum dose of CTLA4Ig needed to treat rheumatoid arthritis"—is 159.4 mg of CTLA4Ig. Pet., p. 30.

The Petition then discusses the differences between bioavailability of intravenous and subcutaneous formulations. Citing only to the unsupported and conclusory statements in the Staples Declaration, the Petition asserts that "a formulator would not start with a smaller dose, per patient kilogram, than that dose known to work intravenously—anything lower would not be expected to work subcutaneously." Pet., p. 31; Ex. 1006, ¶ 40. After that, the Petition says:

> [n]or would a formulator have started with a substantially larger dose, because CTLA4Ig was known to have relatively high bioavailability even when administered subcutaneously. . . . Specifically, it was known that CTLA4Ig was 85% bioavailable after subcutaneous administration in mice."

Pet., p. 31 (citing Ex. 1006, ¶ 41 and Ex. 1009, p. 2).

The only evidentiary support cited on page 31 of the Petition or Paragraph 41 of the Staples Declaration is the *Srinivas* 2-½ column Communication To the Editor (Ex. 1009), reporting on a study involving sixteen mice, eight of which were administered an intravenous formulation of CTLA4Ig, and eight of which were administered a subcutaneous formulation of CTLA4Ig. Based on this single, sixteen-mouse study, the subcutaneous bioavailability of CTLA4Ig was determined to be 85%—*in mice*. Pet., p. 31, Ex. 1006, ¶ 41.

Critically, neither the Petition nor the Staples Declaration provides any facts, evidence, scientific reasoning, or even argument to establish why subcutaneous bioavailability data for CTLA4Ig obtained from a study involving mice is suitable for combining with an intravenous dosage in humans. The Petition relies on Cohen—which discloses a phase II clinical trial involving *humans*—then combines it with *Srinivas*, a study involving a completely different species of mammal—*mice*—to assert that the minimum effective *intravenous* dose of CTLA4Ig found in Cohen's *human* phase II clinical trial should be modified to something else in light of the *Srinivas* mouse data to create a formulation for *subcutaneous* administration of CTLA4Ig. Pet., pp. 31–32. Neither the Petition nor the Staples Declaration provides any articulated reasoning supported by evidence for this interspecies leap. As discussed in greater detail in the following section, this interspecies extrapolation is without scientific merit and neither the Petition nor the Staples Declaration provides any evidentiary support for such an assertion.

Applying the subcutaneous bioavailability data from mice (85%) to the calculated "average minimum dose of CTLA4Ig needed to treat rheumatoid arthritis" in humans (159.4 mg), the Petition next contends that a subcutaneous formulation would be required to contain "187.53 mg of CTLA4Ig to match the intravenous availability," Pet., p. 32, —159.4 mg ÷ 0.85 = 187.53 mg. In a final stroke of hindsight magic, dividing 187.53 mg by a volume of ***1.5 ml*** results in a

concentration of 125 mg/ml, the CTLA4Ig concentration recited in claims 7–13 of the '239 Patent. Pet., p. 32. The Petition triumphantly declares "[t]his is precisely the concentration recited in claim 7." Pet., p. 32.

But in Paragraph 41 of his Declaration, Dr. Staples uses ***two*** volumes—1.0 ml and 1.5 ml—to calculate ***two*** possible CTLA4Ig concentrations for a subcutaneous formulation: 187.5 mg/ml (based on 1.0 ml volume) and 125 mg/ml (based on 1.5 ml volume). Ex. 1006, ¶ 41. Dr. Staples asserts that "I do not see any critical difference between this range of CTLA4Ig concentrations and any value claimed by the '239 patent." *Id.* Yet 187.5 mg/ml is plainly not "about 125 mg/ml," as specified in claim 7.

