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Paper No. 7
Date: January 15, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOMENTA PHARMACEUTICALS, INC.,
Petitioner,

v.

BRISTOL-MEYERS SQUIBB COMPANY,
Patent Owner.

Case IPR2015-01537
Patent 8,476,239

Before DEBORAH KATZ, JACQUELINE WRIGHT BONILLA, and GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. BACKGROUND

Petitioner filed a request for an *inter partes* review ("IPR") of claims 1–15 of U.S. Patent No. 8,476,239 (Ex. 1001, "the '239 patent") (Paper 2 ("Pet.")). Patent Owner timely filed a Preliminary Response (Paper 6 ("Prelim. Resp.")).

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless it is determined that there is "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Petitioner makes that showing with respect to its challenge of claims 1–15. Therefore, we institute review as to those claims.

A. The '239 patent (Ex. 1001)

The '239 patent issued July 2, 2013, and claims priority to an international application filed December 19, 2006, and a provisional application filed December 20, 2005. Ex. 1001, coversheet. According to Petitioner, none of the rejections entered during prosecution of the application that became the '239 patent were based on the references cited by Petitioner in this challenge. *See* Pet. 15–19.

The claims of the '239 patent are directed to formulations and articles of manufacture of the therapeutic molecule CTLA4Ig for subcutaneous administration. CTLA4Ig is a protein molecule that is used to treat immune system diseases and disorders, such as rheumatoid arthritis and adverse transplant reactions. Ex. 1001, 3:45–49. According to the '239 patent, there are advantages to delivering CTLA4Ig subcutaneously, including home administration and improved compliance. *Id.* at 1:24–34.

Independent claims 1 and 7 of the '239 patent are representative. Claim 1 recites:

> A stable formulation suitable for subcutaneous administration comprising
> [1] at least 100mg/ml CTLA4Ig molecule,
> [2] a sugar selected from the group consisting of sucrose, lactose, maltose, mannitol and trehalose and mixtures thereof and
> [3] a pharmaceutically acceptable aqueous carrier, wherein the formulation has a
> [4] pH range of from 6 to 8 and
> [5] a viscosity of from 9 to 20 cps, and
> [6] the weight ratio of sugar:protein is 1.1:1 or higher.

Ex. 1001, 55:16–23 (bracketed numbers and spacing added). Claim 7 recites:

> A stable formulation comprising
> [1] 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,
> [2] sucrose in an amount of about 170 mg/ml,
> [3] at least one buffering agent,
> [4] sterile water for injection and
> [5] optionally a surfactant.

Ex. 1001, 55:35–56:17 (bracketed numbers and spacing added).

B. Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '239 patent under 35 U.S.C. § 103 as being obvious over the combination of the teachings of Cohen (Ex. 1003),[1] Carpenter (Ex. 1004),[2] and Shire (Ex. 1005).[3]

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[1] U.S. Patent Application Publication 2003/0083246 A1, published May 1, 2003.
[2] RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS (John F. Carpenter and Mark C. Manning. eds., 2002).

II. ANALYSIS

Petitioner relies on Cohen to show that those of skill in the art knew that CTLA4Ig is useful for treating rheumatoid arthritis. Pet. 26–28 (citing Ex. 1003 ¶¶ 21, 237–84). Cohen teaches that to maintain therapeutic improvement over time, CTLA4Ig was administered "chronically every two to twelve weeks." Pet. 28 (citing Ex. 1003 ¶ 286). Petitioner explains that the amino acids of SEQ ID NO:2 recited in claim 7 of the '239 patent are the amino acids of CTLA4Ig single chain protein. Pet. 13–14.

Petitioner cites Shire for its teaching that chronic administration of proteins can be successfully achieved by subcutaneous injection, thus, motivating the development of formulations that are stable and suitable for that route. Pet. 28 (citing Ex. 1005, 1390–91: "For products that require frequent and chronic administration, the alternate subcutaneous (SC) route of delivery is more appealing. Particularly when coupled with prefilled syringe and autoinjector device technology, SC delivery allows for home administration and improved compliance of administration . . . ."). Petitioner notes that virtually identical reasons for developing a liquid formulation for subcutaneous administration of CTLA4Ig are provided in the '239 patent. Pet. 28–29 (comparing Ex. 1001, 1:24–34, with Ex. 1005, 1390–91).

