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 RESPONSE
PURSUANT TO 37 C.F.R. § 42.120

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
2011	Wang (1999) Instability, stabilization, and formulation of liquid protein pharmaceuticals *Intl. J. Pharmaceutics*, 185(2):129–188
2012	Transcript, Deposition of Mark A. Staples, Ph.D. (March 16, 2016)
2013	Declaration of Marilyn Morris, Ph.D.
2014	Curriculum vitae of Marilyn Morris, Ph.D.
2015	Declaration of Alexander Klibanov, Ph.D.
2016	Curriculum vitae of Alexander Klibanov, Ph.D.
2017	Gonal-f® Prescribing Information
2018	Randolph & Carpenter (2007) Engineering Challenges of Protein Formulations *AIChE J.*, 53(8):1902–1907
2019	U.S. Patent No. 8,512,691
2020	AVONEX® (interferon beta-1a) Label (Revised 2012)
2021	Rowland & Tozer (1995) *Clinical Pharmacokinetics Concepts and Applications*, Williams & Wilkins, definitions of symbols, chapters 3, 4, 5, and 13
2022	Appeal Brief Under 37 C.F.R. § 41.37, Prosecution of Application No. 11/975,379
2023	Cleland & Shire (1993) The Development of Stable Protein Formulations: A Close Look at Protein Aggregation, Deamidation, and Oxidation, *Critical Reviews in Therapeutic Drug Carrier Systems*, 10(4):307–377
2024	Proos *et al*. (2008) Long-term Stability and *in vitro* Release of hPTH91-34) from a Multi-reservoir Array, *Pharm. Res.*, 25(6):1387–1395
2025	U.S. Patent No. 5,851,795
2026	Orencia® 2005 Label
2027	Actimmune® Label
2028	Srinivas *et al.* (1997) Assessment of Dose Proportionality, Absolute Bioavailability, and Immunogenicity Response of CTLA4Ig (BMS-188667), a Novel Immunosuppressive Agent, Following Subcutaneous and Intravenous Administration to Rats, *Pharm. Res.*, 14(7):911–916
2029	McDonald *et al.* (2010) Subcutaneous administration of biotherapeutics: Current experience in animal models, *Curr. Opin. Mol. Therapeutics*, 12(4):461–470

Exhibit	Description
2030	Porter *et al.* (2000) Lymphatic Transport of Proteins After Subcutaneous Administration, *J. Pharm. Sci.*, 89(3):297–310

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I. Introduction

The Petition filed by Momenta Pharmaceuticals, Inc. fails to meet its burden of proving unpatentability for any claim of U.S. Patent No. 8,476,239 ("'239 Patent"). The '239 Patent—which covers the subcutaneous formulation of Orencia® for treatment of rheumatoid arthritis—claims stable liquid formulations of the protein therapeutic CTLA4Ig which are dramatically different from any prior art protein formulations or teachings of record.

As explained in this response of Patent Owner Bristol-Myers Squibb Company, Petitioner has failed to identify any prior art teaching a stable liquid formulation of CTLA4Ig, any prior art showing that such a formulation could reasonably be achieved for this protein, or any prior art teaching or suggesting the claimed concentrations of CTLA4Ig (claims 1, 7), sugar/sucrose (*e.g.*, claims 1, 7), or Poloxamer 188 (claim 9) in a stable liquid formulation (among others).

Petitioner attempts to fill some (but not all) of these gaps with unsupported testimony from Dr. Staples, who asserts that a formulator could develop a stable liquid formulation of CTLA4Ig by looking to a "toolbox" of excipients and protocols that had been used in *other* protein formulations, and then engaging in "trial-and-error optimization" to arrive at the various formulation parameters claimed in the '239 Patent. *See* Staples Decl., Ex. 1006, at ¶¶ 45–58.

But Dr. Staples flatly abandoned these opinions when cross-examined, and for good reason. The prior art, including the very art he cited, all stands for the opposite conclusion, namely that the skilled person would *not* reasonably expect (or even attempt) such a generic, brute-force approach to protein formulation.

Critically, for example, Dr. Staples recanted his core opinion that parameters for one protein would be expected to work for another, acknowledging that "the conditions necessary for stabilizing one protein *would not necessarily be effective or even reasonably predictive* in stabilizing another protein." Staples Tr., Ex. 2012, at 165:18–166:2 (emphasis added). Dr. Staples also readily conceded that "[y]ou'd need to do the preformulation studies" on CTLA4Ig *before* any formulation work, a process his declaration ignored. *Id.* at 80:2–3.

In fact, a wide body of literature before and after 2005 confirms what Dr. Staples admitted—that achieving a stable liquid formulation of a protein therapeutic like CTLA4Ig is an unpredictable and highly protein-specific challenge, involving numerous parameters with complex interdependencies. Indeed, "[t]he structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Wang, Ex. 2011, at 130. These challenges are highlighted even by the 2002 Carpenter book relied upon by Petitioner and Dr. Staples. Carpenter explains that "for most proteins maintaining physical and chemical stabilities in aqueous solution for an

extended period of time is *extremely difficult*," and the "exquisite sensitivity of protein structure, function, and stability to the primary sequence *does not readily lend itself to a generic approach* for protein formulation." Carpenter, Ex. 1004, at 184–85 (emphasis added).

For other of his opinions, Dr. Staples not only abandoned them, but testified that he was not qualified to give them in the first place. Dr. Staples's opinions on selecting the appropriate CTLA4Ig concentration for subcutaneous administration—which rely on bioavailability data obtained from a single study using rodents instead of humans—are admittedly outside his area of expertise and without any scientific grounding. *See id.* at 117:6–7 ("I'm not an expert in pharmacokinetics."), 123:22–23 ("[T]hat's outside my experience of clinical practice."). Indeed, Dr. Staples admitted that he does not even know "what is the meaningful pharmacokinetic parameter for the effectiveness of CTLA4Ig in treating rheumatoid arthritis." *Id.* at 117:8–11. As explained by Dr. Morris, who *is* an expert in pharmacokinetics, this information (as well as human bioavailability data) would be critical for having a reasonable chance of developing an appropriate CTLA4Ig concentration. Morris Decl., Ex. 2013, at ¶¶ 26–27. Therefore, Dr. Staples's declaration should be accorded little, if any, weight.

Dr. Staples's admissions confirm that a formulator would not follow the approach of the Petition—trial-and-error optimization based on formulation

components and parameters used for *other*, non-CTLA4Ig proteins. But even if she did, she would have had no reasonable expectation of success. This is especially true given the lack of prior art disclosing the relevant degradation pathways of CTLA4Ig, which would be critical for identifying an approach to stabilize this protein.

Moreover, even if one were to try the Petition's generic approach, this would not lead to the formulations claimed in the '239 Patent. For example, with respect to the claimed sugar/sucrose concentrations, those prior art formulations that did use sucrose used *less than 70 mg/ml*—contradicting Dr. Staples's mistaken assumption that using less than 70 mg/ml sucrose "would be unusual," Staples Tr., Ex. 2012, at 126:13–16. Additionally, since Dr. Staples admits that a formulator would have been motivated to "avoid[] unnecessarily high sugar concentrations that would cause . . . excessive hypertonicity," Staples Decl., Ex. 1006, at ¶ 34, a formulator would be unlikely to try a significantly higher sucrose concentration (such as about 170 mg/ml, as in claim 7). Klibanov Decl., Ex. 2015, at ¶¶ 73–85.

Finally, Petitioner did not even attempt to put forth evidence for many of the claimed formulation parameters. Regarding the surfactant of claim 9, for example, neither the Petition nor Dr. Staples's declaration explains why a formulator might have chosen Poloxamer 188 (over other available options), or why she would have done so in a concentration ten times higher than the literature allegedly specifies.

Nor does the Petition introduce any prior art evidence regarding the stability time and temperature requirements of claim 11, or cite anything with respect to the denominator of the sugar/sucrose ratios specified in claims 1, 5, 14, and 15.

At the end of the day, both sides' experts (including Dr. Staples, in his cross-examination testimony) and documentary exhibits (*e.g.*, Wang, Carpenter) agree on the relevant facts. Those facts mean that a skilled artisan would not have a reasonable expectation of success to arrive at the claimed inventions. Petitioner plainly has not met its burden to show how prior art regarding formulations of *other* proteins with *different* parameters would have provided the requisite guidance to overcome the challenges in achieving the formulations claimed in the '239 Patent. Even impermissibly using hindsight to navigate the prior art, Petitioner's arguments fail, and the '239 Patent claims cannot be held unpatentable.

II. Person of Ordinary Skill in the Art

At the time of the inventions claimed by the '239 Patent, a person of ordinary skill in the art would have had expertise in both (1) formulation development, for determining the specific formulation components (excipients) and parameters to ensure storage and delivery stability for the protein; and (2) pharmacology, specifically analyzing pharmacokinetics of protein administration, for determining the appropriate dosing regimen for subcutaneous administration and, based on this dosage, the appropriate protein concentration for the

formulation. Morris Decl., Ex. 2013, at ¶¶ 10–13; Klibanov Decl., Ex. 2015, at ¶¶ 13–18. A person of ordinary skill in the art with respect to aspects of the inventions relating to protein formulation would have a Ph.D. in pharmacy, biochemistry, biophysics, or a related field, plus at least two to five years of experience developing stable aqueous formulations of therapeutic proteins. Klibanov Decl., Ex. 2015, at ¶ 14. A person of ordinary skill working on determining the appropriate concentration of the protein would have a Ph.D. in pharmaceutics, pharmaceutical sciences, or a substantially similar field with an emphasis in pharmacokinetics and pharmacodynamics, and at least 2–5 years of experience analyzing pharmacokinetics and pharmacodynamics of proteins. Morris Decl., Ex. 2013, at ¶ 11.

