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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

CHUGAI PHARMACEUTICAL CO. LTD.,
Patent Owner.

Case IPR2017-01358
Patent 7,927,815 B2

Before GRACE KARAFFA OBERMANN, RAMA G. ELLURU, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

FINAL WRITEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–7, 12, and 13 of U.S. Patent No. 7,927,815 B2 (Ex. 1001, "the '815 patent"). Paper 2 ("Pet."). Chugai Pharmaceutical Co. Ltd. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). On December 1, 2017, we instituted an *inter partes* review of all challenged claims on all grounds asserted. Paper 7 ("Institution Decision" or "Inst. Dec."). Following our institution, Patent Owner filed a Response to the Petition (Paper 19, "PO Resp."), and Petitioner filed a Reply to Patent Owner's Response (Paper 28, "Reply").

Petitioner also filed a Motion to Exclude Evidence (Paper 36), to which Patent Owner filed an Opposition (Paper 44), and Petitioner filed a Reply (Paper 47). In addition, Patent Owner filed an Authorized Statement Regarding Petitioner's Reply Papers Beyond the Proper Scope and Improper Incorporation By Reference (Paper 40), to which Petitioner filed a Response (Paper 42). Patent Owner also filed a Motion for Observations on Cross Examination (Paper 41), to which Petitioner filed a Response (Paper 43).

An oral hearing was held on August 2, 2018. The transcript of that hearing has been entered into the record. Paper 55 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–7, 12, and 13 of the '815 patent are unpatentable. *See* 35 U.S.C. § 316(e).

A. Related Matters

The parties inform us of no related pending litigations. Pet. 4; Paper 5, 2. In addition to the instant proceeding, Petitioner has challenged, and we have instituted *inter partes* review of, U.S. Patent No. 7,332,289 B2 ("the '289 patent"), which is related to the '815 patent. *See Pfizer, Inc. v. Chugai Pharma. Co. Ltd*, Case IPR2017-01357 (PTAB Dec. 1, 2017) (Paper 7). We issue our decision determining that Petitioner has not shown the unpatentability of the challenged claims of the '289 patent concurrently with this Decision.

B. The '815 Patent

The '815 patent, titled "Protein Purification Method," issued April 19, 2011, from U.S. Patent Application No. 12/018,688, filed January 23, 2008. Ex. 1001, at [54], [45], [21], [22]. The '688 application is a division of U.S. Application No. 10/471,374, filed as International Application No. PCT/JP02/02248 on March 11, 2002, and now issued as the '289 patent. *Id.* at [62]. The '815 patent claims priority to Japanese Patent Application No. 2001-067111, filed on March 9, 2001. *Id.* at [30].

The '815 patent describes a "method for purifying proteins, more specifically a method for removing contaminant DNA from a sample containing a physiologically active protein such as antibody molecules." Ex. 1001, 1:12–15. The '815 patent recognizes that methods for removing contaminant DNA from recombinant antibody drug formulations were known in the art. *See, e.g.*, *id.* at 1:34–48. The '815 patent states, however, that the chromatographic processes associated with known purification

methods were "time-, labor-, and cost-consuming, as well as being complicated. Moreover, they fail to provide stable results." *Id.* at 1:49–52.

To address these shortcomings, the '815 patent discloses the "surprising finding that contaminant DNA can be efficiently removed from a sample containing a physiologically active protein without using complicated chromatographic processes." *Id.* at 1:63–66. In particular, the '815 patent teaches that such a sample can be "converted into an acidic aqueous solution of low conductivity, neutralized by addition of a buffer to raise the pH to a neutral level, and then filtered through a filter to remove the resulting particles." *Id.* at 1:66–2:3. The '815 patent goes on to state that "[w]ithout being bound by any particular theory, the inventors of the present invention estimate that each of the[aforementioned] particles is a conjugate formed between physiologically active protein and DNA." *Id.* at 6:12–15.

The '815 patent explains that "[a]s used herein, an acidic aqueous solution of low conductivity generally refers to an aqueous solution of pH 1.5 to pH 3.9, . . . which has a molarity of 0 to 100 mM, . . . or has an ionic strength of 0 to 0.2, or has a conductivity of 0 to 300 mS/m . . . ." *Id.* at 5:29–35. The '815 patent further discloses that "[t]he acidic aqueous solution may be selected from aqueous solutions of hydrochloric acid, citric acid, acetic acid and other acids." *Id.* at 5:35–37. The '815 patent also states that "[t]he type, conductivity and pH of acidic aqueous solution of low conductivity will vary depending on the type of physiologically active protein or antibody to be purified. Those skilled in the art will readily determine optimal conditions for these parameters in preliminary experiments as described herein." *Id.* at 5:37–42.

With regard to the neutralization and particle removal steps of the above-described purification procedure, the '815 patent teaches that neutralization of the solution containing a physiologically active protein to a "neutral pH level" "in turn, produces particles (i.e., becomes clouded). These particles may be removed by filtration through a filter to ensure efficient removal of contaminant DNA." *Id.* at 6:1–5. The '815 patent exemplifies a "1.0–0.2 μm Cellulose Acetate Filter System (Corning) or TFF" as filters available for particle filtration. *Id.* at 6:5–7.

C. Illustrative Claim

Independent claim 1, reproduced below, is illustrative of the claimed subject matter.

> 1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
>
> > 1) converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9;
> >
> > 2) adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less; and
> >
> > 3) removing the particles thereby to remove contaminant DNA in the sample.

Ex. 1001, 12:38–49.

Independent claim 13 closely mirrors claim 1, but additionally requires "neutralizing the pH" of the sample from step 1, and "filtering" the sample from step (2). *Id.* at 14:1–10.

D. Evidence Relied Upon

Petitioner relies upon the following as a prior art reference (Pet. 5):

Shadle WO 95/22389 Aug. 24, 1995 (Ex. 1003)

Petitioner also relies on declarations submitted by Todd M. Przybycien, Ph.D. (Ex. 1002 (Dr. Przybycien's Opening Declaration); Ex. 1036 (Dr. Przybycien's Reply Declaration)).