The Petition further fails to explain why a person having ordinary skill in the art would have made all of these assumptions together—*at the same time*. The Petition does not say why such a person would have selected a volume of 1.5 ml over 1.0 ml, particularly in light of the caution in Carpenter that "in the case of subcutaneous injection, there is a maximal volume (~1 ml) that can be given to a patient without discomfort." Ex. 1004, p. 182. Nor does the Petition explain why such a person would discard the 187.5 mg/ml value calculated by Dr. Staples. To the contrary, it acknowledges that if the volume of the formulation were 1.0 ml then "the CTLA4Ig concentration needed for a 1 ml subcutaneous formulation would still have been *187.5 mg/ml*." Pet., p. 33 (emphasis added). And the

Petition does not explain with any credible scientific reasoning how a person having ordinary skill in the art would have arrived at a subcutaneous bioavailability of 85%.

Thus, even the Petitioner and Dr. Staples concede that the protein concentration that a skilled artisan purportedly would have derived from the prior art would *not* have led exclusively to a concentration of "about 125 mg/ml." Rather, even if one were to adopt their flawed hindsight reasoning, this could also have led to a concentration of 187.5 mg/ml. Pet., p. 33; Ex. 1006, ¶ 41. The Petition does not even attempt to explain, much less provide articulated reasoning with rational underpinning, why a person having ordinary skill in the art, starting from Cohen, Shire, and Carpenter without benefit of the claims of the '239 Patent, would have selected a volume of 1.5 ml instead of 1.0 ml for the formulation, or selected a protein concentration of 125 mg/ml and discarded the 187.5 mg/ml protein concentration that Dr. Staples himself calculated.

3. The Petition does not and cannot explain why a person having ordinary skill in the art would apply mice subcutaneous bioavailability data to a human intravenous dosage

At the time of the invention, it was known that subcutaneous bioavailability of therapeutic proteins varied dramatically between mammalian species. *See, e.g.,* Ex. 2001, p. 258; Ex. 2002, pp. 94–95; Ex. 2003, p. 566. Despite this knowledge

by the "highly skilled" formulators,[5] the Petition assumes that a person having ordinary skill in art at the time of the invention would have used the subcutaneous bioavailability of CTLA4Ig in *mice* to derive a CTLA4Ig concentration for subcutaneous delivery to *humans*. Pet., pp. 31–32. Thus, the Petition's hindsight calculation of a protein concentration of "about 125 mg/ml" relies on its unsupported (indeed, unsupportable) *interspecies* assumption that the bioavailability of subcutaneously administered CTLA4Ig observed in mice reliably can be applied to an intravenously administered human dosage. Pet., pp. 31–32. At the time of the invention, however, there was—and to this day remains—no scientific basis for this assumption. *See* Ex. 2001–2003. Both the Petition and the Staples Declaration are silent with respect to any scientific reasoning, facts, or data to support this interspecies extrapolation. Neither the Petition nor Dr. Staples provides any articulated reasoning, much less supported by evidence, that a person of ordinary skill in the art would have applied murine subcutaneous bioavailability data to a human intravenous dosage. Given that the Petition's calculation of the

[5] The Petition and Dr. Staples assert that a person of ordinary skill in the art would have a "Ph.D. in chemistry, biochemistry, or a related field, and have had at least 2-5 years of experience developing pharmaceutically acceptable formulations of protein drugs." Pet., p. 5; Ex. 1006, ¶ 20.

"125 mg/ml" protein concentration is based on this assumption, the calculation cannot be sustained. *See, e.g.*, 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); Pet., pp. 31–32.

