IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Dali et al.	
U.S. Patent No.:	8,476,239	Attorney Docket No.: 14131-0120IP1
Issue Date:	July 2, 2013	
Appl. Serial No.:	12/086,876	
Filing Date:	December 19, 2006	
Title:	STABLE PROTEIN FORMULATIONS	

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Patent Trial and Appeal Board
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PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 8,476,239 PURSUANT TO 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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Momenta Pharmaceuticals, Inc. ("Petitioner" or "Momenta") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 of claims 1-15 of U.S. Patent No. 8,476,239 ("the '239 patent") assigned to Bristol-Myers Squibb Company. As explained in this petition, review should be instituted because there is a reasonable likelihood that Momenta will prevail with respect to at least one claim challenged in this petition.

The '239 patent covers "stable" formulations of a fusion protein called "CTLA4Ig" that are suitable for subcutaneous administration. CTLA4Ig compositions are useful for treating autoimmune diseases and one composition, sold under the name Orencia®, has been approved by the Food & Drug Administration for treatment of rheumatoid arthritis.

The ability of CTLA4Ig to treat autoimmune diseases, and specifically rheumatoid arthritis, was known well-before the filing date of the '239 patent. The desirability of subcutaneous administration was also recognized, as were the parameters for successfully converting known intravenous formulations to subcutaneous formulations. The '239 patent merely applied the "first-line" textbook formulation approach to a known therapeutic protein to develop the claimed formulations.

Claims 1-15 are unpatentable based on teachings set forth in at least the references presented in the grounds for rejection detailed in this petition. Momenta

therefore respectfully solicits institution of *inter partes* review of claims 1-15, and their cancelation as unpatentable.

I. MANDATORY NOTICES UNDER 37 C.F.R § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Momenta Pharmaceuticals, Inc. is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

U.S.S.N. 13/796,586, which is a divisional of the '239 patent, was filed on March 12, 2013. It is pending and claims priority to the '239 patent. A Notice of Allowance issued on May 28, 2015.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel.

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D. Service Information

Please address all correspondence and service to counsel at the address provided in Section I(C). Petitioner also consents to electronic service by email at IPR14131-0120IP1@fr.com.

II. PAYMENT OF FEES – 37 C.F.R. § 42.103

Petitioner authorizes the Patent and Trademark Office to charge Deposit

Account No. 06-1050 for the fee set in 37 C.F.R. § 42.15(a) for this petition and further authorizes any additional fees to be charged to this Deposit Account.

III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '239 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR.

Challenge under 37 C.F.R. § 42.104(b); Relief Requested

Petitioner requests *inter partes* review of claims 1-15 on the grounds set forth in the following table and requests that each claim be found unpatentable.

Ground	'239 Patent Claims	Basis for Rejection
Ground 1	**1-15**	Obvious under 35 U.S.C. § 103 over Cohen in view of the Carpenter Handbook and Shire

IV. BACKGROUND

Subcutaneous formulations of protein-based pharmaceuticals are known to offer advantages relative to intravenous-administered formulations. *See, e.g.*, Shire, MOM-1005, at 1390-91. Such formulations can be pre-loaded into a syringe, allowing for home administration of the drug and improved patient compliance. *Id*. In addition, the relative ease of administration could "result in expanded product markets." *Id.* at 1391.

The benefits of a stable liquid subcutaneous formulation are especially pronounced for protein drugs that require frequent and chronic administration. *Id*.

at 1390; *see also* '239 patent, col. 17, line 64 to col. 18, line 3 ("One skilled in the art would recognize the inconvenience of an IV [*i.e.*, intravenous] formulation for the patient in need of frequent, chronic therapy [because the] patient has to make frequent trips to the hospital to receive their drug via an IV infusion that may last as long as an hour."). Accordingly, for all therapeutic protein products on the market—and especially for those requiring frequent and chronic administration, *see* Shire, MOM-1005, at 1390—the "most preferred" formulation would be a stable liquid solution in a pre-filled syringe. Carpenter Handbook, MOM-1004, at 183.

The volume of liquid formulation that can be delivered subcutaneously is limited to about 1 to 1.5 ml. *See id.* at 182 ("in the case of a subcutaneous injection, there is a maximal volume (-1 ml.) that can be given to a patient without discomfort"); *see also* Shire, MOM-1005, at 1390 (teaching "the small volume (<1.5 mL) that can be given by the SC [*i.e.*, subcutaneous] routes"). Delivering the needed amount of protein drug in the small volume required for subcutaneous injection, in turn, often requires formulations having high protein concentrations on the order of 100 mg/ml or higher. *E.g., id.* ("Treatments with high doses, e.g., more than 1 mg/kg or 100 mg per dose, require development of formulations at concentrations exceeding 100 mg/mL because of the small volume (<1.5 mL) that can be given by the SC routes."). However, proteins become less stable at high

concentrations. *See id.* at 1393 (detailing the concentration dependency of various protein degradation pathways).

The formulator's task is to develop a liquid, high concentration protein formulation that is stable and suitable for subcutaneous administration. Such formulators are highly skilled, typically having 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. *See* Staples Decl., MOM-1006, at ¶ 20. Such persons would have been aware of—and able to use effectively—the "great deal of research regarding protein stability [that had] been conducted." Carpenter Handbook, MOM-1004, at 1. This research included the fact that there were a limited number of parameters that could be varied in order to achieve a stable, high concentration, liquid formulation.

By the filing date of the '239 patent, the highly skilled protein formulators in this field had synthesized the research regarding protein stability to create a limited toolbox to deploy when developing a stable, liquid formulation for subcutaneous injection—*i.e.*, a limited number of approaches and excipients to use. *See* Staples Decl., MOM-1006, at ¶¶ 27-29. Because of the inherent constraints on what made for a commercially and pharmaceutically acceptable formulation, there were only a finite set of options within a formulator's toolbox.

A. There Were a Number of Constraints Known to Formulators In Preparing a Stable, Liquid, Protein Formulation for Subcutaneous Administration.

A formulator of ordinary skill tasked with developing a stable, liquid, protein formulation for subcutaneous administration would have known that because of certain inherent constraints, there was only a finite set of possible excipients to use and approaches to take. Carpenter Handbook, MOM-1004, at 186. One of those constraints—that a maximum volume of only 1-1.5 ml could be delivered subcutaneously—is discussed above. The constraint on volume defines the protein concentration that must be used. *Id*. at 182. For subcutaneous administration, where the volume is effectively fixed, "the decision point regarding protein concentration is removed from the process." *Id*. Therefore, for subcutaneous formulations, proteins concentrations exceeding 100 mg/mL are typically required. Shire, MOM-1005, at 1391.

A second constraint is that the list of possible excipients is restricted to those already found in approved products in North America, Europe, and Japan. *Id*. "While this is not an immutable rule, few companies are willing to bear the added cost of getting a new excipient on the market while seeking approval for a new drug product." *Id*. Accordingly, a formulator would only select from those excipients found in approved products that had already been shown to be effective in protein formulations. *Id*. at 186.

A third constraint is the patient's comfort, which is affected by the tonicity and pH of the formulation. *Id*. at 182. With respect to tonicity, "[a]lthough isotonicity is not necessarily required for SC [*i.e.*, subcutaneous] administration, it may be desirable for minimizing pain upon administration." Shire, MOM-1005, at 1396; *see also* '239 patent, col. 2, lines 29-31 ("Although isotonicity is not necessarily required for SC administration, it may be desirable for minimizing pain upon administration."). Tonicity will set an upper limit on the amount of excipients that can be added to the formulation. *See* Staples Decl. MOM-1006, at ¶ 43. This is because the larger the amount of excipients added, the higher the formulation's tonicity. *Id*. at ¶ 34. While some moderate level of hypertonicity may be acceptable to achieve a particular purpose, too high a level will be prohibitively uncomfortable for the patient. *See* '239 patent, col. 31, lines 31-36 (choosing an amount of sucrose that "provided optimum stability without resulting in a drug product with *excessive* hypertonicity") (emphasis added).