Patent Owner relies on the Declarations of Steven M. Cramer, Ph.D. (Ex. 2015), Kirston Koths, Ph.D. (Ex. 2016), and Harry G. Brittain, Ph.D. (Ex. 2019).

E. Instituted Challenges

We instituted trial based on each challenge to the patentability of the '815 patent presented in the Petition (Pet. 5):

Claim(s)	Basis	References
1–7, 12 and 13	§ 102(b)	Shadle
1–7, 12 and 13	§ 103(a)	Shadle

II. ANALYSIS

A. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have had "at least a graduate degree, such as a Ph.D.,

and several years of postgraduate training or practical experience in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others." Pet. 6 (citing Ex. 1002 ¶ 28). Petitioner further contends that "[s]uch a person would also understand that protein purification is a multidisciplinary field, and could take advantage of the specialized skills of others using a collaborative approach." *Id*. (citing Ex. 1002 ¶ 28). Patent Owner does not address Petitioner's position on this matter and does not propose its own description for a person of ordinary skill in the art at the time of the invention.

We agree with Petitioner, and adopt Petitioner's description of the level of ordinary skill in the art at the time of invention of the '815 patent. We also note that the applied prior art reflects a level of skill at the time of the claimed invention consistent with our determination. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

In addition, we have reviewed the credentials of Petitioner's and Patent Owner's declarants, and recognize each of them as qualified to provide the proffered opinions on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1004, Attachment A; Ex. 2015, Appendix A; Ex. 2016, Appendix A; Ex. 2019, Appendix A. The relative weight that we assign such testimony, however, is subject to additional factors. *See, e.g.*, 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) (same).

B. Claim Construction

The broadest reasonable interpretation standard applies to the construction of the challenged claims in this proceeding. 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2142 (2016). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "molarity"

In the Institution Decision, we concluded that the broadest reasonable interpretation of the claim term "molarity," as it is used in the '815 patent, is the "total concentration of solute present in the solution." Inst. Dec. 12.

Patent Owner agrees that "molarity" refers to the total concentration of solute in a solution, and avers that this construction is supported by the claims, specification, and file history of the '815 patent, which address the "contributions of *multiple* solutes to the solution's molarity." PO Resp. 15. Patent Owner further asserts that the molarity calculations for Shadle's neutralized eluate provided by Petitioner's declarant, Dr. Przybycien, which account for contributions from different solutes (Ex. 1002 ¶¶ 96–99) are inconsistent with Petitioner's contention that molarity refers to the concentration of a single solute in a solution. PO Resp. 16.

Petitioner does not directly address the construction of "molarity" in its Reply. However, during oral argument, Petitioner explained that it maintains its position that "molarity" refers to the concentration of a single solute in solution. Tr. 13:1–7. In the Petition, Petitioner asserts that "molarity" refers to "a measure of the concentration of a given solute within a solution in terms of the moles of that solute contained per liter of solution." Pet. 30. As we observed in the Institution Decision, however, despite its proposed construction, Petitioner nevertheless appears to recognize that

> "molarity" may take account of multiple solutes present in a solution. Specifically, Petitioner proposes that the term "molarity," as it is used in the greater claim phrase "an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less," should be understood to mean that the molarity of the acidic aqueous solution is 100 mM or less, without considering any effects of the contaminant DNA or protein from the sample."

Inst. Dec. 9 (citing Pet. 30–31).

Consistent with the Institution Decision, we determine that "the plain language of the claims, as well as the specification of the '815 patent, indicates that the term 'molarity' refers to the total concentration of solute present in the solution, rather than the concentration of one particular solute." *Id.* at 10–11. The claims of the '815 patent refer consistently to the overall molarity of solutions, and not of any particular solute in a given solution. For example, claim 1 requires "an *acidic aqueous solution* of low conductivity . . . having a molarity of 100 mM or less" (Ex. 1001, 12:42–44 (emphasis added)), and further recites that the molarity of the "*adjusted sample* is 100 mM or less" (*id.* at 12:45–47 (emphasis added)). Claim 2

similarly limits the molarity of the "acidic aqueous solution." *Id.* at 12:50–52. Notably, these claims do not identify any particular solute to which the term molarity refers; rather, the claims of the '815 patent describe solutions having certain characteristics, of which solution molarity is one. As we stated in our Institution Decision:

> Similarly, the specification of the '815 patent refers to the molarity of the complete solution, rather than one solute in that solution. *See, e.g.*, *id.* at 4:61–64 ("As used herein, a 'neutral aqueous solution . . .' generally refers to an aqueous solution . . . which has a molarity of 0 to 100mM"), 5:28–31 ("an 'acidic aqueous solution of low conductivity' generally refers to an aqueous solution . . . , which has a molarity of 0 to 100 mM"). The file history of the '815 patent likewise references the molarity of the solution, rather than of a given solute in the solution. *See e.g.*, Ex.1005, 82 ("an important feature of the present invention is to adjust pH value of the solution, the eluate, to from 4 to 8 while maintaining the molarity of the solution at 100mM or less."), 107 ("0.1 M buffer was used as an eluent, and 1 M Tris-HCl was used to adjust the pH of the eluted fraction, that is, the fact that 0.1 M and 1 M solutions were used means that the molarity of the eluted fration [sic] must be over 0.1 M (100 mM)").

Inst. Dec. 11.

In the Institution Decision, because the parties did not identify any controversy concerning whether any effects of contaminant DNA or protein from the sample should be taken into account when calculating the molarity of the acidic aqueous solution, we declined to decide that issue. Inst. Dec. 11–12 (citing *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("we need only construe terms 'that are in controversy, and only to the extent necessary to resolve the

controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)))). Nor is resolution of that issue necessary at this junction. In particular, we observe that our anticipation and obviousness analyses below remain the same regardless of whether any effects from contaminant DNA and/or protein from the sample are included in the molarity calculation.