In fact, at the time of the invention of the '239 Patent, it was known that subcutaneous bioavailability of therapeutic proteins varied widely among mammalian species—directly undercutting the Petition's and Dr. Staples' unsupported interspecies assumption. For example, Chen *et al.* (2000) (Ex. 2001) reported widely varying subcutaneous bioavailability of IL-2 and PEG-IL2 in numerous mammalian species including pigs, sheep, mice, rats, rabbits, cynomolgus macaques and human beings:

> However, allometric relationships between clearance and body weight could not be established when either IL-2 or PEG-IL-2 was administered s.c. Bioavailability was much lower in fur-bearing species. For IL-2, the bioavailability ranged between 21 and 41% in mice and 4.3 to 24% in sheep. Therefore, the pig model was selected to study IL-2 and PEG-IL-2 because skin layers and supporting structures are similar to those in humans…In pigs, the bioavailability of s.c. IL-2 was 42.2%...which is comparable to the s.c. bioavailability of IL-2 in cancer patients (35–47%) and in patients infected with human immunodeficiency virus, in whom s.c.

> bioavailability was approximately 62%...After the s.c. administration of PEG-IL-2 to mice, rats, rabbits, and cynomolgus macaques, bioavailability ranged between 22 and 72%; rabbits had the lowest value. In cancer patients, the bioavailability of s.c. PEG-IL-2 was 83%.

Ex. 2001, p. 258.

In the years leading up to the 2005 filing of the '239 Patent's provisional application, the literature continued to report issues relating to interspecies variability and predictability. In 2005, McLennan *et al.* (Ex. 2002) observed that issues related to interspecies scaling involved differences in lymphatic transport and there remained a need to examine issues of interspecies scaling and predictability of absorption patterns in humans:

> A further, potentially complicating factor is that variations in subcutaneous blood flow and lymphatic drainage rates throughout the body can lead to regional differences in absorption rates and corresponding differences in the relative contributions of the vascular and lymphatic absorption pathways. To further understand these processes and to provide a means for assessing lymphatic targeting of therapeutic agents, ***there is a clear need to examine issues of interspecies scaling and the predictability of absorption patterns in humans given that variations in lymphatic architecture can lead***

> ***to differences in lymphatic transport across animal models and humans***.

Ex. 2002, p. 94 (emphasis added). Notably, in a final section of the paper titled "Outstanding Issues," McLennan identifies "[i]nterspecies variations in lymphatic versus vascular absorption from SC absorption sites and the ability to extrapolate animal data to humans" as one outstanding issue. *Id.*, p. 95.

Finally, Richter *et al.* (2012) (Ex. 2003) reviewed the "Mechanistic Determinants of Biotherapeutics Absorption Following SC Administration" and found widely varying bioavailabilities for different therapeutic antibodies and stated that "[f]or mAbs in rodents, as well as for other biotherapeutics in all species, *no clear pattern was observed when correlating SC bioavailability in humans and in the various animal species.*" Ex. 2003, p. 566 (emphasis added).

The Petitioner's undocumented assumption that a person having ordinary skill in the art at the time of the invention would use the subcutaneous bioavailability of CTLA4Ig in mice to derive a CTLA4Ig concentration for subcutaneous delivery to humans is therefore belied by the state-of-the-art described in Exhibits 2001–2003. In the years prior to and including 2005 when the '239 Patent's provisional application was filed, the evidence shows that a person of ordinary skill in the art would have appreciated that interspecies subcutaneous bioavailability varied widely, and that the predictability of

extrapolating subcutaneous animal data to humans was not certain. *See, e.g.,* Ex. 2001, p. 258; Ex. 2002, pp. 94–95. Each of the Petition and the Staples Declaration ignores this knowledge, relying only on an unsubstantiated, conclusory assumption. Accordingly, the Board should accord the "125 mg/ml" calculations no weight as unsupported, and contrary to the evidence presented herein.