With respect to pH, values at or near physiological pH minimize discomfort upon injection. *See* Carpenter Handbook, MOM-1004, at 182 (strict pH considerations to achieve pain-free injection); *see also* Staples Decl., MOM-1006, at ¶ 44. That is one reason why the prior art taught administration of the protein claimed here, CTLA4Ig, at "neutral pH," *i.e.*, "about pH 7-8, e.g., pH 7.5." Cohen, MOM-1003, at [0145]; *see also* Staples Decl., MOM-1006, at ¶ 44 (interpreting

Cohen as choosing that pH to minimize discomfort). While pH at or near physiological values is ideal for patient comfort, it sometimes must be adjusted based on the pH-dependence profile of the particular protein. *See* Staples Decl., MOM-1006, at ¶ 44; Carpenter Handbook, MOM-1004, at 186 (teaching that a protein's pH-dependent stability profile may "guide appropriate choice of excipients"). While some proteins are most stable at or near physiological pH, others may be more stable elsewhere. *See* Staples Decl., MOM-1006, at ¶ 44. For the latter, the optimum pH is one that balances the patient's comfort with stability. *Id*. Importantly, however, the goal would be to achieve a pH as close to physiological pH as possible, and to deviate only if there were significant countervailing stability concerns. *Id*.

A fourth constraint is the viscosity of the formulation. Too high a viscosity would impair the formulation's ability to be delivered via syringe. Shire, MOM-1005, at 1397 ("If the viscosity of a high concentration formulation is sufficiently high, it may impact the ability to load and deliver from a syringe."). The viscosity of the formulation, therefore, had be such that the formulation could practically be loaded and delivered from 26 or 27 gauge syringe needles, the commonly used needles. *See id.* ("Syringes for SC [*i.e.*, subcutaneous] injection are often equipped with 26 or 27 gauge needles.").

B. The Choice of Suitable Excipients for Stable Liquid Formulations Was Limited

The Carpenter Handbook details the process of selecting excipients for stable liquid protein formulations in a section entitled "Proper Choice of Excipients" for "Liquid Formulations." *See id*. at 186-88. As the Carpenter Handbook states: "there will be a finite set of possible excipients, restricting choices to those that are found in approved products and have been shown to be effective in protein formulations." *Id.* at 186. The Carpenter Handbook then provides a list of those possible excipients, categorizing them by function:

Table 2.
Possible Excipients for Use in Liquid Formulations

Excipient Class	Choices
Buffers	Histidine, Succinate, Acetate, Citrate Phosphate, Tris, Carbonate
Salts	Sodium Chloride, Calcium Chloride Magnesium Chloride
Non-Specific Stabilizers	Sucrose, Trehalose, other sugars, Amino acids (e.g., lysine, glycine)
Specific Stabilizers	depends upon the protein
Surfactants	Tween 20, Tween 80, Pluronic F-68 Sodium Dodecyl Sulfate
Chelators	EDTA

Id. at 187.

As protein stabilizers, the Carpenter Handbook teaches that there are two (to some extent interchangeable) types of excipients: non-specific stabilizers and specific stabilizers. *Id*. Non-specific stabilizers, like sugars, interact with the solvent to favor the folded form of the protein over the unfolded form, thereby

"reduce[ing] the amount of aggregation-competent species and the rate of aggregation." *Id*; *see also* Shire, MOM-1005, at 1394 (describing this preferential hydration mechanism for osmolytes like sugars). "The most effective non-specific stabilizers tend to be disaccharides, such as sucrose and trehalose," Carpenter Handbook, MOM-1004, at 187, with "sucrose … the most studied." *Id*. at 66. Specific stabilizers are able to "accomplish the same outcome" as non-specific stabilizers by preferentially binding the folded form. *Id*. at 187.

Among non-specific stabilizers, sucrose and trehalose were the "first-line" choices to stabilize proteins. *See id*. at 187-88 ("[U]nless there is evidence for advantage in use of a [different] particular compound …, sucrose and trehalose should remain the first-line choices."). Non-specific stabilizers like sucrose and trehalose required "relatively high concentrations (ca. > 0.2 M)" to adequately stabilize proteins in aqueous solution. *Id*. at 187. Sucrose, for example, was known to increasingly stabilize proteins up to a concentration of at least 1 M. *See* Kendrick, MOM-1008, at 14145 (Figure 3 charting the effect of sucrose on the rate of protein aggregation, using a range of from 0 to 1 M sucrose).

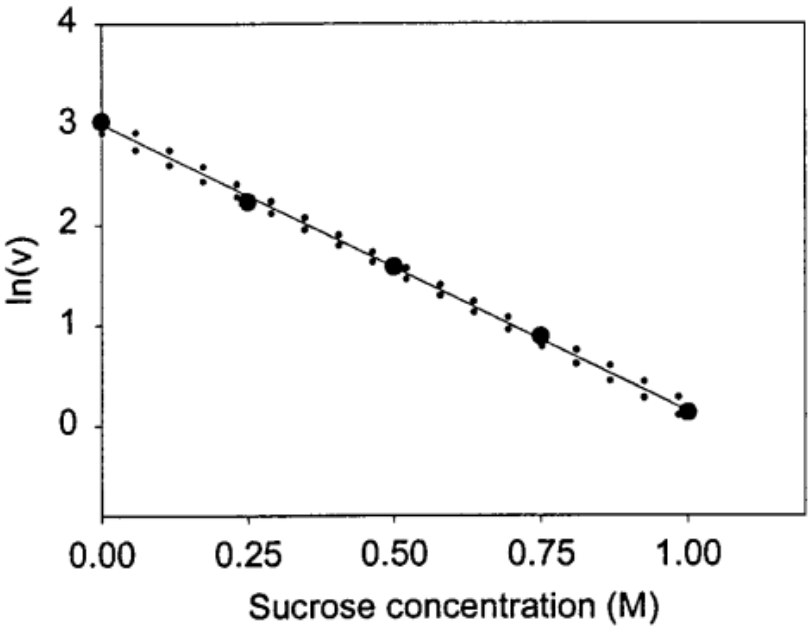

FIG. 3. Effect of sucrose concentration on the rate of rhIFN-γ aggregation. The slope is equivalent to the difference in covolumes of N-sucrose, and N*-sucrose, which is 2.87 ± 0.17 liters/mol (95% confidence interval). Confidence intervals (95%) on the slope are indicated by dotted lines.

While it was known that high concentrations of sugars were needed to stabilize proteins, it was also known that adding too much sugar would make the formulation excessively hypertonic and/or viscous. *See* Shire, MOM-1005, at 1394 (using sugars adds to the viscosity and osmolality, *i.e.,* tonicity, of the formulation and may "render it impractical for use"); *see also* Carpenter Handbook, MOM-1004, at 65 (high concentrations of sugars may not be suitable in cases where isotonicity must be maintained). 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. *See* Staples Decl., MOM-1006, at ¶¶ 28-29, 32-34, 46.

V. THE '239 PATENT AND ITS PROSECUTION HISTORY

A. Background of the '239 Patent

The '239 patent is entitled "Stable Protein Formulations." It contains 15 claims, each of which covers a stable liquid formulation of CTLA4Ig, a fusion protein drug known to treat rheumatoid arthritis.