2. Other Claim Terms

In the Institution Decision, we concluded that the claim phrase "an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH 1.5 to pH 3.9" encompasses an aqueous solution of pH 1.5 to pH 3.9, which has a conductivity of 0 to 300 mS/m and a molarity of 0 to 100 mM. Inst. Dec. 12. Neither Petitioner nor Patent Owner challenges this construction. *See* Pet. 30–31; PO Resp. 11–22. Accordingly, for the reasons set forth in the Institution Decision, we determine that "an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH 1.5 to pH 3.9" encompasses an aqueous solution of pH 1.5 to pH 3.9, which has a conductivity of 0 to 300 mS/m and a molarity of 0 to 100 mM.

In the Institution Decision, we concluded that the claim terms "conductivity" and "ionic strength," for which Petitioner proffered constructions in its Petition (Pet. 30, 35–36), did not require express construction for purposes of this proceeding. Dec. 8. Neither Petitioner nor Patent challenges that determination. *See* PO Resp. 11–22; Reply, *passim*. In its Response, Patent Owner proposes constructions for several additional

terms. Namely, Patent Owner contends that the preambles of claims 1 and 13 should be construed as limiting (PO Resp. 12), "to form particles" should be construed to require that the solution becomes clouded (*id.* at 16), and "the treated sample containing a physiologically active protein," as recited in claim 5, should be interpreted to mean "the sample resulting from performing the method of claim 1, which concludes with removing particles in step 3" (*id.* at 17). Because interpretation of these claim terms is not necessary to our anticipation or obviousness analyses, we need not construe them. *See Nidec*, 868 F.3d at 1017.

C. Prior Art Relied Upon: Overview of Shadle

Petitioner relies on the teachings of Shadle (Ex. 1003) as the basis for its patentability challenges in this proceeding.

Shadle discloses methods for the "purification of antibody molecule proteins" that employ "sequential steps of Protein A affinity chromatography, ion exchange chromatography, and hydrophobic interaction chromatography." Ex. 1003, Abstract. In this regard, Shadle teaches that a "purification protocol should not only provide a protein product that is essentially free of other proteins, . . . but also eliminate or reduce to acceptable levels other host cell contaminants, DNA, RNA, potential pyrogens and the like." *Id.* at 9:12–16. In particular, Shadle discloses:

> The purified antibodies obtained by practicing the process of this invention have the following properties: 1) greater than 97% antibody protein by weight; 2) stable to proteolytic

> degradation at 4°C for at least three months; 3) low(< 0.1 E.U./mg protein) endotoxin; 4) low(< 1 pg/mg protein) DNA; 5) non-antibody protein < 5% by weight; and 6) virally inactive.

Id. at 14:21–27.

Shadle exemplifies the disclosed protein purification method by describing a procedure "for the isolation and purification of a monoclonal antibody against Respiratory Syncytial Virus (RSV)," identified as "RSHZ 19." *Id.* at 15:3–7. Shadle explains that this "process is designed to prepare RSHZ-19 of >95% purity while removing contaminants derived from the host cell, cell culture medium, or other raw materials." *Id.* at 15:7–9.

In Example IA, Shadle teaches the application of 100 liters of conditioned culture medium containing 0.8 grams per liter of RSHZ-19 monoclonal antibody to a previously equilibrated ProSep A affinity column. *Id.* at 21:4–8. Subsequent to washing with 15 liters of PBS/glycine, the "IgG was eluted by applying 15–20 liters of ProSep A elution buffer. Fractions of the non-bound peak and the elution peak were collected and assayed for IgG content using an HPLC assay. The eluate was approximately 15 liters in volume, and contained approximately 5 milligrams protein per milliliter." *Id.* at 21:9–13. Shadle identifies the "ProSep Elution Buffer" as being composed of 25 mM citrate, and having pH 3.5. *Id.* at 20:10. Shadle additionally explains that "[t]he eluate fractions from the Protein A capture . . . are pooled based on the UV tracing on the chromatogram, and the entire peak is collected." *Id.* at 19:3–5.

Shadle further discloses that

> [i]mmediately after elution, the sample was adjusted to pH 3.5 by the addition of 2.5 M hydrochloric acid, held for approximately 30 minutes, and adjusted to pH 5.5 by the addition of approximately 350 milliliters of 1 M Tris base. After neutralizing to pH 5.5, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.

Id. at 21:15–19. Subsequently, the filtered sample was subject to cation exchange chromatography and hydrophobic interaction chromatography. *Id.* at 21:26–22:29.

D. Anticipation Based on Shadle

Petitioner asserts that claims 1–7, 12, and 13 are anticipated under § 102(b) by Shadle. Pet. 33–55. Patent Owner disagrees that Shadle anticipates the challenged claims. PO Resp. 22–52.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016). "To establish that a prior art reference inherently—rather than expressly—discloses a claim limitation, 'the limitation at issue necessarily must be present, or [is] the natural result of the combination of elements explicitly disclosed by the prior art.'" *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018) (alteration in original) (quoting *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014)).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.

> [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991) (alteration in original) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)).

The challenged claims of the'815 patent each require converting a "sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9." Ex. 1001, 12:41–44, 14:1–4. The challenged claims additionally require adjusting the pH of that sample to form particles, wherein the molarity of the adjusted sample is 100 mM or less, but there is minor variation in how the claims characterize the pH adjustment. *Id.* at 12:45–47, 14:5–8. In particular, independent claim 1 recites "adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less," (*id.* at 12:45–47), while independent claim 13 requires "neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles" (*id.* at 14:5–8). Finally, the challenged claims recite a particle removal step. *Id.* at 12:48–49, 14:9–10. Specifically, claim 1 requires "removing the particles thereby to remove contaminant DNA in the sample" (*id.* at 12:48–49), and claim 13 requires "filtering the resulting sample from step (2) to remove particles containing contaminant DNA" (*id.* at 14:9–10).