4. The Petition's simplistic method of determining CTLA4Ig concentration for a subcutaneous formulation fails to account for many other factors that a person of ordinary skill in the art would have considered

To determine the concentration of CTLA4Ig necessary for a subcutaneous formulation, the Petition further assumes that a person having ordinary skill in the art would simply take the minimum effective intravenous dose of CTLA4Ig and convert this dose to an amount for subcutaneous delivery based on the difference in bioavailability between the two modes of administration—ignoring numerous other critical factors. Pet., pp. 31–32. That is, the Petition claims that:

> First, as detailed above, 159.4 mg of CTLA4Ig was needed for the average adult when administered intravenously, *i.e.*, when the bioavailability was 100%. Second, CTLA4Ig administered subcutaneously was known to have a bioavailability of 85% in mice, which would have required 187.53 mg of CTLA4Ig to match the intravenous bioavailability. Third, Shire teaches that the maximum volume for subcutaneous administration is 1.5 ml. Fourth, and finally, 187.53 mg of CTLA4Ig

> placed into a 1.5 ml subcutaneous formulation is 125.0 mg/ml. This is precisely the concentration recited in claim 7. Pet., p. 32 (citations omitted)

Neither the Petition nor the Staples Declaration can sustain this simplistic approach. In fact, a person having ordinary skill in the art would consider many other factors in determining what concentration should be used for a subcutaneous formulation based on a known effective intravenous dosage. Such factors would include, *inter alia*, dosing schedules, efficacy, safety, serum CTLA4Ig concentration, and immunogenicity using various amounts of protein, none of which is accounted for in the Petition or the Staples Declaration.

As one example, Tocilizumab (TCZ) is a humanized monoclonal anti-interleukin-6 receptor antibody that was initially developed for use as an intravenous infusion for the treatment of rheumatoid arthritis. Nakashima *et al.* (2014) (Ex. 2004), Abstract. Zhang *et al.* (2013) (Ex. 2005) reported that TCZ was approved at a recommended intravenous dose of 8 mg/kg every four weeks. Ex. 2005, p. 620. Zhang observed that "[b]ecause of its limited solubility (180 mg/ml) tocilizumab cannot be delivered by the s.c. route at a dose (560 mg for a 70 kg patient) similar to that given by the i.v. route (8 mg/kg) using a 1 ml syringe." *Id*.

To evaluate the optimal subcutaneous TCZ dose that would result in exposure comparable to the approved intravenous TCZ dose in patients with rheumatoid arthritis, Ohta *et al.* (2013) (Ex. 2006) used a pharmacokinetic and

biomarker approach to estimate the clinically optimal dose regimen for subcutaneous TCZ. Ex. 2006, p. 117. The study evaluated efficacy, safety, injection-site pain, serum TCZ concentration, and immunogenicity using various dosing schedules and amounts of TCZ (81 mg every two weeks; or 162 mg every two weeks; or 162 mg weekly). *Id*., pp. 110–112. Ohta also monitored the biomarker, C-reactive protein (CRP), which is used clinically as a biomarker of IL-6 activity and inflammation in rheumatoid arthritis, to help evaluate the dosing regimens and amounts of TCZ included in the study. *Id*., pp. 109, 115.

Ohta concluded that "[m]ode-of-action-based prediction using this PK and biomarker approach was critical in estimating the optimal SC tocilizumab dose." *Id*., p. 118. The appropriate subcutaneous dose was determined to be 162 mg every two weeks. *Id*., p. 118. This is significantly different from the approved intravenous mode of administration, which was 8 mg/kg every four weeks. *See* Ex. 2005, p. 620. But even after determining the appropriate dose of subcutaneous TCZ (for Japanese patients), Ohta stated that "[l]arger clinical trials are needed to confirm the PK, long-term efficacy, and safety of SC tocilizumab." Ex. 2006, p. 118. In fact, in his later review of multiple subcutaneous TCZ clinical studies that were based on Ohta's optimal dosage, Nakashima concluded that "[d]etermining the optimal TCZ-SC dose *requires further comparative investigation*." *See* Ex. 2004, p. 918 (emphasis added).