Each of the two independent claims, 1 and 7, require CTLA4Ig at a particular concentration and with a particular amount of "sugar" used as an excipient. From these shared features, both claim 1 and claim 7 add their own additional limitations on the formulation. For example, claim 1 requires a range of CTLA4Ig concentration of at least 100mg/ml; that the "sugar" be selected from the group of sucrose, lactose, maltose, mannitol, and trehalose; and that the selected "sugar" be in an amount having a weight ratio to CTLA4Ig of 1.1:1 or higher. Claim 1 also requires that the formulation be at a specific pH (of from 6 to 8), have a certain viscosity (9 to 20 cps), and contain a pharmaceutical acceptable aqueous carrier. Claim 1 reads:

> 1. A stable formulation suitable for subcutaneous administration comprising at least 100mg/ml CTLA4Ig molecule, a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof and a pharmaceutically acceptable

> aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20 cps, and the weight ratio of sugar:protein is 1.1:1 or higher.

Claim 7, on the other hand, requires CTLA4Ig at a concentration of about 125 mg/ml and a particular sugar, sucrose, at a concentration of about 170 mg/ml. Claim 7 further requires at least one buffering agent, sterile water, and optionally a surfactant. Claim 7 reads:

> 7. A stable formulation comprising the CTLA4Ig molecule having the amino acid sequence shown in SEQ ID NO:2 starting at methionine at position 27 or alanine at position 26 and ending at lysine at position 383 or glycine at position 382 in an amount of about 125 mg/ml, sucrose in an amount of about 170 mg/ml, at least one buffering agent, sterile water for injection and optionally a surfactant.

Claim 7, just like dependent claim 4, claims the CTLA4Ig fusion protein by reference to the specific amino acid sequence disclosed by SEQ ID NO:2, as shown in Figures 1A & 1B of the '239 patent. *See* '239 patent at claims 4 & 7 (both reciting a CTLA4Ig molecule having "the amino acid sequence shown in SEQ ID NO:2 starting at methionine at position 27 or alanine at position 26 and ending at lysine at position 383 or glycine at position 382"). As the '239 patent states, this specifically claimed sequence refers to the amino acid sequence of the CTLA4Ig single chain fusion protein. *See* '239 patent, col. 7, lines 31-35 ("In one embodiment, 'CTLA4Ig' refers to a protein molecule having the amino acid

sequence of residues (i) 26-383 of SEQ ID NO:2, (ii) 26-382 of SEQ ID NO:2; (iii) 27-383 of SEQ ID NO:2, or (iv) 27-382 of SEQ ID NO:2."); *see also id*. at col. 4, lines 50-53 (Figure 1 of the '239 patent shows the SEQ ID NO:2 amino acid sequence).

Certain dependent claims place further limitations on the sugar. Claim 2 limits the "sugar" of claim 1 to the group of sucrose, mannitol, or trehalose, while claim 5 limits the "sugar" to sucrose only. Claims 14 and 15, which both depend from claim 5, require the weight ratio of sucrose:protein be 1.3-1.5:1 or 1.4:1, respectively.

Other dependent claims require that the claimed formulation have an additional excipient, some particular characteristic, or be packaged in a certain way:

- **Buffers and pH**. Claims 3 and 6 both require that the formulation have a pharmaceutically acceptable buffer, whereas claim 8 requires a buffering agent in the amount of at least 10 mM phosphate buffer. Claim 10 requires that the formulation of claim 7 have a pH of from 6-8.
- **Surfactant**. Claim 9 requires that the formulation of claim 7 have a specific surfactant, Poloxamer, in an amount of about 8 mg/ml.
- **Stability**. Claim 11 requires that the formulation of claim 1, 4, or 7 be stable when stored at 2 to 8 ºC for at least 12 months.

- **Article of manufacture**. Claim 12 requires that the formulation of claim 1, 4, or 7 be packaged in a container and come with instructions for subcutaneous administration to a patient in need. Claim 13 specifically requires that the container be a vial or syringe.

B. The '239 Patent Prosecution History

The '239 patent issued from U.S.S.N. 12/086,876, which was filed as PCT/US2006/062297 on December 19, 2006. The '239 patent claims priority to Provisional Application No. 60/752,150, which was filed on December 20, 2005.

On November 2, 2010, the Examiner entered a first Office Action rejecting all 72 originally filed claims as anticipated under 35 U.S.C. § 102 and as obvious under § 103. For both rejections, the Examiner relied on Peach (U.S. Pub. No. 2002/018221), which the Examiner found to teach "formulations comprising CTLA4Ig molecules, a sugar, a buffer and a plurality of other agents known in the art to be useful in pharmaceutical formulations." MOM-1002, at 347-353 (non-final rejection).

In response, BMS amended its claims to require the use of a particular list of "sugars" to stabilize the protein and that the formulation be at pH of from 6 to 8. For example, claim 1 was amended as follows:

> A stable formulation suitable for subcutaneous administration comprising at least 100mg/ml CTLA4Ig molecule, a sugar <u>selected from the group consisting of sucrose, lactose, maltose, mannitol and</u>

> trehalose and mixtures thereof ~~capable of stabilizing said formulation~~ at a concentration effective for stabilizing said formulation ~~therefore~~ and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8.

Id. at 362. BMS argued that this amendment made the claims patentable because, according to BMS, Peach did not teach or suggest "the addition of sucrose, lactose, maltose, mannitol, trehalose or mixtures thereof to a liquid formulation comprising at least 100mg/ml CTLA4Ig molecules in order to enhance its long-term stability," nor did Peach teach or suggest a pH range of from 6-8. *Id*. at 366-68. The Examiner disagreed, however, entering a final office action on June 8, 2011. *Id*. at 374-80. The Examiner maintained the obviousness rejection over Peach, concluding that both the list of claimed "sugars" and the pH range of from 6-8 were "readily known and widely used by those skilled in the art to produce high-concentration formulations of therapeutic polypeptides." *Id*.

In response to the final rejection, BMS filed a Request for Continued Examination (RCE). *Id*. at 382. In its RCE, BMS re-submitted the previously pending claims, without amendment. *See id*. at 385-88. BMS argued that Peach was "silent as to stability issues related to pharmaceutical formulations" *Id*. at 389-90. The Examiner again disagreed, entering another Office Action rejecting all pending claims. *Id*. at 403.

In the non-final rejection, the Examiner relied on three additional references: Andya (U.S. Pub. No. 2006/0099201), Cleland (U.S. Patent No. 5,804,557), and Li (U.S. Pub. No. 2007/0053871). Each reference, the Examiner found, taught "experimental approaches to obtaining stable protein formulations at high protein concentration by adjusting variables such as pH, the identity and concentration of sugars, the ratios of protein to sugar, the identity and concentrations of surfactants, and others." *Id*. at 407.

BMS responded to the non-final rejection by again amending its claims, this time to add limitations including a ratio covering the amount of sugar used relative to the amount of protein present and the viscosity of the formulation. At the same time, BMS deleted functional language in certain claims that the sugar should be in a concentration effective for stabilizing the formulation. For example, claim 1 was amended as follows:

> A stable formulation suitable for subcutaneous administration comprising at least 100mg/ml CTLA4Ig molecule, a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof ~~at a concentration effective for stabilizing said formulation~~ and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20cps, and the weight ratio of sugar:protein is 1.1: 1 or higher.

Id. at 416.