Petitioner also relies on Carpenter to show the "constraints" those of skill in the art would have had to consider when formulating protein therapeutics for a particular route of administration. Pet. 6. Specifically, Carpenter teaches that those in the art would have had to consider tonicity, pH, choice of excipient (stabilizers), volume, and stability. Pet. 6–8 (citing Ex. 1004, 183). Petitioner

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[3] Shire et al., "Challenges in the Development of High Protein Concentration Formulations," 93 Journal of Pharmaceutical Sciences 1390 (2004).

argues that those of ordinary skill also would have considered viscosity when formulating a protein solution because a solution that is too viscous can be difficult to load into a syringe. Pet. 8 (citing Ex. 1005, 1397).

In consideration of those constraints, Petitioner argues it would have been obvious to those of ordinary skill in the art to formulate CTLA4Ig in a solution of at least 100 mg/ml because it was known that 2 mg/ml of CTLA4Ig was the minimum therapeutically effective amount. Pet. 29–30 (citing Ex. 1003 ¶ 274: "The change from baseline (e.g., reduction in tender joints) appears to be more important in the 2 and10 mg/kg treated groups, than in the placebo or 0.5 mg/kg groups"); *see also* Ex. 1003 ¶¶ 275–76. Dr. Staples, Petitioner's witness,[4] relies on the publication of the average adult weight—79.7 kg (*see* Pet. 30; Ex. 1007)—and the knowledge of using a small volume for subcutaneous administration—less than 1.5 mL (*see* Pet. 30; Ex. 1005, 1391)—to calculate an effective concentration of CTLA4Ig. Dr. Staples also relies on the known high bioavailability of CTLA4Ig after subcutaneous administration in mice (citing Ex. 1009) to show that the claimed concentrations of "at least 100 mg/ml" and "about 125 mg/ml" would have been obvious. Pet. 30–33 (citing Ex. 1006 ¶¶ 39–41).

Petitioner relies on Carpenter to show that those of ordinary skill in the art also would have considered it obvious to use the claimed excipients recited in claims 1, 2, and 5 of the '239 patent. Pet. 33–35 (citing Ex. 1004, 186–88: "The most effective non-specific stabilizers tend to be disaccharides, such as sucrose and trehalose. . . . . unless there is evidence for advantage in use of a particular

[4] Dr. Staples testifies that he has a Ph.D. in biological sciences and has worked in the field of protein formulation and dosage form development in several different companies since 1988. Ex. 1006 ¶¶ 2–14. At this point in the proceeding, we consider Dr. Staples qualified to offer opinions on the subject matter of the Petition.

compound from this group, sucrose and trehalose should remain the first-line choices."). Petitioner presents the testimony of Dr. Staples to show that the claimed ratio of sugar to protein (1.1:1 or higher) was known in the art because Carpenter teaches using sucrose at greater than 0.2 M. Pet. 36 (citing Ex. 1004, 187: "To stabilize proteins (both in aqueous solution and during freezing) with non-specific compounds (e.g., sugars), relatively high concentrations (ca.> 0.2M) of ligand (solute) are needed to affect protein stability"); Ex. 1006 ¶¶ 47–48 (noting that 0.2 M equals 70 mg/mL).

Petitioner argues that beyond the specific teachings of Carpenter, those of ordinary skill in the art would have been able to arrive at the claimed ratio of protein to sugar through empirical testing and routine optimization. Pet. 36–38. Relying on Dr. Staples's testimony, Petitioner argues that the ratio of protein to sugar would have been known to affect the protein stability, solution tonicity, and viscosity, allowing those in the art to have a reasonable expectation of achieving the proper balance. Pet. 36–40 (citing Ex. 1006 ¶¶ 47–49).

In regard to the viscosity range recited in claim 1 of the'239 patent ("9–20 cps"), Petitioner argues that because it was known that solutions with only certain viscosities can be used in a syringe, the recited range would have been obvious. Pet. 40–41. Petitioner relies on the analysis of viscosity in Shire, as explained by Dr. Staples, to show that viscosities of more than 20 cps would have required a long time to load into syringes of a typical size. *Id.* (citing Ex. 1005, 1397, Table 2; Ex. 1006 ¶ 42).