To support its contention that Shadle anticipates the challenged claims, Petitioner asserts, *inter alia*, that Shadle's initial antibody-containing eluate has a conductivity of 300 mS/s or less and a molarity of 100 mM or less, and that Shadle discloses neutralizing the initial antibody-containing eluate to pH 5.5 to form particles, wherein the molarity of Shadle's neutralized eluate is 100 mM or less. Pet. 36–46. For the reasons set forth below, however, we determine that Petitioner has not carried its burden to establish, by a preponderance of the evidence, that Shadle discloses each of these claim requirements.[1]

The antibody purification protocol set forth in Example IA of Shadle discloses the use of ProSep A Elution Buffer to elute antibody from a ProSep A column. Ex. 1003, 21:9–10. In particular, Shadle discloses that subsequent to loading with IgG, i.e., antibody, the ProSep A affinity column was washed with "approximately 15 liters of PBS/glycine." *Id.* Next, the "IgG was eluted by applying 15–20 liters of ProSep A elution buffer. Fractions of the non-bound peak and the elution peak were collected and assayed for IgG content using an HPLC assay. The eluate was approximately 15 liters in volume, and contained approximately 5 milligrams protein per milliliter." *Id.* Table 1 of Shadle, which discloses

[1] Because we determine that Petitioner has not met its burden with respect to the aforementioned claim steps, we need not address whether the preambles of claims 1 and 13 are limiting, or whether Petitioner has established that those preambles are disclosed by Shadle. Neither must we address whether Shadle discloses "removing the particles to thereby remove contaminant DNA from the antibody-containing sample" (Ex. 1001, 12:48–49, 14:9–10).

the formulations for relevant buffers, characterizes the "ProSep Elution Buffer" as "25 mM citrate, pH 3.5." *Id.* at 20:10. Shadle does not further describe the composition of the ProSep A Elution Buffer.

Relying on the concentration of citrate alone present in Shadle's elution buffer, Petitioner argues that the claim requirement of converting the sample containing a physiologically active protein into an acidic aqueous solution having a molarity of 100 mM or less is satisfied. Applying Petitioner's interpretation of "molarity" as referring to the "concentration of a given solute within a solution" (Pet. 30), the Petition asserts that Shadle's disclosure of using 25 mM citrate, pH 3.5 buffer for antibody elution expressly satisfies the initial antibody-containing eluate molarity requirement of the challenged claims. Pet. 36–37; *see also* Ex. 1002 ¶ 87.

Petitioner does not, however, adduce evidence sufficient to show that Shadle expressly discloses that its initial antibody-containing eluate has 100 mM or less *total solute* present in the solution, as required under our interpretation of "molarity," initially set forth in the Institution Decision (Inst. Dec. 12). *See* Pet. 36–37; Reply, *passim*. Specifically, Petitioner's analysis of the molarity of the initial antibody-containing eluate is unpersuasive because it fails to account for the contribution to the molarity of that eluate of any solute other than citrate.

To determine the molarity of total solute present in Shadle's initial eluate, it is, thus, necessary to account for any contributions from the

ProSep A Elution Buffer as well as the wash buffer used by Shadle.[2] But Shadle does not describe how its ProSep A Elution Buffer was prepared, or otherwise define the composition of that buffer, beyond specifying the concentration of citrate and pH. *See* Ex. 1003, 20–21 (identifying the conditions of "ProSep Elution Buffer" as "25 mM citrate, pH 3.5"); *see also* Ex. 2014, 90:23–92:19 (testimony by Dr. Przybycien explaining his reliance on molarity calculations for four different citrate buffer preparations to determine the total molarity of Shadle's elution buffer). Neither does Shadle discuss how much, if any, wash buffer was collected in the initial eluate. Ex. 1003, 20; *see also* Ex. 1036 ¶ 50 (acknowledging that up to 0.582 L of wash buffer may be present in Shadle's neutralized eluate); Ex. 2015 ¶ 71 (stating that by "conservative estimate," 1L of wash buffer could be present in Shadle's eluate); Ex. 2001, 5–6 (EPO examination division finding that Shadle's eluate adjusted to pH 3.5 included 3.75–4.5 L of wash buffer). Accordingly, Shadle cannot be said to expressly disclose "converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less" (Ex. 1001, 12:41–44).

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[2] Because the parties do not dispute that any contribution to the molarity of Shadle's initial antibody-containing eluate from physiologically active protein or contaminant DNA would be negligible, we do not address any contribution to eluate molarity from those solutes. *See* Pet. 36 n.3; PO Resp. 31 (highlighting Petitioner's lack of evidence concerning the contributions of other solutes in the ProSep A Elution Buffer, as well as the wash buffer, but not physiologically active protein or contaminant DNA to solution molarity).

Indeed, neither Petitioner nor its declarant, Dr. Przybycien, contends that Shadle describes any particular method for preparing ProSep A Elution Buffer, or that Shadle specifies the total concentration of solute present in its elution buffer. *See* Reply 6 ("[S]tarting with any of four conventional buffer preparations, Shadle meets the claimed conductivity and molarity limitations."); Ex. 1026, 2 ("Thus, total morality of [Shadle's] 25 mM Citrate elution buffer is 25 mM, 30.73 mM, or 44.08 mM, depending on the method of preparation used."); Ex. 1027, 2 (same). Moreover, to the extent Petitioner asserts that Shadle expressly discloses an elution buffer having 25 mM *total solute* (*see* Tr. 14:13–20), Dr. Przybycien's testimony that an ordinarily skilled artisan "would have understood that there were four conventional, most common methods for preparing such a buffer" (Ex. 1036 ¶ 25), and that the molarities of the resulting solutions varied according to which method was used (*id.* at ¶ 39; Ex. 1026, 1–2; Ex. 1027, 1–2), belies any such contention. *See also* Ex. 2014, 88:22–89:16 (testimony by Dr. Przybycien acknowledging that Shadle's 25 mM citrate elution buffer could be prepared a fifth way, but characterizing that method of preparation as unconventional). Dr. Przybycien's revised testimony concerning the amount of wash buffer that might be present in Shadle's initial eluate similarly confounds any assertion that Shadle expressly discloses an initial eluate with 100 mM or less total solute. *Compare* Ex. 1026 (Dr. Przybycien's updated molarity calculations, excluding any contribution from wash buffer), *with* Ex. 1047 (Dr. Przybycien's further revised molarity calculations, characterizing 0.582 L of wash buffer as a "reasonable amount

of wash buffer contamination" that theoretically could be present in Shadle's initial eluate).