BMS also argued that the three new references, which each taught high concentrations of sugars to stabilize proteins, were not applicable to the problem of developing a stable liquid formulation having a high protein concentration. *Id*. at 420-32. BMS argued that one of ordinary skill in the art would not have looked to Andya, BMS argued, because Andya was directed to lyophilization (or freeze-drying proteins) and the stability issues during lyophilization "differ from the issues faced by the Applicants." *Id*. at 422. Likewise, BMS argued that one of ordinary skill would not have looked to Cleland, because Cleland related to the "encapsulation technology for stabilizers," not to stabilizers high concentrations of proteins in liquid formulations. *Id*. Finally, BMS argued that one of ordinary skill would not have looked to Li, in part because Li related to "stabilizers required in formulations containing destabilizing preservatives," not to the design of stable liquid formulations. *Id*.

On March 5, 2013, the Examiner issued a Notice of Allowance. *Id*. at 430. On July 2, 2013, the application issued as the '239 patent. *Id*. at 448. On November 20, 2014, the Patent Office granted 426 days of patent term adjustment under 35 U.S.C. § 154(b)(4). *Id*. at 469 (relying on *Novartis AG v. Lee*, 740 F.3d 593 (Fed. Cir. 2014)).

Thus, during prosecution BMS argued that the Examiner never relied on a reference specifically teaching how to stabilize high concentrations of proteins in

liquids. According to BMS, the references relied on by the Examiner "addressed different stability issues" than those encountered when trying to stabilize a protein in a liquid formulation. *Id*. at 422.

VI. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(B)(3)

For purposes of IPR, a claim is interpreted by applying its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). As such, the words of claims 1-20 are given their ordinary and customary meaning as understood by one of skill in the art in the context of the entire disclosure. *In re Translogic Tech. Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Petitioner submits that except as set forth below, the terms in claims 1-15 should be given their plain meaning. To Petitioner's knowledge, no court has construed any term of the '239 patent.

Claims 1 and 7 as issued recite in their preambles a "stable" formulation. 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. The '239 patent, however, provides no teaching that would inform one skilled in the art which of the compositions satisfying the other limitations of claims 1 or 7 are stable and which are not. Thus, the term "stable" in claims 1 and 7 should be interpreted as being satisfied where all other limitations of the claim are met. *See* Staples Decl., MOM-

1006, at ¶¶ 22-23. That is, a formulation meeting all other limitations must necessarily be "stable," as that term should be interpreted in claims 1 and 7.

VII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '239 PATENT IS UNPATENTABLE

Where the prior art identifies a problem, teaches a limited set of routine procedures for solving that problem, and provides a skilled artisan with a reasonable expectation that the procedures would work to solve the problem, claims that do nothing more than apply those teachings to achieve the expected result are not patentable. *See, e.g., Merck & Co., Inc. v. Biocraft Labs*, Inc., 874 F.2d 804, 809 (Fed. Cir. 1989) (claims are not patentable "where the prior art would have suggested to one of ordinary skill in the art that [a particular] process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art," that the process would work as taught).

Moreover, that is true even where a skilled artisan would not have been able to predict *exactly where*, within a known and customary range, the routine procedures would have led, so long as there was a reasonable expectation that the routine procedures would have led to a successful outcome. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success"); *see also Biomarin Pharms. Inc. v. Genzyme Therapeutic Products Ltd. P'ship*, IPR2013-00534, Paper

No. 81 (PTAB Feb. 23, 2015) ("a reasonable expectation of success does not require absolute predictability") (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Even where obtained "through the use of trial and error procedures"—and therefore unable to be precisely determined ahead of time—claim limitations that are "nothing more than routine application of a well-known problem-solving strategy" are merely "the work of a skilled artisan, not of an inventor." *Pfizer*, 480 F.3d at 1368. "Indeed, a rule of law equating unpredictability to patentability …. cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Id*. at 1364.

Biomarin, a recent case before the Patent Trial and Appeal Board, illustrates how the patentability standard is not one of absolute predictability, *i.e.*, that a claim can be unpatentable despite requiring some level of trial and error. *Biomarin Pharms. Inc. v. Genzyme Therapeutic Products Ltd. P'ship*, IPR2013-00534, Paper No. 81 (PTAB Feb. 23, 2015). The claims at issue in *Biomarin* covered a method of treating Pompe's disease by "intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase." *Id*. at 4. The only limitation in claim 1 not expressly disclosed in the prior art was the "biweekly" limitation. *Id*. at 11. While recognizing that "a person of ordinary skill in the art could not have predicted with absolute certainty … a safe and effective

dosing regimen," the Board concluded that "that the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [a prior art reference teaching use of the claimed enzyme to treat Pompe's disease], which would have been achievable through the use of standard clinical trial procedures." *Id*. at 12-14. "[T]he experimentation needed to achieve biweekly administration," the Board found, was "'nothing more than the routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan], not of an inventor.'" *Id*. at 14 (quoting *Pfizer*, 480 F.3d at 1368). And, furthermore, that the "motivation to optimize the therapy disclosed in [the prior art] flows from the normal desire of scientists or artisans to improve upon what is already generally known." *Id*.

This is all to say that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). And "[i]f this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id*.

Here, Claims 1-15 of the '239 patent cover "stable" liquid formulations of CTLA4Ig suitable for subcutaneous administration. For the reasons discussed below, they are unpatentable over Cohen in light of the Carpenter Handbook and

Shire. The claims represent nothing more than the efforts of a skilled formulator choosing from among a limited set of known options and textbook protocols for converting intravenous protein liquid formulations to subcutaneous liquid formulations. The claims of the '239 patent merely implement one of those approaches—in fact, the "first-line" approach, *see id*. at 186-88—to attain the expected result: using sugars to stabilize the protein and prevent aggregation at the high protein concentrations needed for subcutaneous formulations.

A. Cohen, the Carpenter Handbook, and Shire Qualify as Prior Art against Claims 1-15

Cohen, MOM-1003, is prior art under 35 U.S.C. § 102(b) because it published on May 1, 2003, which is more than one year earlier than the earliest possible priority date for claims 1-15 of the '239 patent (December 20, 2005). Cohen teaches use of the protein claimed here, CTLA4Ig, to treat autoimmune diseases, including rheumatoid arthritis. *E.g.*, Cohen, MOM-1003, at [0021]. Cohen further teaches how *much* CTLA4Ig is needed, based on the patient's weight, to treat the symptoms of rheumatoid arthritis when delivered intravenously. *E.g., id.* at [0274], [0275] (clinical data established that 2 mg CTLA4Ig per patient kg and 10 mg CTLA4Ig per patient kg—*i.e.*, "2 or 10 mg/kg"—alleviated symptoms of tender and swollen joints).

The Carpenter Handbook, MOM-1004, is prior art under 35 U.S.C. § 102(b) because it first published in April 2002. The Carpenter Handbook teaches how,

starting with a protein of interest, to develop a stable pharmaceutical formulation, including specifically a stable liquid formulation suitable for subcutaneous injection. *E.g.*, Carpenter Handbook, MOM-1004, at 186-88 (teaching a "finite set of possible excipients" for stable liquid protein formulations). The Carpenter Handbook, which was not of record during prosecution, was the type of publication that would have been on the bookshelf of a protein formulation chemist. *See* Staples Decl., MOM-1006, at ¶ 18.

Shire, MOM-1005, is prior art under 35 U.S.C. § 102(b). It is a review published in the *Journal of Pharmaceutical Sciences* in June 2004. Shire teaches that, because subcutaneous formulations can practically be no more than ~1.5 ml in volume, they often require very high protein concentrations of greater than 100 mg/ml. Shire, MOM-1005, at Abstract; *see also id.* at 1391 ("Treatments with high doses, e.g., more than 1 mg/kg or 100 mg per dose, require development of formulations at concentrations exceeding 100 mg/mL because of the small volume (<1.5 mL) that can be given by the SC routes."). Shire then teaches techniques for how to overcome the challenges that come with developing the needed high concentration protein formulations. The '239 patent recites sections of Shire verbatim, without citing it or even mentioning it. *Compare, e.g.*, '239 patent, col. 1, lines 24-45 *with* Shire, MOM-1005, at 1390-91. Like the Carpenter Handbook, Shire was cited by BMS during prosecution of the '239 patent.