Given this level of ordinary skill, Patent Owner offers expert testimony of both Dr. Alexander Klibanov, a chemist and chemical engineer with over 30 years of experience with protein formulation, and Dr. Marilyn Morris, a pharmaceutical scientist with a Ph.D. in Pharmaceutics and over 30 years of experience with pharmacokinetics and pharmacodynamics. Klibanov Decl., Ex. 2015, at ¶¶ 3–12; Klibanov CV, Ex. 2016; Morris Decl., Ex. 2013, at ¶¶ 3–9; Morris CV, Ex. 2014. In contrast, Petitioner relies solely on Dr. Mark Staples, who has no expertise in pharmacology, Staples Tr., Ex. 2012, at 47:19–20, has no expertise "in determining

the bioavailability of a drug product," *id.* at 47:21–23, and is "not an expert in pharmacokinetics," *id.* at 117:3–7.

III. Background on Formulation Challenges

At the time of the '239 Patent's inventions (the 2005 timeframe), achieving a stable liquid formulation of a protein therapeutic like CTLA4Ig was an unpredictable and highly protein-specific challenge. Klibanov Decl., Ex. 2015, at ¶ 19.

At the core of the complexity and unpredictability of formulating a stable liquid protein formulation is the uniqueness of every protein. Klibanov Decl., Ex. 2015, at ¶¶ 20–22. Each protein has different chemical and physical properties, resulting in different degradation (destabilizing) pathways. Klibanov Decl., Ex. 2015, at ¶¶ 20–22; 33–35. Possible destabilizing effects include: non-covalent aggregation, covalent aggregation, deamidation, cyclic imide, cleavages, oxidation, surface denaturation, and adsorption. Carpenter, Ex. 1004, at 13, Table 6. Dr. Staples agreed in his deposition that a skilled artisan in 2005 would be familiar with each of these potential degradation pathways and the possible causes noted in Carpenter. Staples Tr., Ex. 2012, at 71:16–77:17.

"[T]he structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Wang, Ex. 2011, at 130. Indeed, "[e]ven for closely related proteins, the relative stability

and major pathways for degradation might be quite different." Carpenter, Ex. 1004, at 185–86.

Additionally, it was unclear in 2005 what components, parameters, and combinations thereof would have a stabilizing effect on a particular protein. Klibanov Decl., Ex. 2015, at ¶ 21. An excipient, such as a buffer, or formulation parameter, such as pH, that stabilizes one protein may destabilize another protein. *Id.* at ¶¶ 21–24. Moreover, components and parameters of a formulation do not work in isolation, but instead are interdependent. Accordingly, changing one or more of these variables can and typically does profoundly affect the overall stability and suitability of the formulation. *Id.* at ¶¶ 23–24.

Formulating proteins as a liquid (as opposed to a lyophilized, or freeze-dried, formulation) is particularly unpredictable and challenging because the protein must retain its physical and chemical stability in solution for months or years. *Id.* at ¶ 19. This unpredictability is further exacerbated with high protein concentrations (>50 mg/ml), including at the even higher concentrations claimed in the '239 Patent (>100 mg/ml). *Id.* at ¶¶ 26–28; Shire, Ex. 1005, at 1399 ("Protein properties such as self-association/aggregation, solubility, and viscosity pose challenges to developing pharmaceutically and economically acceptable formulations at high concentration.").

These challenges are highlighted in the literature both before and after 2005. Even the 2002 Carpenter book relied upon by Petitioner and Dr. Staples stresses that "for most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is *extremely difficult*." Carpenter, Ex. 1004, at 184 (emphasis added). In fact, "[i]t can be assumed that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." *Id.* at 188. Even in 2007, two years *after* the priority date, it was understood that the "[d]evelopment of these [high protein concentration] formulations poses a number of serious obstacles to commercialization." Randolph & Carpenter, Ex. 2018, at 1905.

Given the protein-specific nature of the formulation challenge, protein formulation "does not readily lend itself to a generic approach." Carpenter, Ex. 1004, at 185; *see also* Cleland, Ex. 2023, at 359 ("The effects of protein degradation such as deamidation or oxidation cannot be predicted *a priori* and have to be determined for each protein."). "Even for closely related proteins, the relative stability and major pathways for degradation might be quite different." Carpenter, Ex. 1004, at 185–86; *see* Klibanov Decl., Ex. 2015, at ¶ 36.

Accordingly, to develop a stable liquid formulation of a protein therapeutic, it is critical to begin by analyzing the specific protein to be formulated, including its individual degradation pathways and their relative importance at various

conditions. Klibanov Decl., Ex. 2015, at ¶¶ 33–36; Wang at 178 ("To develop a liquid protein pharmaceutical, the basic properties of a protein need to be examined first."); Staples Tr., Ex. 2012, at 36:1–11, 67:10–68:5, 70:13–82:16. A person of ordinary skill cannot know the degradation pathways, and their relative importance, for a specific protein, without conducting extensive biochemical and biophysical analyses. Klibanov Decl., Ex. 2015, at ¶¶ 33–36.

This "preformulation study" entails a series of protocols and tests to identify the protein's specific degradation pathways as a function of experimental conditions. Klibanov Decl., Ex. 2015, at ¶¶ 33–36. This information is critical to understand what formulation conditions might be used to achieve adequate stability for a given protein. Klibanov Decl., Ex. 2015, at ¶¶ 33–36; 42–43. Indeed, this approach is consistent with the formulation process described in the specification of the '239 Patent. *See, e.g.*, '239 Patent at 18:27–20:2 (describing preformulation studies) and Examples V, VII, VIII, and IX.

Dr. Staples agreed, during cross-examination, that in developing a stable liquid protein formulation, one would have to "first study and then balance" the effects of formulation parameters on potential degradation pathways. Staples Tr., Ex. 2012, at 84:1–7. Dr. Staples also agreed that "a person of ordinary skill in the art, in 2005, is not going to expect a particular protein to be stable enough in aqueous solution to allow a liquid formulation to be developed without doing the

actual stability studies." Staples Tr., Ex. 2012, at 63:14–20; *see also id.* at 62:19–63:1 (**Q.** "And I take it a person of ordinary skill in the art, without doing these studies, cannot predict whether a particular protein is or is not going to be sufficiently stable in the liquid state. Correct?" **A.** "Correct. That's part of the--that's part of what the initial studies are for, to determine that.").

Based on the information gleaned from examining a protein of interest and its degradation pathways, a formulator would then begin to experiment with test formulations, reflecting her hypotheses as to approaches that might succeed in stabilizing the protein, while hopefully also yielding a formulation that would be appropriate for patient administration. Klibanov Decl., Ex. 2015, at ¶¶ 42–46. This remains a challenging and unpredictable process, especially as the number of formulation components and parameters available are "far too many" "to allow a purely empirical screening approach to be successful." Randolph & Carpenter, Ex. 2018, at 1902. These preliminary formulations are tested in stressed or accelerated conditions, to obtain information about how the formulation performs. Klibanov Decl., Ex. 2015, at ¶¶ 42–43. However, the ultimate suitability of a pharmaceutical formulation cannot be ascertained until it has been measured over the full real-time actual-storage conditions (for example, over a period of a year or longer). Klibanov Decl., Ex. 2015, at ¶¶ 42–46. Accordingly, developing and assessing test formulations of therapeutic proteins is a lengthy and arduous process performed

over many months or, more typically, years, since formulations are tested and then often abandoned (if they are not satisfactory) or iteratively refined (if they appear promising). Klibanov Decl., Ex. 2015, at ¶ 46.

IV. Argument

A. Legal standards

A party alleging obviousness is required to show that "a skilled artisan would have had reason to combine" the cited prior art references and that a "skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). 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). Where "a defendant urges an obviousness finding by 'merely throw[ing] metaphorical darts at a board' in hopes of arriving at a successful result, but 'the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,' courts should reject 'hindsight claims of obviousness.'" *In re Cyclobenzaprine*, 676 F.3d at 1070–71. To protect against any hindsight bias, the appropriate inquiry is not whether "one of ordinary skill in the art could combine [the] references," it is whether "they would have been

motivated to do so." *InTouch Techs., Inc. v. VGo Commc'ns*, 751 F.3d 1327, 1352 (Fed. Cir. 2014).

B. The Petitioner has not proven that a person of ordinary skill in the art would have had a reasonable likelihood of success in developing a stable liquid formulation of CTLA4Ig by looking to formulation approaches used for other proteins.

The inventions claimed in the '239 Patent relate to stable liquid protein (CTLA4Ig) formulations with protein concentrations of 100 mg/ml or greater. '239 Patent, claims 1–15. As is evident from the literature and experts cited by both sides in this proceeding, formulating such a protein, especially in stable liquid form and at high concentrations, is both challenging and highly protein-specific.

Accordingly, Petitioner cannot sustain its argument that a skilled artisan would reasonably expect to achieve the claimed stable liquid formulation of CTLA4Ig generically, based on formulation approaches used for other proteins—especially given Dr. Staples's admissions that "*the conditions necessary for stabilizing one protein would not necessarily be effective, or even reasonably predictive, in stabilizing another protein*," Staples Appeal Br., Ex. 2022, at 14 (emphasis added); *see also* Staples Tr., Ex. 2012, at 165:18–166:2 ("**Q.** And that's true. Correct? **A.** Yes."), and that "a person of ordinary skill in the art, in 2005, is not going to expect a protein, a particular protein to be stable enough in aqueous solution to allow a liquid formulation to be developed without doing the actual stability studies." Staples Tr., Ex. 2012, at 63:6–20.

1. Developing stable liquid formulations of therapeutic proteins is a complicated and unpredictable process.

As explained in the Background on Formulation Challenges section above, each protein is unique, with different chemical and physical properties that result in numerous different degradation pathways that need to be evaluated before formulation can even begin. *E.g.*, Staples Tr., Ex. 2012, at 71:12–89:19; Carpenter, Ex. 1004, at 13. Formulating proteins as a liquid (as opposed to a lyophilized, or freeze-dried, formulation) is particularly unpredictable and challenging because the protein must retain its physical and chemical stability for months or years. Klibanov Decl., Ex. 2015, at ¶¶ 19–20. Aqueous solutions are further complicated because "several chemical degradation pathways (e.g., hydrolysis and deamidation) are mediated by water." Carpenter, Ex. 1004 at 110.