On Reply, Petitioner recasts its theory of the case, shifting its contention that Shadle *expressly* discloses "converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less" (Ex. 1001, 12:41–44) to an assertion that Shadle *inherently* discloses that claim step. *Compare* Pet. 36–37 ("WO '389 [Shadle] expressly discloses that the antibody sample resulting after purification on the Protein A column is converted into an acidic aqueous solution when eluted with the ProSep A buffer solution, and that this solution has a molarity of 100 mM or less at a pH of 1.5 to 3.9."), *with* Reply 8 ("Dr. Przybycien recalculated molarity under the Board's construction, and confirmed that, regardless of the construction, Shadle inherently meets the molarity limitations and anticipates the claims."). To support its new inherency argument, Petitioner relies on updated molarity calculations submitted by Dr. Przybycien after institution, but prior to Patent Owner's filing of its Response. Reply 8; Ex. 1026; *see also* Ex. 1027 (updated calculations made in response to Dr. Cramer's analysis). In describing his updated calculations, Dr. Przybycien explains that he calculated the molarity of four different elution buffers that satisfy Shadle's conditions of 25 mM citrate and pH 3.5, and that were prepared according to the most common and conventional methods. Ex. 1026, 1–2; Ex. 1027, 1–2; Ex. 1036 ¶ 38. The molarities of the four buffer formulations evaluated by Dr. Przybycien range from 25 mM to 44 mM total solute. Ex. 1026, 2; Ex. 1027, 2. Dr. Przybycien testifies that "for each of the four proposed

conventional ProSep A citrate buffer elution solutions . . . it is clear that even when considering the 'total molarity' of the Shadle ProSep A citrate buffer, it would still inherently be below 100 mM (and below 50 mM)." Ex. 1036 ¶ 39. In addition, Dr. Przybycien testifies that no more than 0.582 L of wash buffer would be included in Shadle's initial eluate, and, therefore, an ordinarily skilled artisan "would understand that the total molarity of the adjusted sample would still be well below 100 mM. Ex. 1035 ¶ 52; *see also* Ex. 1047 (Dr. Przybycien's molarity calculations adjusted to account for a "reasonable amount of wash buffer contamination" that theoretically could be present in Shadle's initial eluate).

We do not find Petitioner's inherency arguments persuasive. First, Petitioner's belated change of course and argument on Reply that Shadle *inherently* discloses "converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less" (Ex. 1001, 12:41–44, 14:1–4) is improper. "Unlike district court litigation—where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material—the expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016). In an *inter partes* review, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). Specifically, the petition must identify "with particularity . . . the grounds on which the challenge to each claim is based, and the evidence that

supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3). Thus, although "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings," *Genzyme Therapeutic Prods. LP v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1366 (Fed. Cir. 2016), the shifting of arguments is not, *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017). Petitioner's inherency argument concerning the total molarity of Shadle's initial antibody-containing eluate is an impermissible shift of its anticipation theory because "[r]ather than explaining how its original petition was correct," *id.*, i.e., how Shadle's initial antibody-containing eluate expressly satisfied the recited molarity requirement, Petitioner's "subsequent arguments amount to an entirely new theory of [inherent anticipation] absent from the petition," *id.* For this reason alone, Petitioner has not shown that the challenged claims are unpatentable as anticipated by Shadle.

Second, even if Petitioner's inherency argument were timely, it is nevertheless insufficient to support a finding of anticipation. Petitioner has not shown that the total concentration of solute present in Shadle's initial eluate is necessarily 100 mM or less, as required by the challenged claims. As explained above, Shadle does not disclose the total molarity of its elution buffer, or describe how that buffer is prepared. Ex. 1003, 20–21. Neither does Shadle disclose how much, if any, wash buffer was captured in the initial antibody-containing eluate. *Id.* Moreover, Petitioner does not argue either that there is only a *single method* for making Shadle's elution buffer, which always yields a buffer having 100 mM or less total solute, or that *every method* for producing Shadle's buffer results in a buffer with 100 mM

or less total solute. *See* Ex. 1036 ¶ 26 ("Based on Shadle's disclosure of using a ProSep A elution buffer of 25 mM citrate, pH 3.5, a POSA would have understood that there were four conventional, most common methods for preparing such a buffer."). Rather, Petitioner contends that "starting with any of four conventional buffer preparations, Shadle meets the claimed molarity limitation." Reply 6; *see also* Ex. 1036 ¶ 39 ("I have prepared updated calculations of the 'total molarity' for each of the four proposed conventional ProSep A citrate buffer elution solutions . . . . Based on these calculations, it is clear that even when considering the 'total molarity' of the Shadle ProSep A citrate buffer, it would still inherently be below 100 mM (and below 50 mM)."). That four common and conventional ways of preparing Shadle's buffer yield total molarities within the limits required for the molarity of the initial antibody-containing eluate by the challenged claims is insufficient to establish that Shadle *necessarily* meets that claim requirement. The probability or possibility that an ordinarily skilled artisan would have used one of the four methods described by Dr. Przybycien to prepare Shadle's elution buffer is insufficient to establish inherent disclosure of molarity of Shadle's buffer alone, much less inherent disclosure of the molarity of Shadle's initial antibody-containing eluate. *See Cont'l Can*, 948 at 1269 ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (alteration in original) (quoting *In re Oelrich*, 666 F.2d at 581)).