B. Claims 1-15 Would Have Been Obvious over Cohen in view of the Carpenter Handbook and Shire.

The claims of the '239 patent cover stable liquid formulations of CTLA4Ig, a fusion protein drug known to treat rheumatoid arthritis. All 15 claims require a liquid formulation having a particular amount of CTLA4Ig and containing an amount of sugar. There are certain additional limitations, including that the formulation be at a specific pH (a pH of 6-8, *see* claims 1, 10), have a certain viscosity (a viscosity of 9-20 cps, *see* claim 1), contain a buffer (*see* claims 3, 6; or contain 10 mM phosphate as buffer, *see* claim 8), contain a surfactant (*see* claims 7, 9), be stable when stored at 2 to 8 ºC for at least 12 months (*see* claim 11), or be packaged in a standard way (in a container and accompanied by instruction for subcutaneous injection, *see* claim 12; or that the container be a syringe, *see* claim 13). Claim 1, for example, reads:

> 1. A stable formulation suitable for subcutaneous administration comprising at least 100mg/ml CTLA4Ig molecule, a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof and a pharmaceutically acceptable aqueous carrier, wherein the formulation has a pH range of from 6 to 8 and a viscosity of from 9 to 20 cps, and the weight ratio of sugar:protein is 1.1:1 or higher.

Cohen, the Carpenter Handbook, and Shire in combination render all 15 claims obvious. Together they disclose the use of the CTLA4Ig fusion protein to

treat rheumatoid arthritis, the specific amount of CTLA4Ig needed per patient kilogram to effectively treat rheumatoid arthritis when administered intravenously, that a liquid formulation for subcutaneous delivery is desired where a protein drug requires frequent and chronic administration, that subcutaneous formulations have a limited volume (~1-1.5 ml) that often requires high protein concentrations (> 100 mg/ml), that the resulting high protein concentrations can lead to protein aggregation and protein instability, and that by using a limited set of possible excipients a skilled artisan could be "quite confident" in achieving a stable liquid formulation of the protein. Any additional elements claimed by the '239 patent, *e.g.*, the particular amount of sugar used to stabilize the protein, simply represent the result of a highly trained person of ordinary skill in this art—a formulator—following well-known formulation principles, including routine trial and error, to optimize known variables.

i. CTLA4Ig was known in the art, as was the amount needed to treat rheumatoid arthritis.

Cohen teaches the use of CTLA4Ig to treat rheumatoid arthritis, *see, e.g.*, Cohen, MOM-1003, at [0021]. Furthermore, Cohen discloses the results of a Phase II clinical trial demonstrating *how much* CTLA4Ig is needed when applied intravenously, based on the patient's weight, to relieve the symptoms of rheumatoid arthritis, *see, e.g., id.* at [0237], [0274]-[0275].

CTLA4Ig is a soluble fusion protein comprising the extracellular domain of

CTLA4, a naturally occurring transmembrane protein, fused with constant domain of an immunoglobin (Ig) heavy chain. Cohen, MOM-1003, at [0011]. This fusion protein and its variants "introduce[d] a new group of therapeutic drugs to treat rheumatic diseases," i*d*. at [0014], and were more effective and more potent in treating the diseases than the preexisting treatments. *Id*. at [0018].

Cohen discloses the results of Phase II clinical trials of CTLA4Ig administered to relieve the symptoms of rheumatoid arthritis. *See id.* at Example 3, [0237]-[0284]. Specifically, the clinical study intravenously administered either CTLA4Ig or a particular variant (known as L104EA29YIg or LEA) four times over the course of 57 days. *Id*. at [0237], [0239]. Either CTLA4Ig or the LEA variant were administered in three varying amounts relative to the subject's total weight: 0.5, 2, or 10 mg of the protein per kilogram of the subject's weight (*i.e.*, 0.5, 2, or 10 mg/kg).

The results of the clinical study demonstrated that the groups treated with 2 or 10 mg/ml of CTLA4Ig or its variant experienced greater relief from the symptoms of rheumatoid arthritis than those groups treated with a placebo or 0.5 mg/ml. *See id.* at [0274] (groups treated with 2 or 10 mg/kg experienced greater reduction in tender joints over time); *id*. at [0275] (those same groups experienced reduction in swollen joints); *id*. at [0276] (and greater reduction in pain); *see also id.* at Figures 9-11 (charting clinical differences between 0, 0.5, 2, and 10 mg/kg of

CTLA4Ig). Accordingly, one skilled in the art would have known from Cohen that to treat rheumatoid arthritis successfully, at least 2 mg of CTLA4Ig was needed for each kilogram of the patient's weight. *See* Staples Decl., MOM-1006, at ¶¶ 39-41.

ii. There existed motivation to develop a liquid subcutaneous formulation of CTLA4Ig because it required frequent and chronic administration.

Treating rheumatoid arthritis with CTLA4Ig requires frequent and chronic administrations of the protein. *See, e.g.*, Cohen, MOM-1003, at [0286]. Rheumatoid arthritis—like other rheumatic diseases—is "characterized by chronic inflammation that often leads to permanent tissue damage, deformity, atrophy and disability," *id.* at [0005], with treatment schedules requiring administration of CTLA4Ig "chronically every two to twelve weeks to maintain … therapeutic improvement over time." *Id*. at [0286].

For proteins that require frequent and chronic administration, subcutaneous administration is preferred to intravenous administration. *See* Shire, MOM-1005, at 1391-92. Subcutaneous delivery "allows for home administration and improved compliance of administration, and may result in expanded product markets." *Id*. Thus, a person of ordinary skill would have been motivated to develop a stable liquid formulation of CTLA4Ig that was suitable for subcutaneous injection.

The '239 patent itself acknowledges that, for a protein like CTLA4Ig, there were many known advantages to developing a liquid formulation for subcutaneous

injection. For example, the first five paragraphs of the Background of the Invention repeats almost verbatim Shire's teachings that subcutaneous formulations should be pursued. *See* '239 patent, col. 1, line 24 to col. 2, line 27. Among the quoted portions is the opening paragraph:

> Over the past two decades, recombinant DNA technology has led to the commercialization of many protein therapeutics. The most conventional route of delivery for protein drugs has been intravenous (IV) administration because of poor bioavailability by most other routes, greater control during clinical administration, and faster pharmaceutical development. *For products that require frequent and chronic administration, the alternate subcutaneous (SC) route of delivery is more appealing. When coupled with pre-filled syringe and autoinjector device technology, SC delivery allows for home administration and improved compliance of administration*.

'239 patent, col. 1, lines 24-34 (emphasis added) (compare with Shire, MOM-1005, at 1390-91). The '239 patent adopts wholesale—and thus recognizes the wisdom of—Shire's teaching that a liquid formulation would have been especially advantageous for protein drugs like CTLA4Ig.

iii. The limited volume available for subcutaneous injection dictated the claimed CTLA4Ig concentrations.

The CTLA4Ig concentrations recited in claim 1 ("at least 100 mg/ml") and claim 7 ("about 125 mg/ml") merely reflect the minimum amount of CTLA4Ig known to be therapeutically effective (2 mg of CTLA4Ig per patient kilogram)

placed into the limited volume available for subcutaneous injection.