Petitioner also argues that the pH range recited in claim 1 of the '239 patent is merely physiological pH and would have been the preferred choice to minimize irritation upon injection. Pet. 41–42 (citing Ex 1006 ¶ 44; Ex. 1003 ¶ 145: "The therapeutic agent, compounded with a carrier, is commonly lyophilized for storage

and is reconstituted with water or a buffered solution with a neutral pH (about pH 7–8, e.g., pH 7.5) prior to administration.").

Patent Owner preliminarily responds to Petitioner's arguments by arguing that Petitioner does not present a prima facie case for obviousness. At this point in the proceeding, Patent Owner does not argue or present evidence that CTLA4Ig has unique characteristics requiring a specific formulation or that secondary considerations, such as unexpected results, indicate the claimed formulations would not have been obvious.[5]

Specifically, Patent Owner argues that Petitioner fails to present a modification of a "primary prior art reference" that overcomes differences with the claimed invention. Prelim. Resp. 8. According to Patent Owner, Petitioner inappropriately invites the Board to experiment to arrive at the claimed invention. *Id.* This argument is not persuasive based on the record before us. As explained:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at

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[5] Patent Owner also relies heavily on decisions in *Apple, Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00441, and *Biomarin Pharmaceutical Inc. v. Genzyme Therapeutic Products Ltd.*, IPR2013-00534. *See, e.g.,* Prelim. Resp. 8–9. Neither of these decisions present binding precedent. Further, they are not controlling here because the facts in each case are sufficiently different from the present facts. "Whether a claimed invention is unpatentable as obvious under § 103 is a question of law based on underlying findings of fact." *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000).

> issue. . . . As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007). Petitioner's approach to the obviousness analysis, which relies on evidence to show that a known protein would have been formulated within known "constraints" and on other facts known to an ordinarily skilled artisan, complies with the analysis described by the Supreme Court in *KSR*.

Patent Owner argues further that Petitioner fails to recognize or assess the technical challenges of developing a liquid, high concentration protein formulation for subcutaneous administration. Prelim. Resp. 15–17. According to Patent Owner, accomplishing this goal would require an "integrated approach," not merely "a series of single-factor experiments." *Id.* at 16 (citing Ex. 1005, 1399). Patent Owner cites, specifically, the effect of pH on protein aggregation, arguing that one of skill in the art would have had to consider this effect when determining a pH. Patent Owner argues that Dr. Staples does not consider the effect of pH on protein aggregation. *Id. at* 16–18.

In general, Patent Owner also argues that Petitioner improperly relies on the '239 patent as a roadmap, using inappropriate hindsight in its analysis. According to Patent Owner, Petitioner inappropriately considers only the constraints (volume, excipients, pH, and viscosity) recited in the claims of the '239 patent and inappropriately relies on conclusory statements about common sense as a reason for specific choices. Prelim. Resp. 10–20. At this stage of the proceeding, we are satisfied that a person of ordinary skill in the art at the time of the invention would have recognized those constraints and sought to overcome them.

Based on this record, Petitioner's analysis is not fraught with hindsight bias. For example, Cohen teaches a range of pH (7–8) within the claimed pH range (6–8). Ex. 1003 ¶ 145 (cited at Pet. 41). Patent Owner's generalized arguments that there would have been other ways to approach a determination of the elements recited in claim 1 does not indicate that approach and facts relied upon by Petitioner are insufficient or are tainted by impermissible hindsight reconstruction. Patent Owner has not yet provided evidence that those of ordinary skill in the art would have come to different conclusions when formulating CTLA4Ig because of its particular characteristics.

Patent Owner also argues that Petitioner's assertion that the claimed concentration of CTLA4Ig would have been obvious is flawed. According to Patent Owner, because Petitioner does not cite references that specifically teach administration of "at least 100 mg/ml" or "about 125 mg/ml" CTLA4Ig, Petitioner fails to demonstrate that those amounts would have been obvious. Prelim. Resp. 20–40. As noted above, however, Petitioner's analysis need not present precise teachings directed to the specific subject matter of the challenged claim. *KSR*, 550 U.S. at 418. It is permissible for Petitioner "to take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.*

Patent Owner argues further that Petitioner relies on "unwarranted assumptions and questionable calculations" resulting in "impermissible hindsight" to arrive at the claimed concentrations. Prelim. Resp. 20.