In fact, it is not even clear a person of ordinary skill would have *attempted* a stable liquid formulation: "most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." *Id.* at 188. This is underscored by the prevalence of lyophilized (*i.e.*, freeze dried) formulations, which are not subject to the same degradation concerns. *See id.* at 184 ("Most protein pharmaceuticals currently on the market are sold as lyophilized formulations."); Proos, Ex. 2024, at 1394 ("The issue of longer-term stability was addressed according to the most prevalent method for preservation of polypeptides, lyophilization."); Klibanov Decl., Ex. 2015, at ¶ 32. Indeed, it was understood that

"lyophilization should be considered as a primary mode for product development," given the stability complications with aqueous formulations. Carpenter, Ex. 1004, at 110; Klibanov Decl., Ex. 2015, at ¶ 32.

The unpredictability of aqueous formulations is further exacerbated with high protein concentrations (>50 mg/ml). *See* Klibanov Decl., Ex. 2015, at ¶¶ 26–28; Shire, Ex. 1005, at 1399. Additionally, it was unclear in 2005 what components, parameters, and combinations thereof would have a stabilizing effect on a particular protein. Klibanov Decl., Ex. 2015, at ¶ 21. An excipient, such as a buffer, or formulation parameter, such as pH, that stabilizes one protein may destabilize another protein. *Id.* at ¶¶ 22–26.

These formulation challenges are confirmed by a wide body of literature both before and after 2005 (as well as both sides' expert testimony). For example, the 1999 Wang article stresses that "[i]n the development of a protein formulation, *the most challenging task* is the stabilization of a protein to achieve an acceptable shelf life." Wang, Ex. 2011, at 178 (emphasis added). Indeed, "the structural differences among different proteins are so significant that *generalization of universal stabilization strategies has not been successful*." *Id.* at 130 (emphasis added). Even in 2007, two years *after* the priority date, it was understood that the "[d]evelopment of these [high protein concentration] formulations poses a number

of serious obstacles to commercialization." Randolph & Carpenter, Ex. 2018, at 1905.

The formulation challenges are underscored in the very references on which Petitioner relies. For example, Carpenter explains that "for most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is *extremely difficult*," and the "exquisite sensitivity of protein structure, function, and stability to the primary sequence *does not readily lend itself to a generic approach* for protein formulation." Carpenter, Ex. 1004, at 184–85 (emphasis added). Thus, "developing conditions to keep proteins stable in a liquid form for a pharmaceutically relevant storage time (e.g., two years) is not a simple task." Carpenter, Ex. 1004, at 10–11; *see also* Shire, Ex. 1005, at 1399.

Accordingly, a person of ordinary skill reading Petitioner's own cited references would not have a reasonable expectation of success in being able to achieve the claimed stable liquid formulations of CTLA4Ig. Klibanov Decl., Ex. 2015, at ¶¶ 56–61.

2. The Petition's generic, brute-force approach to formulation would not be expected to succeed.

Despite these formulation challenges, the Petition does not identify any stable liquid protein formulations of CTLA4Ig, much less with a concentration approaching 100 mg/ml or 125 mg/ml.

Rather, the Petition argues that a formulator could have developed a stable, high-concentration, liquid formulation of CTLA4Ig based on excipients and approaches that had been used to stabilize *other proteins*. Pet. at 33–42; Staples Decl., Ex. 1006, at ¶¶ 27–28. Pointing to the declaration of Dr. Staples (which he largely recanted during cross-examination, and which is contradicted by the prior art cited by both Petitioner and Patent Owner), the Petition argues that a formulation could have been developed via "trial-and-error optimization" based on a series of generalized "known constraints" purportedly taught by the prior art. *See* Pet. at 26, 38; Staples Decl., Ex. 1006, at ¶ 45. The evidence cannot sustain this.

First, nothing in the prior art supports that a person of skill in the art would take such a generic approach to formulation or expect it to work if they did. As Dr. Staples acknowledged, a person of ordinary skill in the art would not "expect two proteins having different amino acid sequences, structures, and translational modifications" could be stabilized in the same manner. Staples Tr., Ex. 2012, 164:24–165:25, 168:3–12. "Even for closely related proteins, the relative stability and major pathways for degradation might be quite different." Carpenter, Ex. 1004, at 185–86.

Accordingly, to develop a stable liquid formulation of CTLA4Ig, a person of ordinary skill would need to understand CTLA4Ig's specific degradation pathways

(*e.g.*, by intense preformulation study), in order to have any guidance on how to inhibit its degradation with excipients and formulation parameters. Staples Tr., Ex. 2012, at 36:1–11, 67:10–68:5, 70:13–82:16; Klibanov Decl., Ex. 2015, at ¶¶ 33–36. For example, Cleland explains that "[t]he effects of protein degradation such as deamidation or oxidation cannot be predicted *a priori* and have to be determined for each protein." Cleland, Ex. 2023, at 359. And Carpenter itself confirms that "[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*." Carpenter, Ex. 1004, at 185 (emphasis added).

Second, the Petition does not identify any prior art information teaching the relevant degradation pathways for CTLA4Ig—despite Dr. Staples's admissions that such information is necessary. *See* Staples Tr., Ex. 2012, at 63:2–20, 71:12–89:19, 170:9–20. In fact, Petitioner cites only two references relating to CTLA4Ig, Cohen, Ex. 1003, and Srinivas (1995), Ex. 1009. The formulation in Cohen is a lyophilized formulation, which is irrelevant to formulation parameters for a liquid formulation. Indeed, Dr. Staples admitted that a skilled artisan "*would learn nothing* from a lyophilized formulation for purposes of the stable liquid formulation." Staples Tr., Ex. 2012, at 164:1–6 (emphasis added); *see also* Staples Appeal Br., Ex. 2022, at 13. Likewise, the formulation administered in Srinivas (1995) was prepared on the study day and is not a stable liquid protein formulation.

Thus, without such guidance on how CTLA4Ig might reasonably be formulated, a person of ordinary skill is left "'merely throw[ing] metaphorical darts at a board' in hopes of arriving at a successful result." *In re Cyclobenzaprine*, 676 F.3d at 1070–71. Petitioner cites no prior art that gives "[any] indication of which parameters were critical [to formulating CTLA4Ig] or [any] direction as to which of many possible choices is likely to be successful." *Id.*

Moreover, even if a formulator *did* have or learn information about the relevant properties of CTLA4Ig, developing a stable liquid formulation of this protein would remain a challenging and unpredictable process, requiring significant further experimentation and study. Klibanov Decl., Ex. 2015, at ¶¶ 42–46. That is, the number of formulation components and parameters available are "far too many" "to allow a purely empirical screening approach to be successful." Randolph & Carpenter, Ex. 2018, at 1902. Specifically, Table 2 in Carpenter, which Dr. Staples characterizes as a "relatively small, limited toolbox," Staples Decl., Ex. 1006, at ¶¶ 27–28, includes 7 buffers, 3 salts, 4 surfactants, 1 chelator, at least 34 non-specific stabilizers, and unidentified specific stabilizers (with no concentrations for any of these components provided in the table). Carpenter, Ex. 1004, at 187. Thus, Table 2 alone includes at least 2,856 possible formulation combinations without taking into account the specific stabilizers. Klibanov Decl., Ex. 2015, at ¶ 63. In addition, Table 2 includes only "possible" excipients, not all

excipients. Carpenter, Ex. 1004, at 187, Table 2. The breadth of choices and possible combinations of parameters and excipients "indicate[s] that these disclosures would not have rendered the claimed invention obvious to try." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013).

Nor can *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989) sustain Petitioner's generic, brute-force approach. In *Merck*, the prior art disclosed an oral dose of a combination of two diuretics that "selectively enhance[s] the excretion of sodium ions without causing an increase in excretion of potassium ions." 874 F.2d at 806. The court ruled this disclosure rendered obvious claims to a combination of the *same two oral diuretics* formulated for the *same purpose* as the prior art, albeit in a specific ratio, because the ratio did no more than optimize the previously observed effect. *Id.* at 809.

Here, unlike *Merck*, there is no known result to optimize, because Petitioner has cited no prior art disclosing a stable liquid formulation of CTLA4Ig, or any art teaching the relevant degradation pathways for CTLA4Ig. Petitioner thus has failed to show through "articulated reasoning with some rational underpinning," *KSR*, 550 U.S. at 418, that a person of ordinary skill would have a reasonable expectation to successfully develop a stable liquid formulation of CTLA4Ig.

Third, the Petitioner's approach is based on the flawed premise that formulation of a stable liquid formulation of CTLA4Ig could be accomplished with

a series of single factor experiments. The Petition suggests that a person of ordinary skill would start with protein concentration, Pet. at 31, and then move through a series of parameters (buffer, *id.* at 34, 42; surfactant, *id.* at 34, 43; stabilizer (*e.g.*, sugar), *id.* at 35; viscosity, *id.* at 40; pH, *id.* at 41; aqueous carrier, *id.* at 42), addressing each parameter serially, one at a time. According to Petitioner, these factors could be optimized through routine trial and error. Pet. at 33–35.

However, Petitioner's approach ignores the fact that components and parameters of a formulation do not work in isolation, but instead are interdependent. Klibanov Decl., Ex. 2015, at ¶ 23. Changing one or more of these variables can and typically does profoundly affect the overall stability and suitability of the formulation. Klibanov Decl., Ex. 2015, at ¶¶ 23–24. A change to one parameter, for example pH, may very well render another parameter ineffective, for example the stabilizer. *Id.*

Accordingly, the Petitioner is far from reaching its burden of showing that a skilled artisan would have had a reasonable expectation of success in attempting the Petition's generic, brute-force approach for developing the claimed stable liquid formulations of CTLA4Ig.