The same defects mar Petitioner's parallel argument, timely made in the Petition, that Shadle inherently discloses that the acidic aqueous solution containing physiologically active protein is also "of low conductivity of 300 mS/m or less" (Ex. 1001, 12:41–44, 14:1–4). *See* Pet. 37–40. Unable to point to any disclosure by Shadle concerning the conductivity either of the initial antibody-containing eluate, or the ProSep A Elution Buffer included in that eluate, and absent description by Shadle of how its buffer is prepared, Petitioner returns to Dr. Przybycien's calculations to support its contentions regarding the conductivity of Shadle's initial antibody-containing eluate. *See* Pet. 37–40; Reply Ex. 1036 ¶ 25; Ex. 1007; Ex. 1016; Ex. 1026; Ex. 1027. But, as with molarity, the probability or possibility that an ordinarily skilled artisan would have prepared Shadle's elution buffer according to one of Dr. Przybycien's methods is insufficient to establish that Shadle inherently discloses that its initial antibody-containing eluate is "of low conductivity of 300 mS/m or less" (Ex. 1001, 12:41–44).

Indeed, Patent Owner's declarant, Dr. Cramer, identifies a fifth way to prepare Shadle's 25 mM citrate, pH 3.5 ProSep A elution buffer. PO Resp. 28; Ex. 2015 ¶ 56. Specifically, Dr. Cramer testifies that "Shadle's ProSep A elution buffer (25 mM citrate, pH 3.5) could very well have been prepared using 25 mM trisodium citrate and hydrochloric acid," and avers that "making a buffer using trisodium citrate and hydrochloric acid was well known to [ordinarily skilled artisans] at the time of Shadle and at the time of the '815." Ex. 2015 ¶ 56. Dr. Cramer further testifies that such an artisan would have considered a trisodium citrate and hydrochloric acid "buffer preparation as among the numerous readily-available and reasonable choices

for Shadle in preparing its citrate buffer of Example 1A [sic]" (*id.*). *See also* Ex. 1036 ¶ 26 (testimony by Dr. Przybycien "agree[ing] that it is theoretically possible to make the 25 mM citrate, pH 3.5 ProSep A elution buffer using trisodium citrate and HCl," but disputing that would be the normal and usual way of making the buffer); Ex. 2014, 88:22–89:8 (testimony by Dr. Przybycien acknowledging 25 mM citrate buffer could be prepared using trisodium citrate and hydrochloric acid, but stating that is not a conventional manner of preparing the buffer). Dr. Cramer additionally testifies that an ordinarily skilled artisan "reading Shadle would not know how the 25 millimolar citric buffer was made and, therefore — therefore, could have made that buffer in a wide variety of ways and one of them is with a trisodium citrate." Ex. 1034, 103:21–104:5. According to Dr. Cramer, factors such as the reagents available in the lab, personal preferences, and level of experience in making buffers, rather than any disclosure or suggestion in Shadle, would have motivated an ordinarily skilled artisan to select one buffer formulation over another. *Id.* at 105:3–107:23. Based on the record before us, we credit Dr. Cramer's testimony.

With particular regard to the conductivity requirement of the challenged claims, Dr. Cramer and Dr. Brittain, another of Patent Owner's declarants, each testify that the conductivity of a 25 mM citrate buffer of pH 3.5 prepared using trisodium citrate and hydrochloric acid would be well above the 300 mS/m required by those claims. Ex. 2019 ¶ 21 (testimony by Dr. Brittain that the measured conductivities of 3 different samples of Shadle's elution buffer prepared using trisodium citrate and hydrochloric acid each exceed 600 mS/s); Ex. 2015 ¶ 58 (testimony by Dr. Cramer

estimating the conductivity of 25 mM trisodium citrate alone to be 500 mS/m, and expressing confidence that "the conductivity of a 25 mM citrate buffer, pH 3.5 prepared as described is greater than 300 mS/m"). On this record, we credit Dr. Brittain's and Dr. Cramer's testimony.

Petitioner takes issue with Patent Owner's contention that a fifth elution buffer could be used to practice Shadle's antibody purification process, but Petitioner's arguments are unpersuasive on this record. The purported disadvantages of making Shadle's elution buffer with trisodium citrate and hydrochloric acid identified by Petitioner (*see* Reply 11–13 (citing Ex. 1036 ¶¶ 25–35)) do not override the undisputed fact that an ordinarily skilled artisan *could* "make the 25 mM citrate, pH 3.5 ProSep A elution buffer using trisodium citrate and HCl" (Ex. 1036 ¶ 26 (testimony by Petitioner's declarant, Dr. Przybycien); *see also* Ex. 2014, 88:22–89:8). In addition, we credit Dr. Cramer's testimony that preparation of Shadle's elution buffer with trisodium citrate and hydrochloric acid would have been a "well known[,] . . . readily-available and reasonable choice" (Ex. 2015 ¶ 56). For example, as Dr. Cramer testifies (*see id.*), Roth discloses preparing two elution buffers using trisodium citrate, and adjusting the pH of those buffers to 3.07 and 4.25 with hydrochloric acid (Ex. 2005, 1). Furthermore, we agree with Dr. Cramer that an ordinarily skilled artisan having trisodium citrate in the lab and interested in Shadle's purification method could reasonably elect to prepare Shadle's elution buffer using trisodium citrate and hydrochloric acid rather than by one of the four methods identified by Dr. Przybycien. Ex. 1034, 102:24–107:23. Finally, we observe that Patent Owner's representation to the European Patent Office

("EPO") that "the molarity of [Shadle's] eluent can be calculated to *at least*: (375 + 350)/15.35 = 47.2 mM" (Ex. 1006, 28 (emphasis added)) is consistent with Dr. Cramer's testimony, as this calculation does not account for how the elution buffer was prepared or the contribution of solutes other than citrate present in the elution buffer to the molarity of the eluate (or the contribution of hydrochloric acid). *Id.* Furthermore, the calculation provided by Patent Owner to the EPO sets a floor, rather than a ceiling for molarity of the neutralized eluate.