The Petition does not discuss why a person having ordinary skill in the art would or could ignore these factors in purportedly arriving at the claimed CTLA4Ig protein concentrations. Deriving a clinically optimum dose of a therapeutic protein for subcutaneous administration based on a known intravenous dose involves much more than a single calculation based on an interspecies difference in intravenous versus subcutaneous bioavailability of the protein. The Petition—and Dr. Staples—simply ignore these other factors, such as dosing schedules, efficacy, safety, serum CTLA4Ig concentration, and immunogenicity.

* * *

For the foregoing reasons, the Petition fails to provide articulated reasoning supported by evidence for the protein concentrations set forth in both independent claims of the '239 patent—claims 1 ("at least 100 mg/ml") and 7 ("about 125 mg/ml"). Therefore, the Petition should be denied as to all claims.

D. The Petition Lacks Articulated Reasoning Supported by Evidence for Many Additional Claim Limitations

As explained in *KSR,* obviousness cannot be sustained by "mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418. And the regulations require that a petition for *inter partes* review must include "a detailed explanation of the significance of the ***evidence***," 37 C.F.R. § 42.22(a)(2) (emphasis added), and "specify where each element of the claim is

found in the prior art patents or printed publications relied upon," 37 C.F.R. § 42.104(b)(4).

Disregarding these requirements, the Petition is replete with further conclusory statements unsupported by evidence, and the Petition fails to include any evidence for a number of claim limitations. Because the Petition fails to provide articulated reasoning supported by evidence for additional limitations in independent claims 1 and 7 from which all other claims ultimately depend (as well as further limitations appearing in dependent claims), the sole ground of the Petition is unsupported and the Petition should be denied.

1. Claim 1 – "viscosity of from 9 to 20 cps"

Independent claim 1 requires that the formulation have "a viscosity of from 9 to 20 cps." Neither the Petition nor the Staples Declaration provides evidence with articulated reasoning to support a finding that it would have been obvious to one of ordinary skill in the art to select a viscosity ***within*** the claimed range. Rather, the Petition asserts in conclusory fashion that "the viscosity range recited in the claims was merely the ***logical choice*** for a subcutaneous formulation deliverable via a syringe." Pet., p. 41 (emphasis added).

In true hindsight fashion, the Petition starts from the claimed viscosity range of 9 to 20 cps, alleging that this range "recognizes what was already known in that art: that the time to load a liquid formulation through a syringe needle quickly

becomes impractically long at viscosities greater than 20 cps." Pet., p. 40 (citing Staples Dec., ¶ 42). Paragraph 42 of the Staples Declaration refers to Figure 2B of Ex. 1005 that illustrates viscosity and syringe loading time as a function of NaCl concentration, observing that "the loading times for viscosities of greater than 20 cps rapidly rise from about 50 seconds to more than 300 seconds." From this, Dr. Staples concludes that "one of ordinary skill would understand that the viscosity of a subcutaneous formulation could ***not be much higher than 20 cps*** for a formulation having a high protein concentration like that claimed." Ex. 1006, ¶ 42 (emphasis added). Even assuming that Dr. Staples' conclusion is correct (which it is not as discussed below), a viscosity "not [] much higher than 20 cps" provides no evidence or articulated reasoning of a viscosity ***within the range of 9 to 20 cps*** as claimed.

Dr. Staples provides no articulated reasoning with rational underpinning to support his conclusion—it is merely an unsupported conclusory statement entitled to little or no weight. 37 C.F.R. § 42.65(a). For example, nowhere does Dr. Staples explain the effect the varying NaCl concentration would have on the formulation as a whole, even though Paragraph 43 of his declaration purports to address the "tonicity" constraint that he admits is affected by solutes, such as salts. *See* Ex. 1006, ¶ 43. Moreover, Figure 2B on which Dr. Staples relies is concerned with ***loading time***—the time to draw the sample from a vial into the syringe. But

such a "loading time" would be irrelevant to administration through a ***pre-filled*** syringe, and Dr. Staples never even attempts to explain why, in spite of this irrelevancy, a person of ordinary skill would nonetheless conclude from Figure 2B that viscosity "could not be much higher than 20 cps." Ex. 1006, ¶ 42.