3. Dr. Staples's declaration is inconsistent with his cross-examination testimony, his prior statements to the Board, and the cited references, and therefore should be given little, if any, weight.

Further, Dr. Staples's declaration testimony on developing a stable liquid CTLA4Ig formulation is inconsistent with his cross-examination, his prior statements to the Board of Patent Appeals and Interferences, the references he cited, and the weight of the evidence.

To formulate a protein, Dr. Staples's declaration claims that there is a "relatively small, limited toolbox," Staples Decl., Ex. 1006, at ¶¶ 27–28, of excipients and parameters, and that formulation approaches that had been used for different proteins could be used to develop a stable liquid formulation of CTLA4Ig through "trial-and-error optimization," *id.* at ¶ 45. In his declaration, Dr. Staples attempted to paint a picture that protein formulation was routine and standardized in 2005. In addition to this position being contradicted by the literature, *see supra* pages 15–16, Dr. Staples's cross-examination testimony fundamentally undercuts his approach. For example, during cross-examination Dr. Staples testified:

> **Q.** And then if you'll turn to Page 188 in the Carpenter Handbook [MOM-1004].
>
> **A.** I'm there.
>
> **Q.** Do you see the sentence right after lyophilized formulation that reads, "It can be assumed that most proteins will not exhibit sufficient

> stability in aqueous solution to allow a liquid formulation to be developed"?
>
> **A.** Yes.
>
> **Q.** And that was true as of 2005. Correct?
>
> **A.** It was generally true.
>
> **Q.** ***And so a person of ordinary skill in the art, in 2005, is not going to expect a protein, a particular protein to be stable enough in aqueous solution to allow a liquid formulation to be developed without doing the actual stability studies.*** Correct?
>
> **A.** ***Correct.***

Staples Tr., Ex. 2012, at 63:2–20 (emphasis added). In addition, Dr. Staples admitted the necessity of stability and degradation studies as a critical initial step in developing a stable liquid protein formulation:

> **Q.** So a person of ordinary skill in the art looking to formulate a particular protein, in 2005, would not view formulations of other proteins as providing particular guidance for the formulation of a new protein. Correct?
>
> **A.** Not in a specific sense.
>
> **Q.** ***And each protein needed to be studied itself to determine the relative importance of the various degradation pathways*** and instability mechanisms for that protein. Correct?
>
> **A.** ***Correct.*** That's -- that would all be determined in the initial preformulation studies.

Id. at 65:22–66:8 (emphasis added).

> **Q.** But in all cases, one needs to analyze the degradation profile and understand the degradants?
>
> **A.** Exactly. In all cases, you have to have that process. What -- and I'm just pointing out the level of detail of that varies across those phases.
>
> **Q.** And the reason it varies is because ***it is a complex process to determine degradation profiles***, so one's understanding evolves over time. Correct?
>
> **A.** ***Yes.***

Id. at 170:9–20 (emphasis added); *see also id.* at 71:12–89:19 (discussing stability concerns in Table 6 of Carpenter). Yet, Dr. Staples does not cite a single study relating to stability or degradation of CTLA4Ig in his declaration:

> **Q.** So a person of ordinary skill in the art, in 2005, looking to develop a stable liquid formulation of CTLA4-Ig would recognize that it was important to first test the CTLA4-Ig protein under a variety of physical and chemical stresses in order to provide a good simulation of the degradation products that can be generated. Correct?
>
> **A.** Yes.
>
> **Q.** And do you, in your declaration, describe any such test results?
>
> **A.** Well, ***I wouldn't have that access to any for CTLA4.***
>
> **Q.** So the results of that sort of testing for--scratch that. The results of testing under physical and chemical stresses to provide a good simulation of the degradation products that could be generated for CTLA4-Ig would not be in the public domain?
>
> **A.** ***I don't know. I don't have that knowledge.***

Staples Tr., Ex. 2012, at 70:13–71:8.

Furthermore, when addressing the Patent Office for his own patent, Dr. Staples has stressed the unpredictability of protein formulation. Dr. Staples is listed as an inventor on U.S. Patent No. 8,512,691 ("'691 Patent"), titled "Stable Liquid Interferon Formulations," which claims priority to an application filed in 1997. During prosecution of the application that eventually issued as the '691 Patent, an appeal brief was filed to overcome prior art rejections. The appeal brief—which Dr. Staples endorsed at his deposition—explains that "*it was difficult to produce a liquid composition that had the long-term storage characteristics* that were required for the [protein] compositions to be produced, shipped, stored and distributed to patients and then conveniently stored by them for ultimate use." Staples Appeal Br., Ex. 2022, at 6 (emphasis added). The brief further argued that "the skilled worker would not expect two proteins having different amino acid sequences, structures and post-translational modifications . . . would be stabilized in the same manner" and that "the skilled worker would have understood . . . *that the conditions necessary for stabilizing one protein would not necessarily be effective, or* <u>*even reasonably predictive*</u>*, in stabilizing another protein*." *Id.* at 14 (emphasis added); *see also* Staples Tr., Ex. 2012, at 165:18–166:2 ("**Q.** And that's true. Correct? **A.** Yes."). The same representations that Dr. Staples made

regarding the protein that he formulated apply to CTLA4Ig in 2005. *See* Klibanov Decl., Ex. 2015, at ¶¶ 47–50.

Because Dr. Staples's declaration and cross-examination testimony conflict, the Board should look to the weight of the evidence to determine which of his testimony (if any) to credit. Dr. Staples's declaration is inconsistent with his cross-examination testimony, the references cited by Petitioner and Patent Owner, *see supra* pages 15–16, and Dr. Klibanov's testimony. Therefore, Dr. Staples's declaration should be given little, if any, weight.

C. The concentrations of CTLA4Ig claimed in the '239 Patent are not taught in the prior art.

Every claim of the '239 Patent requires a concentration of at least 100 mg/ml of CTLA4Ig. *See* '239 Patent, claims 1, 7. Neither the Petitioner nor Dr. Staples has identified a single prior art stable liquid protein formulation with such CTLA4Ig concentrations. Staples Tr., Ex. 2012, at 150:11–18. In fact, consistent with Carpenter and Wang, Shire discusses the complications with formulating such high concentration liquid protein formulations. Shire, Ex. 1005, at 1399 ("Protein properties . . . pose challenges to developing pharmaceutically and economically acceptable formulations at high concentrations.").

The Petition asserts based on Dr. Staples's declaration that the CTLA4Ig concentrations recited in claim 1 ("at least 100 mg/ml") and claim 7 ("about 125 mg/ml") are "merely the logical result" of known dose, bioavailability, and volume

data. *See* Pet. at 33. Petitioner argues that a skilled formulator would have calculated the necessary concentration of CTLA4Ig for a fixed subcutaneous dose from the weight-based IV dose disclosed in Cohen before beginning development of a stable liquid formulation. *See id*. But as both Dr. Staples and Dr. Klibanov agree, a formulator would not have performed this calculation. *See* Staples Tr., Ex. 2012, at 124:12–16 ("Well, as a protein formulator, you're -- you have your specific expertise. And I believe a person of ordinary skills relies on guidance from the clinicians for what [the dose] should be."); Klibanov Decl., Ex. 2015, at ¶¶ 15–18. Consequently, Dr. Staples's exercise of calculating a fixed CTLA4Ig concentration for subcutaneous dosing from a weight-based IV dose is nothing more than hindsight.

As described below, Dr. Staples's calculations are fundamentally flawed. To start, Dr. Staples acknowledged that he is unqualified to make the calculations. Staples Tr., Ex. 2012, at 117:6–7, 122:7–14. Dr. Staples also admitted that his calculation would have determined *an ineffective concentration* for a large portion of the population. Staples Tr., Ex. 2012, at 121:17–22. And Dr. Morris—the only pharmacokinetics expert to offer testimony in this proceeding—explains that the calculation inappropriately applied mouse bioavailability data. Morris Decl., Ex. 2013, at ¶¶ 29–35. Each of these errors is sufficient on its own for the Board to disregard Dr. Staples's calculation of a fixed CTLA4Ig concentration.

1. The Board should accord no weight to Dr. Staples's protein concentration calculation because he is not a pharmacokinetics expert.

To move from a weight-based IV dose to a subcutaneous dose, a skilled artisan would investigate how a therapeutic protein renders its effect in patients. Morris Decl., Ex. 2013, at ¶¶ 21–25. Specifically, a skilled artisan would focus on pharmacokinetic ("PK") parameters, such as bioavailability, AUC, average steady state concentration, and trough concentration, which enable a PK expert to estimate how much of a subcutaneous dose will enter systemic circulation and how long an effective concentration will remain in the blood. *See id*. Estimates of this sort are performed by trained scientists capable of identifying the PK parameters that correlate most closely with efficacy, who then use that knowledge to approximate the expected concentration for subcutaneous dosing. *See* Staples Tr., Ex. 2012, at 124:12–16; Morris Decl., Ex. 2013, at ¶¶ 21–28.

Yet, Dr. Staples, by his own admission, is "*not an expert in pharmacokinetics*," Staples Tr., Ex. 2012, at 117:6–7 (emphasis added), has no expertise in pharmacology, and has no expertise in determining bioavailability:

Q. Do you have expertise in pharmacology?

A. ***No.***

Q. Do you have expertise in determining the bioavailability of a drug product?

A. ***No.***

Id. at 47:19–23 (emphasis added).

> **Q.** Do you know what is the meaningful pharmacokinetic parameter for the effectiveness of CTLA4-Ig in treating rheumatoid arthritis?
>
> **A.** ***I couldn't speak to that.***

Id. at 117:8–11 (emphasis added). Thus, Dr. Staples is unqualified to opine on PK issues, such as bioavailability, and the Board should accord no weight to Dr. Staples's calculation of a fixed CTLA4Ig concentration for subcutaneous dosing.