This is not a case where the prior art discloses a machine or process, which in normal operation or practice, would have produced a result required by a claim. *See In re Ackenbach*, 45 F.2d 437, 439 (CCPA 1930) ("[I]f a previously patented device, in its normal and usual operation, will perform the function which an appellant claims in a subsequent application for process patent, then such application for process patent will be considered, to have been anticipated by the former patented device."). On the contrary, because Shadle's disclosure does not define the total concentration of solute present in its elution buffer, or restrict how that buffer is prepared beyond characterizing the concentration of citrate and pH, here the ordinarily skilled artisan would have had at her disposal a number of buffer formulations from which to choose—and selecting among them would not necessarily have resulted in a method that meets the claims. Even if we accept that the four options, identified by Dr. Przybycien, would have been more probable choices than the fifth, identified by Dr. Cramer, this is still a case that is based on odds or probabilities, rather than a result that flows naturally from the disclosure of the prior art. *See Perricone v. Medicis*

Pharm. Corp., 432 F.3d 1368, 1378 (Fed. Cir. 2005) ("[W]hen considering a prior art method, the anticipation doctrine examines the natural and inherent results *in that method* without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure." (emphasis added)). Petitioner's position is based on the very kind of probability that precludes a finding of inherent disclosure. *See Endo*, 894 F.3d at 1381–82 ("the prior art was replete with *potential* co-solvents such that a skilled artisan, reviewing the Articles [the cited art], *would not have necessarily recognized* that the Articles' authors used *benzyl benzoate as a co-solvent* for their reported clinical studies." (emphases added)). Stated somewhat differently, the record before us does not adequately support Petitioner's contention that Shadle's elution buffer would necessarily be made using one of the four methods proposed by Dr. Przybycien.[3]

The cases Petitioner relies on do not support its contention that the "law looks to the 'normal and usual' way a POSA would practice the prior art" (Reply 10–11) to fill gaps in the disclosure. Rather, these cases embody the above-stated principle that that if a prior art method or device in its "normal and usual operation" *will perform the function claimed* in the challenged patent, "then such [patent] will be considered to have been anticipated by the [prior art]." *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275–1276 (Fed. Cir. 2010) (internal quotations omitted); *see also*

[3] We are likewise unpersuaded by Petitioner's suggestion that we should discount arguments advanced by Patent Owner in this proceeding if they were not previously advanced before the EPO. *See* Reply 11–12 (citing Ex. 1011, 39).

In re King, 801 F.2d 1324, 1327 (Fed. Cir. 1986) ("[T]he law is, and long has been, that 'if a previously patented device, in its normal and usual operation, will perform the function which an appellant claims in a subsequent application for process patent, then such application for process patent will be considered to have been anticipated by the former patented device.'" (quoting *Ackenbach*, 45 F.2d at 439)). As explained above, that principle does not apply here. The challenged claims of the '815 patent require that the initial antibody-containing eluate must be of low conductivity of 300 mS/m or less, and have a molarity of 100 mM or less *total solute* in order to perform the recited methods. Ex. 1001, 12:41–44. Shadle, in contrast, is silent regarding conductivity, and discloses only that the elution buffer includes 25 mM *citrate* and has a pH of 3.5. Ex. 1003, 20–21. Furthermore, the elution buffer of Shadle is not a *product resulting from* the performance of Shadle's method. Rather, it is a *reagent for use in* that method. Thus, neither the conductivity nor molarity of the elution buffer can be said to be inherent in Shadle's method.

Petitioner's analysis "goes astray because it assumes what [Shadle] neither disclosed nor rendered inherent." *Perricone*, 432 F.3d at 1379. Specifically, beyond the stated requirements for citrate concentration and pH, Shadle is agnostic as to how its elution buffer is prepared, what solutes are present in the initial antibody-containing eluate, and the conductivity of that eluate. Ex. 1003, 20–21. Accordingly, it is not accurate to say that performance of Shadle's antibody purification method in its normal and usual way discloses an initial antibody-containing eluate with a conductivity of 300 mS/m or less, and a total solute concentration of 100 mM or less.

See Endo, 894 F.3d at 1381–82 ("First, Custopharm has not demonstrated that a skilled artisan could extrapolate the vehicle formulation used in the Articles from pharmacokinetic performance data. . . . Second, the prior art was replete with potential co-solvents such that a skilled artisan, reviewing the Articles, would not have necessarily recognized that the Articles' authors used benzyl benzoate as a co-solvent for their reported clinical studies."); *Perricone*, 432 F.3d at 1379 ("Because Pereira does not disclose topical application to skin sunburn, this court reverses the district court's holding that Pereira anticipates claims 1–4 and 7 of the '693 patent.").

Our rejection of Petitioner's inherency analysis does not turn on whether Petitioner has established that it would be "impossible" to practice Shadle without practicing the claimed invention, but rather, Petitioner's failure to prove that Shadle's disclosure is sufficient to show that the natural result flowing from performance of the method as taught would result in the claimed invention. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) ("Apotex did not need to prove that it was impossible to make PHC anhydrate . . . that contained no PHC hemihydrate, but merely that 'the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in' the claimed product." (quoting *Oelrich*, 666 F.3d at 581)); *see also Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999) (finding inherent disclosure of a claim limitation even though "the record showed that special mixing techniques – such as grinding and screening the AN particles – remove interstitial air from the blasting compositions" because the asserted reference "did not teach or suggest any such

techniques"). In this regard, we highlight our finding, set forth above, that practice of the antibody purification method of Shadle in its normal and usual way does not require use of one of the four elution buffer preparations identified by Dr. Przybycien as common and conventional. Instead, we find, in view of Shadle's silence concerning how its elution buffer is prepared, its conductivity, and how much total solute it includes (Ex. 1003, 20–21), as well as Dr. Cramer's testimony that an ordinarily skilled artisan reasonably could have employed buffer formulations other than those described by Dr. Przybycien (Ex. 2015 ¶ 59; Ex. 1034, 103:21–104:5, 105:3–107:23), that Shadle does not necessarily require use of one of Dr. Przybycien's four buffer formulations, and does not inherently disclose an initial antibody-containing eluate with a conductivity of 300 mS/m or less and a concentration of total solute of 100 mM or less. *See MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) ("Occasional results are not inherent.").