And in fact Dr. Staples' conclusion that viscosity "could ***not be much higher than 20 cps*** for a formulation having a high protein concentration like that claimed" (Ex. 1006, ¶ 42 (emphasis added)) is incorrect, as evidenced by the CIMZIA® product. The CIMZIA® product, which is indicated for the treatment of, *inter alia*, rheumatoid arthritis, may be supplied as a single-use prefilled syringe with a 25-½ gauge needle for subcutaneous injection of certolizumab pegol, a humanized antibody Fab' fragment. Ex. 2007, pp. 6, 10, 21 of pdf. The concentration of the protein in the CIMZIA® product is 200 mg/mL, Ex. 2007, p. 6 of pdf, even higher than the 125 mg/mL recited in independent claim 7, and its ***viscosity is greater than 80 cps***. *See* Ex. 2008, p. 220, Figure 1 (Left) ("Dashed line represents the viscosity of the marketed Cimzia® solution (200 mg/mL = 2.2 mM) as a reference").[6] As evidenced by the CIMZIA® product, a viscosity of ***more than four times greater than 20 cps*** is possible for a subcutaneous formulation having a protein concentration even higher than that claimed. Dr.

[6] As known to one skilled in the art, 1 cps = 1 mPas. *See* Ex. 2010, p. 12.

Staples' conclusion is not only unsupported, it is incorrect and entitled to no weight.

Accordingly, the Petition fails to provide articulated reasoning supported by evidence for the viscosity range set forth in claim 1. For this reason as well, the Petition should be denied as to claim 1 and the claims depending therefrom.

2. Claims 1, 14, 15 – "weight ratio of sugar:protein"

Independent claim 1 requires that the "weight ratio of sugar:protein" be 1.1:1 or higher. Claims 14 and 15 depend from claim 5, which specifies that the sugar is sucrose, and require a weight ratio of sucrose:protein of 1.3:1 to 5:1, and 1.4:1, respectively. The Petition fails to explain the ***protein concentration*** that results in the claimed ratios, and, therefore, fails to specify where the weight ratio element of claims 1, 14, and 15 is found in the prior art as required by § 42.104(b)(4).

Page 36 of the Petition states that a concentration of sugar greater than 0.2 M was needed to achieve protein stability, alleging that this corresponds to greater than about 70 mg/ml for sucrose.[7] Without once mentioning protein concentration,

[7] Although the Petition alleges that "sucrose and trehalose were the logical choices" for a formulator, Pet., p. 35; Ex. 1006, ¶ 32, neither the Petition nor the Staples Declaration provides any rationale or explanation why sucrose would ultimately be selected over trehalose.

the Petition pronounces that sucrose in a range of greater than about 70 mg/ml "overlaps with the ranges recited in claim 1 ('weight ratio of sugar [sic] protein is 1.1:1 or higher') and claim 14 ('weight ratio of sucrose:protein is 1.3:1 to 1.5:1') . . . and in claim 15 ('weight ratio of sucrose:protein of 1.4:1')." The Petition cites Paragraph 47 of the Staples Declaration in support, but that paragraph does not cure the Petition's deficiency as it also focuses only on the amount of sugar and never once mentions ***protein*** concentration.

The Staples Declaration asserts that the amount of sugar claimed "reflects nothing more than the routine, trial-and-error optimization of a single variable (the amount of sugar) based on two known, competing considerations (the protein's stability against the solution's viscosity and tonicity)."[8] Ex. 1006, ¶ 45. But even if the "single variable" sugar amount was optimized, a weight ratio of sugar:protein introduces yet another variable—the amount of protein. The Petition and the Staples Declaration fail to account for protein concentration in the "trial-and-error" optimization argument, and, therefore, fail to adequately explain how the claimed ***ratios*** of sugar:protein result from the "optimized" amount of sugar.