2. The Board should also accord no weight to Dr. Staples's protein concentration calculation because it is designed to estimate an ineffective concentration for many individuals.

Dr. Staples's declaration explains, "[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." Staples Decl., Ex. 1006, at ¶ 40 (emphasis added). Both the Petition and Dr. Staples apply Cohen's 2 mg/kg dose as the minimum effective dose. *See* Pet. at 30; Staples Decl., Ex. 1006, at ¶ 39.

In order to convert the weight-based IV dose in Cohen into a fixed concentration of CTLA4Ig, Dr. Staples multiplies "the minimum effective dose" against the average body weight of an adult. Staples Decl., Ex. 1006, at ¶ 39. Dr. Staples's approach necessarily results in a protein concentration that should be

ineffective for everyone who weighs more than the average body weight. Dr. Staples admitted this in his cross-examination.

> **Q.** So the average man in the United States is actually about 8 percent above 80 kilograms. Correct?
>
> **A.** Yes.
>
> **Q.** And of course, then, half of men, it would be even more than that. Correct?
>
> **A.** Yes.
>
> **Q.** So under the approach you've set forth, the average man is not going to receive 2 milligrams per kilogram but will receive about 8 percent less. Correct?
>
> **A.** Well, yeah. According to those exact calculations.

Staples Tr. , Ex. 2012, at 121:10–22. In other words, the basic assumptions of Dr. Staples's calculations are so flawed that he calculates a concentration that *should be ineffective* for any man above average weight. Given these flaws in Dr. Staples's analysis, his calculations should be rejected.

3. The Board should also accord no weight to Dr. Staples's protein concentration calculation because mouse data is not predictive of human bioavailability.

A PK expert in 2005, just like today, would not have been able to estimate the proper CTLA4Ig concentration for subcutaneous dosing without knowing the percentage of a subcutaneous dose that enters the bloodstream. *See* Morris Decl. at ¶¶ 25, 29. This value is the protein's bioavailability, and it can range from 20% to

100%. *See id*. at ¶¶ 17, 31. A PK expert cannot predict a drug's bioavailability in humans using animal data. *Id*. at ¶¶ 17–19. Dr. Staples's calculation of a fixed CTLA4Ig concentration for subcutaneous dosing is unreliable because it inappropriately assumes that a drug has the same bioavailability in both mice and humans, even though a PK expert would have known this assumption to be false. *See id.* at ¶¶ 29–35; McLennan, Ex. 2002 at 94; Richter, Ex. 2003 at 566.

All prior art of record and all expert testimony, with the sole exception of the Staples Declaration, is in agreement on this point. *See, e.g.*, Patent Owner Preliminary Response at 34–36 (citing Exs. 2001–2003). As Dr. Morris writes, "animal bioavailability data does not and cannot accurately predict human bioavailability of a protein." Morris Decl., Ex. 2013, at ¶ 18. Dr. Staples even agreed with this reasoning during his deposition, despite not being an expert in pharmacokinetics:

> **Q.** And now, the bioavailability of a protein in humans can be very different than it is in rodents. Correct?
>
> **A.** ***That's correct.***
>
> **Q.** And a person of ordinary skill in the art, in 2005, would know that the bioavailability of a protein administered subcutaneously in humans can be very different than its bioavailability in rodents. Correct?
>
> **A.** Well, it's -- ***yeah***.

Staples Tr., Ex. 2012, at 112:1–10 (emphasis added). Indeed, Dr. Staples has not identified a single stable liquid formulation of any protein where the concentration was determined using mouse data. *See* Staples Tr., Ex. 2012, at 115:14–18.

Bioavailability is also unpredictable because formulation components can contribute to the drug's absorption. *See* Morris Decl., Ex. 2013, at ¶ 20; Staples Tr., Ex. 2012, at 111:3–7 ("**Q.** And, in addition, the excipients with which a protein is administered subcutaneously can affect the bioavailability of the protein. Correct? **A.** Yes. That's true.").

Thus, the bioavailability data relied on by the Petitioner is insufficient for a person of ordinary skill to reasonably predict the CTLA4Ig concentration necessary for subcutaneous dosing. The only reference cited by Dr. Staples and Petitioner to support a bioavailability of 85% is Srinivas (1995), Ex. 1009. Srinivas (1995) measures bioavailability in mice, not humans. Srinivas (1995), Ex. 1009. Moreover, the formulation administered in Srinivas (1995) is not a stable liquid formulation of CTLA4Ig. *Id.* at 1488; Staples Decl., Ex. 1006 at ¶ 37. Consequently, Dr. Staples's calculation of a fixed CTLA4Ig concentration for subcutaneous dosing is unreliable because it inappropriately uses mouse bioavailability data obtained from administration of a different formulation of CTLA4Ig. *See* Staples Tr., Ex. 2012, at 115:9–11; Morris Decl., Ex. 2013, at ¶¶ 29–35. And even if relying on animal bioavailability data was predictive (it is

not), a skilled artisan would not rely on Srinivas 1995 and ignore another, more robust bioavailability study of CTLA4Ig in rodents. Morris Decl., Ex. 2013, at ¶ 35; Srinivas 1997, Ex. 2028.

Overall, Dr. Staples's calculation of a fixed CTLA4Ig concentration for subcutaneous dosing is plainly an exercise in hindsight. First, Dr. Staples conceded that he is unqualified to opine on the pharmacokinetics that govern such a calculation. Staples Tr., Ex. 2012, at 117:6–7. Second, Dr. Staples admitted that his calculation is flawed because it estimates a value that should be ineffective for the average man. Staples Tr., Ex. 2012, at 121:17–22. Third, no matter what dose Dr. Staples uses, his calculation is also flawed because it equates human bioavailability with a mouse value determined using a different formulation, even though a skilled artisan would know that such an assumption is improper. *See* Staples Tr., Ex. 2012, at 112:1–10, 111:3–7. The Board should disregard Dr. Staples's hindsight-driven declaration testimony to the contrary.

D. The Petition fails to prove that a skilled artisan would have arrived at the unique formulation parameters claimed in the '239 Patent.

Even if a person of ordinary skill in the art were to follow the Petition's simplistic approach, and Dr. Staples's unreliable testimony, the Petition fails to prove that this would lead to the unique formulation parameters claimed in the '239 Patent. That is, even if a formulator attempted to develop a stable liquid

protein formulation of CTLA4Ig by simply looking to approaches that had been used for formulating other proteins—and by calculating a desired protein concentration based on bioavailability data for rodents and Dr. Staples's flawed assumptions—this would not lead to the claimed inventions.

For example, Petitioner has identified no prior art showing an actual stable liquid formulation of a protein therapeutic with sucrose in concentrations approaching 170 mg/ml or even 110 mg/ml (*e.g.*, claims 7, 5), Poloxamer 188 in an amount of about 8 mg/ml (claim 9), or a 10 mM phosphate buffer (claim 8), among other claimed requirements.

Nor does the Petition show, through "articulated reasoning with some rational underpinning," *KSR*, 550 U.S. at 418, that it would have been obvious to arrive at formulations with the claimed parameters. In fact, Petitioner's cited evidence leads a skilled artisan away from the claimed sugar concentrations (given the admitted goal of avoiding hypertonicity) and pH range (given stability concerns). Moreover, there is a complete failure of proof on many limitations, including the claimed surfactant, buffer, and sugar:protein ratio parameters.

1. Sucrose/sugar limitations (claims 1, 2, 5, 7, 14, 15)

Claims 1, 2, 5, 7, 14, and 15 of the '239 Patent include various limitations directed to the use of sucrose (or a sugar selected from groups of specific sugars, in claims 1 and 2)—all of which require concentrations of at least 110 mg/ml, and

often much higher (*e.g.*, "about 170 mg/ml" in claim 7). The Petition identifies no stable liquid protein formulations satisfying these requirements as of 2005, and has at least three flaws for these limitations.

First, the Petition fails to prove that a formulator would even use sucrose to stabilize CTLA4Ig. Second, the concentration values are far in excess of what was taught in the prior art for stable liquid formulations as of 2005. In fact, the claimed values would result in hypertonic formulations—which even Dr. Staples says that a formulator would seek to avoid. Therefore, if a formulator were to follow the Petition's approach—*i.e.*, to "empirically determine the optimized amount of sugar, taking into account tonicity and viscosity issues," Pet. at 11—this would not result in the claimed concentrations. Third, for the sugar:protein ratios of claims 1, 14 and 15, neither the Petition nor Dr. Staples addresses the denominator of this ratio, or speaks to any relationship between the sugar and protein concentrations. Thus, there is a failure of proof for these limitations.

a) The Petition fails to prove that a formulator would use sucrose (or other sugars).

The Petition asserts that it would have been obvious to use sucrose, and thus satisfy claims 1 and 2 of the '239 Patent (which require use of a sugar selected from a group of specific sugars), as well as claims 5 and 7 (which specifically require sucrose). Read most favorably, the Petition argues that a formulator could have turned to sucrose (or, potentially, other sugars), because it was an excipient

used in certain other formulations. Yet the Petition fails to prove that a formulator would have used sucrose in seeking to develop a stable liquid formulation of CTLA4Ig. *See InTouch Techs.*, 751 F.3d at 1351 (explaining the relevant analysis is not "that one of ordinary skill in the art *could* combine [the] references," it is whether "they *would* have been motivated to do so").

Citing to Carpenter, the Petition asserts that the use of sucrose or trehalose in a formulation would have been a "first-line" approach for a formulator, and on that basis argues that it would have been obvious to use sucrose. Pet. at 35. But while Carpenter identifies certain benefits of sucrose and trehalose in the abstract, this does not establish that a formulator would have turned to sucrose (or trehalose) in attempting to stabilize CTLA4Ig, or that she would have had a reasonable expectation of success in doing so—especially in the absence of information about CTLA4Ig's degradation pathways.