Cohen teaches the minimum amount of CTL4Ig needed when delivered intravenously. Cohen teaches that to treat rheumatoid arthritis, a minimum of 2 mg of CTLA4Ig is needed for every kilogram of patient weight. *See* Cohen, MOM-1003, at [0274]-[0276]; *see also, supra*, § VII.B.i. Because the average adult weight is 79.7 kg, *see* MOM-1007, the average minimum dose of CTLA4Ig needed to treat rheumatoid arthritis is 159.4 mg of CTLA4Ig (*i.e.*, 2 mg/kg multiplied by 79.7 kg).

Likewise, it was known that the volume of a liquid formulation for subcutaneous could be no more than 1-1.5 ml. *See* Carpenter Handbook, MOM-1004, at 182 ("in the case of a subcutaneous injection, there is a maximal volume (~1 ml.) that can be given to a patient without discomfort."); *see also* Shire, MOM-1005, at 1391 ("Treatments with high doses, e.g., more than 1 mg/kg or 100 mg per dose, require development of formulations at concentrations exceeding 100 mg/mL because of the small volume (<1.5 mL) that can be given by the SC routes.").

When 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. *See* Staples Decl., MOM-1006, at ¶¶ 39-41. A dose administered intravenously is

considered 100% bioavailable, or by definition 100% of the drug enters systemic circulation, thereby accessing the site of action. *Id*. One skilled in the art would have expected that the bioavailability of CLTA4Ig after subcutaneous injection would have been, *at most*, 100%. *Id*. One skilled in the art, therefore, would have expected that the total amount of CTLA4Ig needed subcutaneously would be at least that needed intravenously. *Id*. at ¶40 (stating that a subcutaneous dose, which has to cross additional biological barriers to be active, may have a bioavailability of less than 100%). Thus, 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. *Id*.

Nor would a formulator have started with a substantially larger dose, because CTLA4Ig was known to have a relatively high bioavailability even when administered subcutaneously. *See* Staples Decl., MOM-1006, at ¶ 41. Specifically, it was known that CTLA4Ig was 85% bioavailable after subcutaneous administration in mice. MOM-1009, at 2 ("The extent of absorption of CTLA4Ig after subcutaneous dosing was relatively complete, 85%."). There would have been a strong desire not to use more CTLA4Ig than was needed—at higher protein concentrations a formulation becomes increasingly prone to aggregation or solubility limitations. *Id*. at ¶ 41.

Compensating for the differences in bioavailability between intravenous and

subcutaneous administration (100% and 85%, respectively) would have led a protein formulator to include at least 125.0 mg/ml of CTLA4Ig in a 1.5 ml subcutaneous formulation. *See* Staples Decl., MOM-1006, at ¶ 41. The math behind this calculation is straightforward, depending only on known and recognized variables. 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, *see* MOM-1009, at 2; Staples Decl., MOM-1006, at ¶ 41, 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. *See* MOM-1004, at 1391. Fourth, and finally, 187.53 mg of CTLA4Ig placed into a 1.5 ml subcutaneous formulation is 125.0 mg/ml. *See* Staples Decl., MOM-1006,. at ¶ 41. This is precisely the concentration recited in claim 7. Similarly, it falls squarely within the range recited in claim 1 of "at least 100 mg/ml" of CTLA4Ig.

Even if slightly different variables were chosen (*e.g.*, a 1 ml volume was chosen instead of 1.5 ml or a slightly different subcutaneous bioavailability was used), there would not have been any critical difference between the amount of CTLA4Ig chosen for the formulation and any value claimed by the '239 patent. For example, after compensating for the known, slightly lower bioavailability of

subcutaneous administration (85%) relative to intravenous administration (100%), the CTLA4Ig concentration needed for a 1 ml subcutaneous formulation would still have been 187.5 mg/ml. *Id*. at ¶ 41. Thus, the CTLA4Ig concentrations claimed are merely the logical result of incorporating the needed amount of CTLA4Ig, as taught by Cohen, into the limited volume of a subcutaneous formulation, as taught by the Carpenter Handbook and Shire.

iv. A skilled formulator would have known how to prepare a stable liquid formulation of CTLA4Ig for subcutaneous administration by selecting from among a limited set of excipients according to well-known formulation protocols

It was known that proteins could be unstable at the relatively high concentrations required of a subcutaneous formulation. *See, e.g.*, Shire, MOM-1005, at 1391 ("Development of formulations at high concentrations also poses stability, manufacturing, and delivery challenges related to the propensity of proteins to aggregate at the higher concentrations.").

By using only a limited set of possible excipients, however, a formulator could be "quite confident" in successfully developing a stable liquid formulation. *See* Carpenter Handbook, MOM-1004, at 182, 186-88, 195. The Carpenter Handbook teaches how a skilled artisan would have only looked to a limited set of possible excipients when developing a stable liquid formulation for subcutaneous injection. *See id.* at 182 ("the list of possible additives is effectively limited to those already found in approved products …"). The Carpenter Handbook then

discloses that limited list of possible excipients, categorized by function:

Table 2.
Possible Excipients for Use in Liquid Formulations

Excipient Class	Choices
Buffers	Histidine, Succinate, Acetate, Citrate Phosphate, Tris, Carbonate
Salts	Sodium Chloride, Calcium Chloride Magnesium Chloride
Non-Specific Stabilizers	Sucrose, Trehalose, other sugars, Amino acids (e.g., lysine, glycine)
Specific Stabilizers	depends upon the protein
Surfactants	Tween 20, Tween 80, Pluronic F-68 Sodium Dodecyl Sulfate
Chelators	EDTA

Id. at 187.

The formulator's toolbox was thus limited. There were a half dozen or so categories of excipients one could choose from, with each category only having a handful of excipients that were known to be safe and effective, and that had already been found in an approved product. *Id*. at 182, 186. For example, "there is a limited set of buffers that will exhibit sufficient buffering capacity" within the customary pH range. *Id*. at 186. Likewise, only four surfactants—which were known to inhibit protein aggregation during agitation—had "been approved for use in parenteral products in the" United States. *Id*. at 188.

Therefore, when developing a stable liquid formulation there would have been "a finite set of possible excipients, restricting choices to those that are found in approved products and have been shown to be effective in protein formulations."

Id. at 186. Table 2 of the Carpenter Handbook, by itself, thus provided "a finite number of identified, predictable solutions" for how to develop a stable liquid formulation. *See KSR*, 550 U.S. at 421. But confirming the obviousness of these claims, the Carpenter Handbook goes further, saying that sugars—specifically sucrose and trehalose—should be the formulator's "first-line choices." *Id*. at 187-88.

v. Using sucrose or trehalose in the claimed amounts to stabilize a high concentration, liquid formulation of CTLA4Ig would have been the "first-line" approach for a formulator.

Claims 1-15 require incorporating a sugar such as sucrose or trehalose in the formulation. However, sugars, and specifically sucrose and trehalose, were known to be the "first-line choices" for stabilizing high concentration liquid protein formulations. Carpenter Handbook, MOM-1004, at 186-88 ("unless there is evidence for advantage in use of a [different non-specific stabilizer], sucrose and trehalose should remain the first-line choices."); *see also id.* at 66 ("In terms of stabilizing interactions with proteins sucrose is the most studied cosolvent/excipient."). Thus, sucrose and trehalose were the logical choices and starting place for a formulator faced with the task of preparing a stable liquid formulation of CTLAIg4 suitable for subcutaneous administration. *See* Staples Decl., MOM-1006, at ¶ 32.