[8] Dr. Staples cites *three* competing considerations (stability, tonicity, and viscosity), while the Petition itself refers only to stability and tonicity.

The Petition utterly fails: (i) to compare the formulations of claims 1, 14, and 15 to the alleged prior art; (ii) to explain with particularity the differences between the prior art and the claimed weight ratios of sugar:protein; and (iii) to explain why it would have been obvious for one of ordinary skill in the art to modify the prior art to arrive at the formulation with the claimed weight ratios of sugar:protein. Instead, the Petition merely asserts that through "trial-and-error" optimization a person of ordinary skill in the art could reconstruct the claimed weight ratios of sugar:protein using only an "optimized" amount of sugar, without taking into account the protein concentration that is the other half of the ratio. In addition, the Petition never explains what effect, if any, the protein concentration has on viscosity and the other "constraints" used in the "trial-and-error" optimization.

As such, the Petition fails to specify where the weight ratio element of claims 1, 14, and 15 is found in the prior art as required by § 42.104(b)(4). For this reason as well, the Petition should be denied as to claims 1, 14, and 15, and the claims depending therefrom.

3. Claim 7 - "sucrose in an amount of about 170 mg/ml"

Independent claim 7 requires "sucrose in an amount of about 170 mg/ml." Neither the Petition nor the Staples Declaration provides articulated reasoning with

rational underpinning to support a finding that it would have been obvious to one of ordinary skill in the art to select sucrose in an amount of ***about 170 mg/ml***.

All the Petition and the Staples Declaration muster on this point is a discussion of a possible *range* of sugar concentrations that *could* have been used in a formulation (greater than about 70 mg/ml and less than 350 mg/ml). Pet., pp. 36, 38; Ex. 1006, ¶ 33. Nowhere in the Petition or the Staples Declaration is there an explanation of why a person of ordinary skill would select "about 170 mg/ml" from this range, much less an explanation of why such a person would select this sucrose concentration for use in the same formulation with a 125 mg/ml protein concentration.

Accordingly, the Petition fails to provide articulated reasoning supported by evidence for the sucrose concentration set forth in claim 7. For this reason as well, the Petition should be denied as to claim 7 and the claims depending therefrom.

4. Claim 9 – "Poloxamer 188 in an amount of about 8 mg/ml"

Dependent claim 9 requires that the formulation of claim 7 include a particular surfactant—Poloxamer 188—in an amount of about 8 mg/ml. The Petition cites Ex. 1004 as disclosing a surfactant known as Pluronic F-68. Pet., p. 43; Ex. 1004, p. 187. The Petition then asserts that Poloxamer 188 and Pluronic F-68 "refer to the identical polymer composition" (Pet., p. 44), citing "MOM-1010" and Staples Declaration ¶ 56. However, neither the Petition nor the Staples

Declaration provides any ***evidence*** that Poloxamer 188 and Pluronic F-68 refer to the identical polymer composition, nor any ***evidence*** of the claimed concentration. Therefore, the Petition fails to specify where the recited element of claim 9 is found in the prior art as required by § 42.104(b)(4). For this reason as well, the Petition should be denied as to claim 9.

The exhibits filed with the Petition are listed on page iv of the Petition, and include "MOM-1001" through "MOM-1009." The exhibit list does not include "MOM-1010" that is cited on page 44 of the Petition for the proposition that Poloxamer 188 and Pluronic F-68 refer to the identical polymer composition. That "MOM-1010" was not filed with the Petition is confirmed by Ex. 2009, showing a PRPS screen shot of the exhibits (1001 to 1009) filed with the Petition.