Sucrose—and other sugars—are not universal protein stabilizers. Klibanov Decl., Ex. 2015, at ¶ 69. As confirmed by Wang, Ex. 2011, at 166: "Not all proteins can be stabilized by sugars or polyols." Likewise, in Dr. Staples's '691 Patent (regarding interferon-beta formulations), he noted that "[n]on-ionic additives such as sucrose and mannitol appear to offer no protection, *or may actually promote protein loss* at physiological pH." '691 Patent, Ex. 2019, at 17:59–61 (emphasis added); *see also* Staples Tr., Ex. 2012, at 99:19–22 (admitting

that "a person of ordinary skill in the art cannot predict the effect of sucrose on the stability of a particular protein").

As discussed above, there were myriad excipients (and excipient combinations) available to a protein formulator in 2005. *See* Carpenter, Ex. 1004, at 187, Table 2; Wang, Ex. 2011, at 165; Klibanov Decl., Ex. 2015, at ¶¶ 21, 63. Moreover, "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Wang, Ex. 2011, at 130. The Petition has failed to explain which of those myriad excipients would be expected to succeed *in developing a stable liquid formulation of CTLA4Ig*. "[W]here the prior art, at best, '[gives] only general guidance as to the particular form of the claimed invention or how to achieve it'" the claims are not obvious. *In re Cyclobenzaprine*, 676 F.3d at 1073; *see also Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008) (explaining the "selection of components" "when there is no prediction in the prior art as to the results obtainable from a selected component" is not obvious).

b) The Petition fails to prove that a formulator would use sucrose (or other sugars) in the required concentrations.

Claims 1, 2, 5, 7, 14, and 15 of the '239 Patent additionally require specific sucrose (or sugar) concentrations. Claim 7 requires "sucrose in an amount of about 170 mg/ml," while other claims require a minimum of 110 mg/ml sugar (claims 1,

2, 5), 130 mg/ml sucrose (claim 14), or 140 mg/ml sucrose (claim 15).[1] The Petition identifies no prior stable liquid protein formulations with sugar concentrations anywhere near these numbers. Nevertheless, the Petition and Dr. Staples assert that a "formulator would have known how to determine, through trial and error, the 'sweet spot' between . . . highest and lowest reasonable values" of 70 mg/ml and 350 mg/ml. Pet. at 38; Staples Decl., Ex. 1006, at ¶ 33.

As a threshold matter, the Petition does not attempt to explain, how such trial-and-error optimization within a broad alleged "sweet spot" of 70–350 mg/ml would lead a formulator to the actual concentrations claimed. Further, the evidence cannot sustain Petitioner's "sweet spot." The prior formulations of record that used sucrose had values *below* 70 mg/ml, and the 350 mg/ml value comes from an experimental paper that is not a stable liquid formulation and would

[1] Claim 1 specifies a protein concentration of at least 100 mg/ml and that the "weight ratio of sugar:protein is 1.1:1 or higher." Thus, a formulation would need a sugar concentration of at least 110 mg/ml, and perhaps much higher (in the case of >100 mg/ml protein), in order to satisfy claim 1. Claims 2 and 5 further limit the types of sugar, *e.g.*, sucrose in claim 5. Claims 14 and 15 further specify sucrose:protein weight ratios of 1.3:1–5:1 (requiring at least 130 mg/ml sucrose) and 1.4:1 (requiring at least 140 mg/ml sucrose).

not be instructive to a formulator seeking to achieve one. *See* Klibanov Decl., Ex. 2015, at ¶¶ 73–78. Thus, even if achieving a successful formulation could be simplistically reduced to "varying one parameter, the amount of sugar to balance . . . the stability of the protein and the tonicity of the formula," Pet. at 38, without considering all of the other interdependent formulation parameters, the claimed concentrations are well above any "sweet spot" suggested in the art as of 2005.

For the low end of the "sweet spot" (70 mg/ml) the Petition cites to Carpenter. Yet the discussion in Carpenter is not based on any stable liquid protein formulation, but rather it is merely a suggestion that 70 mg/ml might possibly work for unidentified proteins. *See* Carpenter, Ex. 1004, at 187 ("To stabilize proteins (both in aqueous solution and during freezing), with non-specific compounds (e.g., sugars), relatively high concentrations (ca. >0.2 M) of ligand (solute) are needed to affect protein stability. . . . The most effective non-specific stabilizers tend to be disaccharides, such as sucrose and trehalose."). Additionally, as Dr. Staples admitted, whether 70 mg/ml of sucrose will stabilize any given protein is not predictable. Staples Tr., Ex. 2012, at 99:19–22 (**Q.** "So a person of ordinary skill in the art cannot predict the effect of sucrose on the stability of a particular protein. Correct?" **A.** "Correct.").

Further, neither the Petition nor Dr. Staples has identified any prior art stable liquid protein formulations with sugar concentrations of at least 70 mg/ml. *See*

Staples Tr., Ex. 2012, at 127:5–13 (**Q.** "[C]an you identify any stable liquid protein formation that uses at least 70 milligrams per milliliter of sucrose, other than the product at issue here, Orencia? **A.** "I can't . . . .").

Despite this lack of evidence, Dr. Staples wrongly assumed that "it would be unusual" for a stable liquid protein formulation to use less than 70 mg/ml sucrose. Staples Tr., Ex. 2012, at 126:13–16. This is inconsistent with the evidence. The Gonal-f® RFF Pen, a stable liquid protein formulation approved in 2004, uses 60 mg/ml sucrose. Klibanov Decl., Ex. 2015, at ¶ 81; Gonal-f® Prescribing Information, Ex. 2017. In addition, of the products described in the background of the '239 Patent, there is only one stable liquid protein formulation that uses sucrose (ENBREL®), and it used a much lower 10 mg/ml concentration. '239 Patent, 2:61–66; Klibanov Decl., Ex. 2015, at ¶ 81. In light of Dr. Staples's misunderstanding of the state of the prior art, his opinions with respect to sucrose and the concentration of sucrose should be given little, if any, weight.

For the high end of the "sweet spot" (350 mg/ml) the Petition and Dr. Staples cite to Kendrick (Ex. 1008). But the Kendrick reference does not disclose a stable liquid protein formulation and has no bearing on sugar concentrations appropriate for developing one. Klibanov Decl., Ex. 2015, at ¶¶ 73–78. Instead, it reports an experiment in which a protein was purposefully induced to unfold and aggregate with a denaturant. Sucrose was added at concentrations between 70

mg/ml and 350 mg/ml and the effects of the denaturant were evaluated. Indeed, at concentrations of 350 mg/ml, Kendrick reports that the protein is "not adequately stable." Staples Tr., Ex. 2012, at 134:4–12; Kendrick, Ex. 1008; Klibanov Decl., Ex. 2015, at ¶ 77.

Accordingly, even if a formulator were to look to sugar concentrations for stable liquid formulations of *other* proteins, in trying to formulate CTLA4Ig, the "sweet spot" would be in the range of 10–60 mg/ml. At most, if a formulator were to view Carpenter's high-level statement regarding relatively high concentrations of "non-specific compounds (e.g., sugars)," Carpenter, Ex. 1004, at 187, as "teaching sucrose concentration of greater than . . . 70 mg/ml sucrose," Staples Decl., Ex. 1006, at ¶ 47, the "sweet spot" would extend only slightly higher—and certainly not to 110, 130, 140, or 170 mg/ml, as required by the claims.

Finally, the Petitioner's own evidence would lead a formulator away from attempting a concentration higher than 70 mg/ml sucrose. As Dr. Staples admits, a formulator would have been motivated to "avoid[] unnecessarily high sugar concentrations that would cause undesirable solution characteristics such as excessive hypertonicity [*i.e.*, osmolarity significantly above the physiological level] or viscosity." Staples Decl., Ex. 1006, at ¶ 34. As explained by Carpenter, avoiding hypertonicity was understood to be particularly important for subcutaneous formulations. *See* Carpenter, Ex. 1004, at 65 ("Normally excipients

that act as general protein stabilizers are needed in fairly high concentrations to give a significant stabilization (> 0.25 M), and may not be suitable in cases where isotonicity must be maintained (e.g., subcutaneous doses)."); Klibanov Decl., Ex. 2015, at ¶ 83.

Indeed, all of the claims require hypertonic formulations to varying degrees of excess, with osmolarity above the physiological level due to the sugar content alone (*see* claims 1, 2, 5, 7, 14, and 15)—and with the hypertonicity further exacerbated due to the other solutes present in the claimed formulations, including buffers and surfactants (*see* claims 3 and 6–10). Klibanov Decl., Ex. 2015, at ¶ 85. While the Petition attempts to sidestep this fact by stating that "*some level* of hypertonicity may be needed," its citation for this proposition is *the '239 Patent itself*. Pet. at 40 (citing '239 Patent at 31:32–36). This disclosure of the patent-in-suit is not prior art. That the Petition seeks to rely on it only underscores that it is grounded in impermissible hindsight.

Thus, if a formulator were to follow the Petition's approach, it would not lead to sugar or sucrose concentrations greater than 70 mg/ml—and certainly not to at least 110, 130, 140, or about 170 mg/ml, as required by the claims—because a formulator in 2005 would have no reason to use, or expect success from, such hypertonic formulations for subcutaneous administration.

c) The Petition fails to address the claimed sugar:protein weight ratios.

Neither the Petition nor Dr. Staples addresses the denominator of the sugar:protein weight ratios of claims 1, 14, and 15, or speaks to any relationship between the sugar and protein concentrations. While the Petition includes the (flawed) argument that a formulator could attempt to optimize sugar concentrations within the supposed "sweet spot" of 70–350 mg/ml, Pet. at 38, it never seeks to relate these sugar concentrations to the protein concentrations in the formulation, and points to absolutely no evidence on this. Accordingly, the Petitioner has not met its burden to show obviousness of claims 1, 14, and 15.