We are not persuaded that, even if those of skill in the art might make other assumptions or calculate the resulting concentration differently (for example by beginning with 10 mg of CTLA4Ig instead of 2 mg as also taught in Cohen or a final volume of 1.0 mL as taught in Carpenter instead of 1.5 mL as taught in Shire (*see* Prelim. Resp. 24–25)), the analysis presented by Petitioner is insufficient to go

forward with a trial. In general, we consider Petitioner's argument to be persuasive based on the record before us because Cohen teaches a specific dosage of CTLA4Ig and it is reasonably likely that those of ordinary skill in the art would have been able to determine an effective concentration for a subcutaneously administered formulation from that dosage.

Patent Owner argues further that Petitioner's analysis is flawed because it relies on the reported bioavailability of CTLA4Ig in mice, not humans, and it is known that reports of bioavailability of a drug in one species are not reliably predictive of bioavailability in a different species. *See* Prelim. Resp. 29–37 (citing Exs. 2001–2003). Even if this is correct, in view of the record before us, we are persuaded to go forward with a trial on this issue. We note that "'[n]ormally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification.'" *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). In *Merck*, the court rejected the argument that recited dosage limitations render a claim nonobvious where the results achieved were not shown to be unexpectedly good. *Id.* Thus, given the effective dosage reported in Cohen, the absence of any specific information about CTLA4Ig indicating that an ordinary artisan could not have determined an effective concentration for subcutaneous administration using routine optimization, and the absence of evidence of secondary considerations, we are persuaded at this point in the proceeding that the recited concentration is likely to be an unpatentable modification.

At this stage of the proceeding, we are also unpersuaded by Patent Owner's argument regarding the claimed viscosity. Prelim. Resp. 41–44. Claim 1 of the '239 patent recites "a viscosity of from 9 to 20 cps." Based on Figure 2 of Shire (Ex. 1005), Dr. Staples testifies that viscosity above 20 cps results in long syringe

loading times. Ex. 1006 ¶ 42. Although Patent Owner argues that a teaching of "not [] much higher than 20 cps" is not evidence of the claimed range of "a viscosity of from 9 to 20 cps," we are not persuaded on this record. Even without complete overlap of the claimed range and the prior art range, a minor difference may show a prima facie case of obviousness, absent a showing of some criticality or unexpected result. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) ("The proportions are so close that prima facie one skilled in the art would have expected them to have the same properties. Appellee produced no evidence to rebut that prima facie case."). Patent Owner's further arguments regarding salt concentration, prefilled syringes, and other drugs are also not persuasive because the current record does not indicate that such components are relevant to Patent Owner's claimed formulation. *See* Prelim. Resp. 42–44.

Patent Owner argues that the Petition fails to provide sufficient evidence that the weight ratio of sugar to protein recited in claim 1 (1.1:1 or higher) or the weight ratio of sucrose to protein ratio recited in claims 14 (1.3:1 to 5:1) and 15 (1.4:1) would have been obvious. Prelim. Resp. 44–46. According to Patent Owner, Petitioner fails to explain how the protein concentration resulting in these ratios is found in the prior art. *Id.* Despite Patent Owner's argument, Petitioner's reliance on Dr. Staples's testimony regarding the amount of sugar, including sucrose as taught in Carpenter, and the concentration of CTLA4Ig taught in Cohen persuades us that Petitioner is reasonably likely to prevail at trial on this issue. *See* Ex. 1006 ¶¶ 46–50. At this stage of the proceeding, we find persuasive Dr. Staples's testimony that optimizing the ratio of sugar to protein, based on the known constraints of stabilization versus tonicity and viscosity, would have been routine at the time. Pet. 36–37 (citing Ex. 1006 ¶¶ 45–46; Ex. 1004, 65; Ex. 1005,

1396–97). Patent Owner is free to provide any argument or evidence to the contrary in its Response.