The Staples Declaration does not cure the evidentiary deficiency of the Petition, merely asserting, with no evidentiary support, that "Poloxamer 188 and Pluronic F-68 refer to identical polymer compositions." Ex. 1006, ¶ 56. Paragraph 56 of the Staples Declaration provides no evidentiary support for any of the discussion therein regarding naming conventions, polymer compositions, or molecular weight, and, as such, is entitled to little or no weight. 37 C.F.R. § 42.65(a).

Claim 9 recites a concentration of 8 mg/ml of Poloxamer 188. The Petition, relying only on attorney argument, asserts that the claimed 8 mg/ml "was not

critically different" than the concentration of surfactant that Carpenter states are "typically" used in therapeutic protein formulations—"(*ca.* 100 micromolar)." Ex. 1004, p. 167.[9] Even Paragraph 56 of the Staples Declaration proffers no insight on the differences between the claimed 8 mg/ml and the "typical" concentration cited in Carpenter, proclaiming only, without evidentiary support, that "Poloxamer 188 has an average molecular weight of 7680-9510 g/mol, meaning that the claimed concentration of 8 mg/ml Poloxamer 188 is on the order of 1 mM." But even if that were correct, it is ***an order of magnitude different*** than the "*ca.* 100 micromolar" cited in Carpenter, which corresponds to 0.1 mM.

Moreover, the Petition's treatment of claim 9 is nothing more than blatant hindsight reconstruction—the Petition and the Staples Declaration start with the claimed 8 mg/ml concentration and then attempt to explain why that is not different from the "typical" surfactant concentration noted in Carpenter. Here again the Petition fails to conduct the proper analysis—starting from the prior art and explaining why it would have been obvious to a person of ordinary skill to arrive at the claimed concentration of Poloxamer 188. For this reason as well, the Petition should be denied as to claim 9.

[9] Notably, page 167 of Ex. 1004 makes no mention of Poloxamer 188 or Pluronic F-68.

5. Claim 11 – "stable when stored at 2 to 8 C for at least 12 months"

Dependent claim 11 requires that the formulation be stable "when stored at 2 to 8 C for at least 12 months." Page 45 of the Petition asserts that "' [i]n general, a shelf life of 18 month[s] is considered acceptable for commercialization' of protein pharmaceuticals," citing to Carpenter, Ex. 1004, p. 16. However, neither the Petition nor the Staples Declaration provides any ***evidence*** regarding the cited storage temperature. Therefore, the Petition fails to specify where the recited element of claim 11 is found in the prior art as required by § 42.104(b)(4).

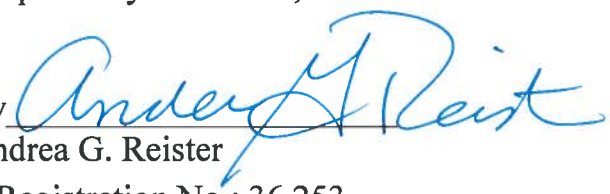
Nowhere on page 16 of Carpenter cited in the Petition is the storage temperature even mentioned. The Petition cites Paragraph 57 of the Staples Declaration, which does not cure the evidentiary deficiency. Paragraph 57 merely provides a conclusory statement that "[t]o be commercially viable, a pharmaceutical formulation should be stable for at least 18 months," with no mention whatsoever of storage temperature, much less any evidentiary support, and, therefore, should be accorded little, if any, weight. 37 C.F.R. § 42.65(a). The Petition completely fails to provide any evidentiary support for the storage temperature, and its support for the duration of stability is conclusory at best. For these reasons as well, the Petition should be denied as to claim 11.

IV. Conclusion

The Petition has not demonstrated that there is a reasonable likelihood that at least one of the challenged claims is unpatentable. For this reason, the Petition should be denied in its entirety.

Dated: October 20, 2015

Respectfully submitted,

By 

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on this 20th day of October 2015, the foregoing **Patent Owner Preliminary Response Pursuant to 37 C.F.R. § 42.107, together with Exhibits 2001–2010**, was served by electronic mail, by agreement of the parties, on the following counsel of record for Petitioner:

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