The Carpenter Handbook also teaches that high concentrations of sugars were needed to achieve protein stability. Carpenter Handbook, MOM-1004, at 187. Specifically, the Carpenter Handbook teaches that a concentration in a range of *greater than* 0.2 M was needed, which for sucrose works out to a range of greater than about 70 mg/ml. This range from the prior art overlaps with the ranges recited in claim 1 ("weight ratio of sugar protein is 1.1:1 or higher") and claim 14 ("weight ratio of sucrose:protein is 1.3:1 to 1.5:1"), and encompasses the values recited in claim 7 (170 mg/ml sucrose) and in claim 15 ("weight ratio of sucrose:protein of 1.4:1"). There are no critical differences between the range of sucrose taught by the Carpenter Handbook and the amounts in claim 1, claim 7, claim 14, or claim 15. *See* Staples Decl., MOM-1006, at ¶ 47; *see also ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340 (Fed. Cir. 2012) (prior art discloses claimed range where "there is no allegation of criticality or any evidence demonstrating any difference" between the ranges).

The particular sugar:protein ratios and sugar amounts recited in claims 1-15 represent no more than the optimized values obtained via empirical testing, *i.e.*, standard trial-and-error procedures. *See Pfizer*, 480 F.3d at 1368 (claims obvious where "nothing more than routine application of a well-known problem-solving strategy"). Formulators routinely performed such testing after identifying a stabilizer candidate to identify an optimal amount to be included in a liquid

formulation. *See* Staples Decl., MOM-1006, at ¶¶ 33, 45-46. The selection of the amount was governed by certain constraints. Specifically, a formulator would empirically balance the stabilization effect against tonicity and viscosity. Regarding tonicity, it was known that the tonicity of the solution increased with added sucrose, and that while some tonicity may be permitted, an *excessively* hypertonic formulation caused irritation and discomfort upon injection. *See* Carpenter Handbook, MOM-1004, at 65 (adding too much sugar causes unacceptably high isotonicity for subcutaneous formulations); *see also* Shire, MOM-1005, at 1396 ("Although isotonicity is not necessarily required for SC administration, it may be desirable for minimizing pain upon administration."); '239 patent, col. 2, lines 29-31 (repeating Shire). In addition, the viscosity of the formulation had to remain low enough such that the formulation could be administered through a syringe, thereby imposing yet another limit on the overall amount of sugar that could be added. *See* Shire, MOM-1005, at 1397.

Faced with these known tonicity and viscosity restraints, a formulator would have also known that, in general, adding more sucrose would further stabilize the protein up to a certain point. *See* Staples Decl., MOM-1006, at ¶¶ 33-34, 46. There would have been a lowest reasonable value of sucrose that would have been expected to stabilize a protein. *Id*. at ¶ 33. This lowest reasonable value of sucrose would have been about 0.2 M, or 70 mg/ml. *See* Carpenter Handbook, MOM-

1004, at 187; *see also* Staples Decl., MOM-1006, at ¶ 33. There also would have been a highest reasonable value of sucrose, 1 M or 350 mg/ml, above which adding more sucrose would no longer have been expected to increasingly stabilize the protein. *See id.* at ¶ 33. Above this highest reasonable value, adding more sucrose would have led to further hypertonicity without helping to stabilize the protein.

Using known protocols and operating subject to known constraints, a skilled formulator would have known how to determine, through trial and error, the "sweet spot" between these highest and lowest reasonable values—*i.e*., enough sugar to stabilize the protein, but not so much to cause excessive hypertonicity or viscosity. *See id.* at ¶ 46-47. Such a trial-and-error approach involved nothing more than varying one parameter, the amount of sugar, to balance two known, competing considerations: the stability of the protein and the tonicity of the formula. This could be done through standard, routine procedures. *See id.* at ¶ 33, 45-47.

There would have been a reasonable expectation that such a balance could be successfully achieved. *See id.* at ¶ 46 (stating that, as of 2005, a protein formulator would have reasonably expected to successful develop a stable liquid formulation suitable for subcutaneous injection within an acceptable timeframe); *see also* Carpenter Handbook, MOM-1004, at 186-88, 195 (those in the industry could be "quite confident" that the disclosed approaches for achieving a stable

liquid formulation, including to use sucrose or trehalose as the first-line stabilizers, could successfully "facilitate drug development within the inherent time and resource constraints of the pharmaceutical industry"). This reasonable expectation of success came not only from the clear teachings in the prior art to perform such an empirical balancing, but from the very high level of skill in the field, which required at least a Ph.D in chemistry, biochemistry, or a related field, and at least 2-5 years of experience developing pharmaceutically acceptable formulations of protein drugs. *See, e.g., Butamax Advanced Biofuels LLC v. Gevo, Inc.,* IPR2014-00142, Paper No. 34 (PTAB May 21, 2015) ("A person with a doctoral degree in chemistry would not need a reference detailing the process steps between D'Amore and ASTMD4814 in order to create a product that would comply with the specification in ASTMD4814").

This trial-and-error approach is exactly the approach used by the '239 patent to arrive at its claimed sugar ranges and values. In Example V, the '239 patent describes "[f]ormulation development studies" conducted to evaluate the effect of sucrose on CTLA4Ig. *See* '239 patent, col. 30, line 65 to col. 31, line 36 (the "Effect of Sucrose" section). The '239 patent describes testing three ratios of sucrose to protein: 1:1, 1.7:1, and 1.75:1. *Id*. Based on the results, a "protein to sucrose ratio of 1:1.36 (wt.:wt.) was chosen for the development of the SC solution because it provided optimum stability without resulting in drug product with

excessive hypertonicity." *Id.* at col. 31, lines 32-36. Importantly, the '239 patent acknowledges that *some level* of hypertonicity may be needed to best balance the stability of the protein against the formulation's tonicity. *See id.* (avoiding *excessive* hypertonicity, not *any* hypertonicity); *see also id*. at col. 2, lines 29-31 ("isotonicity is not necessarily required for SC administration, it may be desirable for minimizing pain upon administration").

vi. The claimed viscosity range merely reflects the known range of viscosities that could have been loaded into and delivered from a syringe.

Claim 1 and its related dependent claims require that the viscosity of the formulation fall within the range of 9 to 20 cps. Only certain viscosities could practically be used in a syringe. *See* Shire, MOM-1005, at 1397 ("higher viscosity preparations may be difficult to administer by injection"); *see also id.* ("If the viscosity of a high concentration formulation is sufficiently high, it may impact the ability to load and deliver from a syringe.").

The viscosity range in claim 1 and its related dependent claims ("9 to 20 cps") merely 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. *See* Staples Decl., MOM-1006, at ¶ 42. Shire teaches that "[s]yringes for SC injection are often equipped with 26 or 27 gauge needles." Shire, MOM-1005, at 1397. For an even larger needle, a 25 gauge

needle, Shire teaches that viscosities of less than 20 cps provide acceptable loading times, but as the viscosity exceeds 20 cps the load time for 1.2 ml rapidly goes from about 50 seconds to about 300 seconds. *See id*. at Figure 2B; *see also* Staples Decl., MOM-1006, at ¶ 42. Therefore, the viscosity range recited in the claims was merely the logical choice for a subcutaneous formulation deliverable via a syringe.

vii. The claimed pH was the logical choice for avoiding injection site irritation.