Moreover, ignoring the denominator of the protein concentration is especially problematic, since both the sugar and the protein are present at sufficiently high concentrations in the claims that their solutions behave in a non-ideal fashion, which leads to further unpredictability in how the solutions would behave. *See* Klibanov Decl., Ex. 2015, at ¶ 87. Thus, a formulator would recognize that the amount of sugar and protein would not be viewed in isolation, as Petitioner argues, *see* Pet. at 38 ("Such a trial-and-error approach involved nothing more than varying one parameter, the amount of sugar . . . ."). To determine an appropriate sugar:protein ratio, a formulator would need to consider both variables, not just one. *See* Klibanov Decl., Ex. 2015, at ¶ 87.

2. pH limitations (claims 1, 10)

Claims 1 and 10 of the '239 Patent require "a pH range of from 6 to 8." Yet, rather than identifying prior art teaching the use of the claimed pH range in an actual stable liquid protein formulation, the Petition asserts that "[a] formulation at or near physiological pH would have been the preferred choice for a liquid protein formulation," and "[o]nly if unable to achieve a stable formulation at physiological pH would a formulator deviate from the claimed pH range." Pet. at 41 (citing Staples Decl., Ex. 1006, at ¶ 44). The Petition argues that a pH range of 6 to 8 encompasses physiological pH. *Id.*

To support its argument, the Petitioner relies on Dr. Staples's declaration, Carpenter, and Cohen. But the formulation in Cohen is a lyophilized formulation, not a stable liquid protein formulation. As Dr. Staples admits, a person of ordinary skill in the art would understand that the formulation parameters used in Cohen for a lyophilized formulation would not be expected to succeed in a stable liquid protein formulation. Staples Tr., Ex. 2012, at 164:1–6.

Regarding Carpenter, the language cited by the Petition says nothing about a preferred pH range, but only that "pH considerations . . . have to be met for a pain-free injection." Carpenter, Ex. 1004, at 182. In fact, the Carpenter book suggests a preference for pH between 5.0 and 6.0 in order to avoid deamidation in protein pharmaceuticals generally. Carpenter, Ex. 1004, at 13, Table 6.

As for Dr. Staples, during cross-examination he agreed with this reading of Carpenter, and admitted that there was "a general preference for stable liquid protein formulations in 2005 to have a pH *between 5 and 6* in order to avoid deamidation." Staples Tr., Ex. 2012, at 75:8–12 (emphasis added). Thus, he contradicted his declaration testimony that "[p]rotein formulators prefer to develop a subcutaneous formulation with a pH at or near physiological pH" and that "the claimed pH range of from 6 to 8 . . . would have been the obvious starting point." Staples Decl., Ex. 1006, at ¶ 44. Accordingly, Dr. Staples's declaration testimony should be accorded no weight for the pH limitation, as it is contrary to his cross-examination testimony and the teaching in Carpenter.

Moreover, a person of ordinary skill formulating a stable liquid protein formulation would primarily be concerned with the stability of CTLA4Ig (as opposed to injection site pain), when considering the pH range for the formulation. Klibanov Decl., Ex. 2015, at ¶ 91. After all, if the protein is not stable, then it cannot be administered to patients. *Id*. Thus, pH must be evaluated based on degradation and stability studies. Indeed, Dr. Staples acknowledged at his deposition that a formulator in 2005 looking to develop a stable liquid protein formulation "would not look to optimize pH, but, rather, to balance -- to develop a formulation at a pH that balanced the various degradation pathways." Staples Tr., Ex. 2012, at 84:21–85:3. Accordingly, a person of ordinary skill would not simply

choose "physiological pH" and have a reasonable expectation of success in formulating a stable liquid formulation of CTLA4Ig.

3. Stability limitations (claims 1, 7, 11)

a) "stable formulation" (claims 1, 7)

As the Petition points out, the '239 Patent defines a "stable formulation" as "one in which the CTLA4Ig molecule therein essentially retains its physical and chemical stability and integrity upon storage." '239 Patent at 5:29–31; Pet. at 19. Indeed, Dr. Staples agrees with this definition of "stable":

> **Q.** Is it fair to describe a stable liquid formulation as a liquid formulation that retains its physical and chemical stability and integrity for many months?
>
> **A.** I think that's a fair general statement.
>
> **Q.** And that would be the way a person of ordinary skill in the art would have understood it in 2005?
>
> **A.** I think it's fair as a general statement.

Staples Tr., Ex. 2012, at 24:23–25:8; *see also id*. at 23:5–10 (explaining that in 2005 a person of ordinary skill would have targeted "approximately 12 to 18 months" of stability for a liquid protein formulation).

But the Petition offers no prior art evidence that would have led a skilled artisan to reasonably expect that a liquid formulation of CTLA4Ig would have been stable for a period of months. The Petition identifies no formulation of CTLA4Ig other than Cohen's lyophilized IV formulation. But as Dr. Staples

explained, "lyophilized formulations are entirely different from . . . liquid formulations . . . ." Staples Appeal Br., Ex. 2022, at 11; *see also* Staples Tr., Ex. 2012, at 162:1–9 (confirming this opinion). Consequently, he admitted that a skilled artisan "*would learn nothing* from a lyophilized formulation for purposes of the stable liquid formulation." Staples Tr., Ex. 2012, at 164:1–6 (emphasis added).

The Petition's absence of proof relating to the "stable" limitation is especially glaring because its own reference indicates that such a formulation would have been expected to be *unstable*. *See* Carpenter, Ex. 1004, at 188 ("It can be assumed that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed."); *see also* Staples Tr., Ex. 2012, at 63:13 (confirming that the Carpenter quote was "generally true" in 2005). Stability was the exception for liquid protein formulations in 2005, and a skilled artisan would not have reasonably expected to successfully develop a stable CTLA4Ig formulation in the absence of stability data. The Petition does not cite any stability data for CTLA4Ig from the prior art, so the Petition cannot, and does not, show that a "stable" formulation would have been obvious.

b) "stable when stored at 2 to 8 C for at least 12 months" (claim 11)

The record also contains no prior art evidence demonstrating that a skilled artisan would have predicted a high-concentration liquid formulation of CTLA4Ig to be "stable when stored at 2 to 8 C for at least 12 months" (Claim 11). Instead,

the Petition argues the obviousness of Claim 11 by relying on Dr. Staples's conclusory assertion that a formulator "would have reasonably expected to successfully develop a liquid formulation" with the claimed stability limitation despite no citation support from the prior art. *See* Pet. at 45; Staples Decl., Ex. 1006, at ¶ 57. This is insufficient to prove the obviousness of Claim 11—especially since, as Carpenter unambiguously states, "most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed." Carpenter, Ex. 1004, at 188.

The Board should accord no weight to Dr. Staples's conclusory assertion, not only because of the absence of evidentiary support, but also because Dr. Staples himself discredited it during his deposition. Dr. Staples acknowledged that his declaration contains no evidence of CTLA4Ig stability studies, and as a result, that the declaration offers insufficient evidence for a person of ordinary skill in 2005 to predict whether CTLA4Ig would be stable as a liquid formulation:

> **Q.** Do you cite to any degradation studies on CTLA4-Ig in your declaration?
>
> **A.** I don't recall that I did.
>
> **Q.** And I take it that ***a person of ordinary skill in the art, without doing these studies, cannot predict whether a particular protein is or is not going to be sufficiently stable in the liquid state***. Correct?
>
> **A.** ***Correct.***

Staples Tr., Ex. 2012, at 62:16–24 (emphasis added); *see also id.* at 61:23–62:6, 63:14–20. Thus, a skilled artisan could not have predicted whether a stable liquid formulation of CTLA4Ig was feasible, or whether she would have had a reasonable expectation of meeting the requirements of claim 11.

4. Surfactant limitations (claims 7, 9)

Claim 7 of the '239 Patent recites an optional surfactant, and claim 9 requires that "the surfactant is Poloxamer 188 in an amount of about 8 mg/ml." Again, the Petition identifies no stable liquid protein formulations satisfying these parameters as of 2005, and its obviousness arguments are clearly deficient.

The Petition does not introduce any evidence that a skilled artisan *would* use such a surfactant in formulating CTLA4Ig, and expect to succeed in doing so, but rather argues that it is an excipient that *could* be used for formulating proteins generally: "[C]ertain surfactants were included in the 'finite set of possible excipients' that had 'been shown to be effective in protein formulations,'" Pet. at 43 (quoting Carpenter, Ex. 1004, at 186–87), with "[o]ne of the four surfactants taught" by Carpenter being Poloxamer 188, Staples Decl., Ex. 1006, at ¶ 56. For example, there is no evidence in the record showing that Poloxamer 188—or any other surfactant—was known or expected to have a stabilizing effect on CTLA4Ig, either alone or in the presence of other claimed excipients. Nor does Dr. Staples's

declaration include any statement that using Poloxamer 188 would have been obvious. *See id.*

Critically, regarding the 8 mg/ml concentration of Poloxamer 188 specified in claim 9, the Petition does not cite any evidence within even an order of magnitude of this value. Instead, it offers a conclusory attorney argument—unsupported by any expert testimony—that the 8 mg/ml value "was not critically different than the 'low concentrations of surfactant (*ca.* 100 micromolar) typically used in formulations of therapeutic proteins.'" Pet. at 44 (quoting Carpenter, Ex. 1004, at 167). Petitioner does not explain why Carpenter's general disclosure of surfactants at a concentration of 100 μM is "not critically different" than the claimed value of Poloxamer 188 at approximately 1 mM, *see* Staples Decl., Ex. 1006, at ¶ 56, which is *ten times* more concentrated. Nor does the Petition attempt to explain why a skilled artisan might have modified Carpenter's disclosure by a full order of magnitude to arrive at the claimed concentration. There is thus no evidence suggesting the use of Poloxamer 188 at 8 mg/ml for any formulation, let alone a stable liquid formulation of CTLA4Ig.