Similarly, we are not persuaded by Patent Owner's arguments regarding the limitation of "sucrose in an amount of about 170 mg/ml" in claim 7. Prelim. Resp. 46–47. Although Patent Owner argues that Petitioner does not provide a reason why one of ordinary skill would have selected this amount, Petitioner relies on the teaching in Carpenter to use sucrose in an amount greater than 70 mg/ml (0.2 M) to stabilize proteins in liquid formulations. Pet. 36 (citing Ex. 1004, 187; *see* Ex. 1006 ¶ 47).

Regarding claim 9, Patent Owner argues that Petitioner's assertion that Poloxamer 188 (recited in claim 9) and Pluronic F-68 (taught in Carpenter) are identical is unsupported. Prelim. Resp. 47–48. Although Petitioner cites to Exhibit 1010, which we do not find in the record (*see also* Pet. iv, listing the exhibits cited in the Petition, but failing to list Exhibit 1010), at this point in the proceeding Dr. Staples's testimony explaining the naming conventions for the tradename "Pluronics" of the polymer "Poloxamer" is reasonable and shows sufficiently that these are the same compound. Pet. 43–44 (citing Ex. 1006 ¶ 56). Patent Owner has not yet provided evidence or argument to show that they are not the same.

Patent Owner argues further that Petitioner has failed to provide sufficient support to show that it would have been obvious to those of ordinary skill to use Poloxamer at 8 mg/ml, as claimed, because the claimed amount is an order of magnitude more than the amount recited in Carpenter (*see* Ex. 1004, 167 (teaching "low concentrations of surfactant (*ca.* 100 micromolar)")), compared to the claimed amount, which Dr. Staples calculated to be on the order of 1 mM (Ex. 1006 ¶ 56). Prelim. Resp. 48–49. At this stage of the proceeding, we are

persuaded that Petitioner shows sufficiently that it would have been obvious to obtain it through routine optimization. *See Merck*, 874 F.2d at 809.

Patent Owner additionally argues that the Petition should be denied in relation to claim 11. Claim 11 depends from either claim 1, 4, or 7 and recites the additional limitation "wherein the formulation is stable when stored at 2 to 8 C for at least 12 months." Ex. 1001, 56:24–25. According to Patent Owner, Petitioner presents no evidence regarding a storage temperature. Prelim. Resp. 50. We are not persuaded by that argument at this time. Petitioner cites to Carpenter as teaching that proteins formulated within the constraints discussed would be suitable for commercialization with a shelf life of 18 months. Pet. 45 (citing Ex. 1004, 16). Petitioner also cites to Dr. Staples's testimony stating that one would have known that the conditions recited in claim 11 were the minimum stability required for commercialization of a protein formulation. *Id*. (citing Ex. 1006 ¶ 57). Patent Owner has not yet provided arguments or evidence to the contrary. Based on the record before us, we are persuaded there is a reasonable likelihood that Petitioner would prevail with respect claim 11.

Furthermore, Petitioner shows that Carpenter teaches a phosphate buffer (*see* Ex. 1004 at 186) and that Dr. Staples testifies that 10 mM would have been within the customary range used by those in the art (*see* Ex. 1006 ¶ 55), as recited in claims 3, 6, and 8. Pet. 42–43.

We are also persuaded at this time that there is a reasonable likelihood that Petitioner will prevail regarding the articles of manufacture recited in claims 12 and 13 because Petitioner cites Carpenter as teaching that formulations are typically stored in syringes. Pet. 45–46 (citing Ex. 1004 at 183).

III. CONCLUSION

We are persuaded that there is a reasonable likelihood that Petitioner will prevail as to the unpatentability of claims 1–15 of Patent Owner's '239 patent under 35 U.S.C. § 103(a) over Cohen, Carpenter, and Shire.

Our findings of fact and conclusions of law are based on the record developed thus far, prior to Patent Owner's Response. This is not a final decision as to the patentability of any challenged claim. If a final decision is issued in this case, it will be based on the full record developed during trial.

IV. ORDER

For the reasons given, it is

ORDERED that an *inter partes* review is instituted as to claims 1–15 of the '239 patent as being unpatentable under 35 U.S.C. § 103(a) over Cohen, Carpenter, and Shire;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '239 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial is limited to the grounds stated above.

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