Claim 1 and its dependent claims, as well as claim 10, recite that the formulation has a pH range of 6 to 8. This range corresponds to physiological pH. A formulation at or near physiological pH would have been the preferred choice for a liquid protein formulation in order to minimize irritation upon subcutaneous injection. Staples Decl., MOM-1006, at ¶ 44; *see also* Carpenter Handbook, MOM-1004, at 182 ("If a protein drug is to be administered … subcutaneously, rather than by continuous infusion, there are strict … pH considerations that have to be met for a pain-free injection."). Only if unable to achieve a stable formulation at physiological pH would a formulator deviate from the claimed pH range. Staples Decl., MOM-1006, at ¶ 44. Here, Cohen expressly teaches administration of the claimed protein at "about pH 7-8, e.g., pH 7.5." Cohen, MOM-1003, at [0145]. Accordingly, one of ordinary skill in the art would have followed Cohen's teaching and chosen to develop a subcutaneous formulation of

CTLA4Ig at a pH of about 7-8. Staples Decl., MOM-1006, at ¶¶ 44, 53.

viii. The prior art discloses the remaining claim limitations.

None of the remaining limitations of the '239 patent make any of its claims patentable. Instead, the additional limitations merely recite another commonly used excipient, a certain known desirable characteristic, or that the formulation be packaged in some standard way. Two limitations, in fact, require only that the formulation contain water.

Aqueous Carrier. In addition to the limitations discussed above, both claims 1 and 7 require that the formulation contain water. *See* '239 patent, claim 1 (requiring a "pharmaceutically acceptable aqueous carrier"); *id*. at claim 7 (requiring "sterile water for injection"). There was nothing inventive in using water as a pharmaceutically acceptable carrier. *See*, *e.g.*, Shire, MOM-1005, at 1396 (teaching the use of "sterile water for injection" in caption to Figure 1); *see also* Cohen, MOM-1003, at [0134] (standard carriers included water).

pH Buffer. Claims 3, 6, and 8 all add a limitation that the formulation use a pharmaceutically acceptable buffer or, more particularly, 10mM of a phosphate buffer. *See* '239 patent, claim 3 (a formulation "further comprising a pharmaceutically acceptable buffer"); *id*. at claim 6 (same); *id*. at claim 8 (where "the buffering agent is in an amount of at least 10 mM phosphate buffer"). The Carpenter Handbook teaches: "Given that most protein formulations will exist at

pH values between 4 and 9, there is a limited set of buffers that will exhibit sufficient buffering capacity." Carpenter Handbook, MOM-1004, at 186; *see also id*. at 187 (Table 2) (listing that limited set of acceptable buffers as Histidine, Succinate, Acetate, Citrate, ***Phosphate***, Tris, and Carbonate) (emphasis added). Furthermore, Cohen teaches that, "[a]s is standard practice in the art," CTLA4Ig formulations "preferably include suitable carriers and adjuvants," including "buffer substances such as phosphates." Cohen, MOM-1003, at [0134]. The amount of phosphate buffer recited by claim 8—10mM—was within the customary range used by those skilled in the art. *See* Staples Decl., MOM-1006, at ¶ 55 (person of ordinary skill in the art would have used a range of from about 5 to 50 mM phosphate buffer).

Surfactant. Independent claim 7 requires "optionally" using a surfactant, with dependent claim 9 requiring that the surfactant be Poloxamer 188 in an amount of 8 mg/ml. Just as with buffers, certain surfactants were included on the "finite set of possible excipients" that had "been shown to be effective in protein formulations." *See* Carpenter Handbook, MOM-1004, at 186-87 (Table 2). One of the four surfactants taught by the Carpenter Handbook was Pluronic F-68. *Id*. Poloxamers are polymers, known also by the trade name "Pluronics." *See* Staples Decl., MOM-1006, at ¶ 56. Furthermore, under the established naming conventions for the generic Poloxamers and the branded Pluronics, Poloxamer 188

and Pluronic F-68 refer to the identical polymer composition. *See id*. (explaining naming convention); *see also* MOM-1010 ("Poloxamer 188 solution" product, sold by Sigma-Aldrich, is comprised of "100 g Pluronic F-68" in solution). Finally, the amount of surfactant recited in claim 9, *i.e.*, 8 mg/ml, was not critically different than the "low concentrations of surfactant (*ca*. 100 micromolar) typically used in formulations of therapeutic proteins." Carpenter Handbook, MOM-1004, at 167.

CTLA4Ig Sequence. Claims 4 and 7 both recite limitations that the CTLA4Ig molecule have the "amino acid sequence shown in SEQ ID NO:2 starting at methionine at position 27 or alanine at position 26 and ending at lysine at position 383 or glycine at position 382." This claimed amino acid sequence is merely the sequence of the CTLA4Ig fusion protein taught by Cohen. *See* '239 patent, col. 7, lines 31-35 ("In one embodiment, 'CTLA4Ig' refers to a protein molecule having the amino acid sequence of residues (i) 26-383 of SEQ ID NO:2, (ii) 26-382 of SEQ ID NO:2; (iii) 27-383 of SEQ ID NO:2, or (iv) 27-382 of SEQ ID NO:2."); see also id. at col. 4, lines 50-53 (Figure 1 of the '239 patent shows the SEQ ID NO:2 amino acid sequence). Cohen teaches this same sequence, disclosing it in Figure 24. *See* Cohen, MOM-1003, at [0127]. Cohen teaches that "[p]referred embodiments of the invention are soluble CTLA4 molecules such as CTLA4Ig (as shown in Fig. 24, starting at methionine at position +1 and ending at lysine at position +357)." *Id*. "Methionine at position +1" and "lysine at position

+357" in Figure 24 of Cohen correspond to methionine at position 27 and lysine at position 383, respectively, in Sequence 2 of the '239 patent.

Stability. Claim 11 requires that its claimed formulations be stable when stored at 2 to 8 ºC for at least 12 months. *See* '239 patent, claim 11 ("The formulation of claim 1, 4, or 7 wherein the formulation is stable when stored at 2 to 8 C for at least 12 months."). The Carpenter Handbook teaches that "[i]n general, a shelf life of 18 month[s] is considered acceptable for commercialization" of protein pharmaceuticals. Carpenter Handbook, MOM-1004, at 16. Thus, when the Carpenter Handbook teaches that one could be "quite confident" in developing a stable liquid formulation of a protein drug, *see id.* at 195, it means "quite confident" in developing a formulation with the stability necessary for commercialization, *i.e.*, one having a shelf life of at least 18 months. *See also* Staples Decl., MOM-1006, at ¶ 57.

Articles of Manufacture. Claims 12 and 13 require that the claimed protein formulation be packaged in a particular "article of manufacture." Specifically, claim 12 requires:

> 12. An article of manufacture comprising:
>
> a) at least one container which holds the formulation of claim 1, 4, or 7 and
>
> b) instructions for administering the formulation subcutaneously to a subject in need thereof.

Claim 13, which depends from claim 12, requires that the container be a vial or syringe. The Carpenter handbook teaches that the "most preferred" "therapeutic protein product[]" "would be a solution formulation that is typically stored in the refrigerator and preferably in a pre-filled syringe." Carpenter Handbook, MOM-1004, at 183. Nor was there anything inventive in packaging the protein pharmaceutical product with accompanying use instructions. *E.g.*, *id.* at 19 ("Commercially viable and market competitive formulations have some common features. Most of all, the formulation should maintain the safety and efficacy profile of the protein drug during all the handling and *uses specified on the label*.") (emphasis added).

VIII. CONCLUSION

This petition identifies relevant prior art references and provides a detailed analysis demonstrating why each claim of the '239 patent is unpatentable as being obvious. Accordingly, Petitioner respectfully requests institution of an IPR for claims 1-15 of the '239 patent on the ground presented herein.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.105(a) and (b), the undersigned certifies that on July 2, 2015, a complete and entire copy of this Petition for *Inter Partes* Review, and all supporting exhibits were provided via Express Mail to the Patent Owner by serving the correspondence address of record as follows:

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