Moreover, Dr. Staples admitted during deposition that a formulator would have been unable to predict how to create a stable liquid formulation of a given protein using a surfactant or any other excipient. *See, e.g.*, Staples Tr., Ex. 2012, at 63:6–20. In particular, he explained in his deposition why a skilled artisan could

not have predicted the success of 8 mg/ml of Poloxamer 188 (also referred to as Pluronic F-68) for two separate reasons. First, surfactants may destabilize a protein, and a protein formulator cannot predict *a priori* whether a particular surfactant will stabilize or destabilize a particular protein.

> **Q.** And then [Carpenter] goes on, "Randolph and colleagues report that some proteins in nonionic surfactants, including Tween 20, form mixed protein detergent complexes"?
>
> **A.** Yes.
>
> **Q.** And the concern there is that if the surfactant is binding to the protein, either in the folded or unfolded state, it can have a powerful impact, positive or negative, on the stability of the protein formulation. Correct?
>
> **A.** Correct.
>
> **Q.** And that's something that has to be studied; it can't be predicted. Correct?
>
> **A.** That's correct.

Staples Tr., Ex. 2012, at 152:20–153:8. *See also* Klibanov Decl., Ex. 2015 at ¶¶ 94–97.

Second, Dr. Staples admitted that a surfactant's stabilizing or destabilizing effect varies for a given protein formulation based on the other components in the formulation. In fact, Dr. Staples previously described this form of surfactant unpredictability to the Patent Office. *See* Staples Appeal Br., Ex. 2022, at 16 ("Shaked recites that interferon-beta formulations containing Pluronic F-68 were

problematic in that the interferon-beta precipitated out of solution."). As Dr. Staples elaborated during his deposition:

> **Q.** And you're referring to the fact that the effects of the particular surfactant there, Pluronic F-68, even for the same protein varied depending upon conditions?
>
> **A.** Yes.
>
> **Q.** For that reason, the effects of a surfactant such as Pluronic F-68 on a particular protein can be unpredictable, depending upon the other elements of the formulation?
>
> **A.** Yes.

Staples Tr., Ex. 2012, at 170:21–171:17.

Accordingly, Dr. Staples's deposition testimony confirms that using a surfactant such as Poloxamer 188, as specified in claims 7 and 9, would be *non*-obvious. A formulator would have expected that any surfactant may destabilize a liquid protein formulation instead of stabilizing it. *See* Staples Tr., Ex. 2012, at 152:25–153:5. She also would have known that the surfactant's effect may vary based on other excipients in the formulation. *See id*. at 171:8–12. And she would have known that a surfactant's stabilizing or destabilizing effect is unpredictable. *See id*. at 153:6–8; 171:13–17. Given the unpredictability, the Petition cannot demonstrate that a skilled artisan would have reasonably expected to successfully develop a stable liquid formulation of CTLA4Ig using 8 mg/mL of Poloxamer 188.

5. Phosphate buffer limitation (claim 8)

Claim 8 of the '239 Patent requires a buffering agent "in an amount of at least 10 mM phosphate buffer." Other than noting that phosphate buffer was named in a "limited set of [seven different] acceptable buffers" in Carpenter, the Petition and Dr. Staples never explain why a formulator would have chosen to use a phosphate buffer in particular, or expected to succeed in doing so, in seeking to develop a stable liquid formulation of CTLA4Ig. *See* Pet. at 42–43.

Additionally, neither the Petition nor Dr. Staples cite any prior art patents or publications disclosing the claimed concentration. Rather, Dr. Staples asserts:

> In my opinion, a protein formulator would have used a phosphate buffer in a range of from about 5 to 50 mM because a concentration of 10 mM is the typical concentration for a phosphate buffered solution, being available in many commercially available products that can be bought off the shelf.

Staples Decl., Ex. 1006, at ¶ 55. An opinion that a protein formulator would have used a range of from *about 5* to 50 mM does not establish obviousness of using <u>*at least 10*</u> mM. Additionally, the (unsupported) proposition that a 10 mM concentration is used "in many commercially available products" does not establish that this concentration would have been obvious *in a liquid protein formulation* (for CTLA4Ig or otherwise).

The absence of evidence is particularly troubling, given the concerns expressed in Carpenter that phosphate has been reported to catalyze reactions that lead to protein deamidation. Carpenter, Ex. 1004, at 186–87; Klibanov Decl., Ex. 2015, at ¶ 92. Indeed, Dr. Staples admitted that such deamidation, as reported in Carpenter, is "undesirable in a protein formulation." Staples Tr., Ex. 2012, 174:12–25. Thus, given the lack of support for statements in the petition concerning a buffering agent, Petitioner has failed to carry its burden of proving unpatentability with respect to the claimed phosphate buffer.

6. Viscosity limitation (claim 1)

The Petition argues that the claimed viscosity range of claim 1 of the '239 Patent ("a viscosity of from 9 to 20 cps") was "merely the logical choice" based on practical considerations, such as loading times for syringes. Pet. at 40–41. The Petition relies on hindsight to argue that no more than the knowledge of a desirable viscosity range for any liquid formulation would have rendered obvious the '239 Patent's unique formulations within the claimed viscosity ranges. *See id.* at 41. "However, knowledge of the goal does not render its achievement obvious." *Abbott Labs.*, 544 F.3d at 1352. As Dr. Staples and the prior art demonstrate, a skilled artisan would not have reasonably expected to develop a stable liquid CTLA4Ig formulation with appropriate viscosity because a skilled artisan would not have expected to successfully formulate CTLA4Ig in solution, as explained

above. Given the lack of prior art evidence for a stable liquid formulation of CTLA4Ig (with or without the claimed viscosity ranges), and the unpredictability in the field, Petitioner fails to demonstrate obviousness of claim 1.

E. In sum, given the unpredictability in the field and the failure to identify specific prior art teachings, the Petition's arguments can only be explained by improper hindsight.

Given the foregoing deficiencies—including the lack of prior art patents or printed publications that would have suggested a successful approach for developing a stable liquid formulation of CTLA4Ig, let alone at the parameters claimed—it is plainly apparent that the Petition is grounded in hindsight.

The Petition begins 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. at 5. Thus, the Petition takes the '239 Patent's solution as the starting place for its obviousness analysis, and assumes that it is achievable—despite the teaching in its own evidence that "[i]t can be assumed that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed," Carpenter, Ex. 1004, at 188, and despite Dr. Staples's recognition that "the conditions necessary for stabilizing one protein would not necessarily be effective, *or even reasonably predictive*, in stabilizing another protein." Staples Appeal Br., Ex. 2022, at 14 (emphasis added); Staples Tr., Ex. 2012, at 165:18–166:2.

Additionally, rather than identifying prior art stable liquid formulations with the claimed parameters (whether CTLA4Ig or otherwise), or identifying some handful of relevant formulations that a skilled artisan would have modified or combined consistent with *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the Petition focuses on an array of "known constraints" about protein formulation generally—and asserts that a formulator could use them to arrive at the claimed inventions via "trial-and-error optimization." That is, the Petition invites the Board to assume a successful multi-factor "optimization" experiment (in an unpredictable field and where the parameters are interdependent), with a series of questionable calculations that allegedly result in the claimed formulation parameters.

Perhaps the most egregious example of the Petition's hindsight-focused approach appears in Dr. Staples's protein-concentration calculation of *2 mg/kg* × *79.7 kg* ÷ *1.5ml* ÷ *85%*—conveniently resulting in 125.0 mg/ml CTLA4Ig, the precise concentration of claim 7. Pet. at 29–32; Staples Decl., Ex. 1006, at ¶¶ 37–41. Yet, this "straightforward" calculation rests on plucking one of two weight-based intravenous doses from Cohen, multiplying it by "average adult weight," and dividing by (unreliable) mouse bioavailability data, along with other assumed figures as discussed above. Especially since Dr. Staples conducted this analysis despite having no expertise "in determining the bioavailability of a drug product," Staples Tr., Ex. 2012, at 47:21–23, or in pharmacology, *id.* at 47:19–20, and he is

"not an expert in pharmacokinetics," *id.* at 117:3–7, there can be no doubt that Petitioner used the challenged patent as a "roadmap for putting . . . pieces of a 'jigsaw puzzle' together," as the Federal Circuit has repeatedly admonished against. *InTouch Techs.*, 751 F.3d at 1351; *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 . . . .").

This is far from the only example of where the Petition worked backwards. Indeed, in asserting that the claimed sugar/sucrose concentrations are in the middle of an alleged "sweet spot" of 70–350 mg/ml—even though they would result in a hypertonic solution that a formulator would admittedly seek to avoid—the Petition relies upon the '239 Patent itself for the proposition that "*some level* of hypertonicity may be needed." Pet. at 40 (citing '239 Patent at 31:32–36).

Moreover, Petitioner does not even cite prior art references in support of many of the claim limitations, including the claimed surfactant, buffer, stability, and sugar:protein ratio parameters, relying on conclusory assertions (and, at times, unsupported expert testimony) that the claimed formulations nevertheless would have been obvious. Therefore, given the Petition's improper hindsight and failure to cite patents or printed publications that teach or suggest the claimed formulation parameters, *see* 35 U.S.C. § 311(b), it has not come close to meeting Petitioner's burden of proving unpatentability.

V. Conclusion

For at least all of these reasons, Petitioner has failed to show by a preponderance of evidence that any of the challenged claims is unpatentable in view of the cited references. Patent Owner respectfully requests the Board confirm the patentability of claims 1–15.

Date: April 15, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on this 15th day of April 2016, the foregoing **Patent Owner Response Pursuant to 37 C.F.R. § 42.120** was served by electronic mail, by agreement of the parties, and **Exhibits 2011–2030** were served by FedEx, a means at least as fast and reliable as Priority Mail Express®, on the following counsel of record for Petitioner:

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