Petitioner's further reliance on inherency to prove that Shadle discloses "adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less" (Ex. 1001, 12:45–47), as required by claim 1, and "neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles, wherein the molarity of the neutralized sample is 100 mM or less (*id.* at 14:5–7), as required by claim 13, suffers from the same deficiencies described above. Moreover, because they are layered atop each other, the defects in Petitioner's inherency arguments are magnified.

Petitioner acknowledges that Shadle does not expressly disclose the molarity of the neutralized eluate of Example IA, but contends that it can be calculated based on other disclosures in that reference. Pet. 41. In addition to the wash and elution steps of Shadle's Example IA, described above, Shadle further explains that "[i]mmediately after elution, the sample was adjusted to pH 3.5 by the addition of 2.5 M hydrochloric acid, held for approximately 30 minutes, and adjusted to pH 5.5 by the addition of approximately 350 milliliters of 1 M Tris base." Ex. 1003, 21. In order to determine the molarity of total solute present in Shadle's neutralized eluate, it is, thus, necessary to account for any contributions from the wash buffer, elution buffer, hydrochloric acid, and Tris base solutions used in each step of Example IA. *See* Ex. 1026 (calculating molarity based on contributions from elution buffer, hydrochloric acid, and Tris base); Ex. 1047 (additionally accounting for contribution from wash buffer).

As explained previously, however, Shadle does not describe how to prepare its elution buffer, define the total concentration of solute present in the initial antibody-containing eluate, or state how much, if any, wash buffer is included in that eluate. *See* Ex. 1003, 21. Neither does Shadle expressly describe the amount of hydrochloric acid added to that eluate. *See id.* As such, it cannot be said that Shadle's neutralized eluate *necessarily* has 100 mM or less total solute, or that a neutralized eluate with 100 mM or less total solute is the "natural result of the combination of elements *explicitly disclosed* by the prior art." *Endo*, 894 F.3d at 1381 (emphasis added) (quoting *PAR*, 773 F.3d at 1196).

Petitioner's arguments to the contrary do not merit a different result. Absent disclosure, either express or inherent, of the molarity of Shadle's initial antibody-containing eluate, it is impossible to discern the molarity of Shadle's neutralized eluate, or to determine whether it satisfies the challenged claims. For example, Dr. Przybycien and Dr. Cramer testify regarding the effect of different ProSep A elution buffers, each prepared according to the requirements of Shadle, on the molarity of Shadle's neutralized eluate, and their combined calculations indicate that, even excluding any contribution of wash buffer from the analysis, only some—not all—elution buffers result in a neutralized eluate with 100 mM or less total solute. Ex. 2015 ¶¶ 60–64 (determining that the total molarity of the neutralized eluate obtained using elution buffer prepared with trisodium citrate and hydrochloric acid would be 102–108 mM); Ex. 1026, 2–5 (determining that the total molarity of the neutralized eluate obtained using elution buffer prepared according to one of the four methods identified by Dr. Przybycien would be 50.8–69.4 mM); *see also* PO Resp. 31–32 (discussing Dr. Cramer's calculations). Although Petitioner bears the burden of proving inherent disclosure of any claim step, Patent Owner's evidence, in the form of Dr. Cramer's calculations, that at least one preparation of Shadle's ProSep A elution buffer fails to satisfy the pH-adjusted eluate molarity and neutralized eluate molarity requirements recited in the challenged claims highlights the shortcomings of Petitioner's inherency argument. The fact that Shadle's neutralized eluate may additionally contain an unknown amount of wash buffer further undercuts Petitioner's inherency analysis. *See* Ex. 1036 ¶ 50 (acknowledging that up

to 0.582 L of wash buffer may be present in Shadle's neutralized eluate); Ex. 2015 ¶ 71 (stating that by "conservative estimate," 1L of wash buffer could be present in Shadle's eluate); Ex. 2001, 5–6 (EPO examination division finding that Shadle's eluate adjusted to pH 3.5 included 3.75–4.5 L of wash buffer).

Finally, because Petitioner has established neither that Shadle discloses that its initial antibody-containing eluate is of low conductivity of 300 mS/m or less and includes 100 mM or less total solute, nor that it discloses a pH-adjusted or neutralized eluate including 100 mM or less total solute, Petitioner's assertion that Shadle inherently discloses the particle formation step of the challenged claims necessarily fails. *See Cont'l Can*, 948 F.2d at 1268 ("To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."). Even assuming that adherence to the steps of the challenged claims would inherently result in particle formation, it cannot be said that particle formation inherently results from the performance of Shadle's antibody purification process, because Petitioner has not established the molarity either of Shadle's initial antibody-containing eluate or of Shadle's neutralized eluate.

Accordingly, we find that Petitioner has not established by a preponderance of the evidence that claims 1–7, 12, and 13 of the '815 patent are anticipated by Shadle.

E. Obviousness Based on Shadle

Petitioner's second ground challenges the same set of claims over the same reference as challenged in the first ground, except on obviousness under 35 U.S.C. § 103(a). Pet. 55–59. Patent Owner disagrees that Shadle renders the challenged claims obvious. PO Resp. 52–61.

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

The Petition addresses obviousness with only perfunctory assertions. For example, with regard to its contention that Shadle teaches or suggests the elution buffer molarity, neutralized eluate molarity, and particle formation requirements of the challenged claims, the Petition states:

> In view of the disclosures of WO '389 [Shadle] as discussed above for Ground I, all limitations of claims 1–7 and 12–13 were expressly or inherently disclosed. Thus, for the reasons explained above, it would also have been at least obvious for a POSA, based on the purification process disclosed in WO '389, to arrive at and perform the method steps of claims 1–7 and 12–13—with a reasonable expectation of success. Ex. 1002 ¶¶ 130–133.
>
> As discussed above for anticipation, WO '389 discloses an antibody purification process that falls within the scope of claims 1–7 and 12–13 in the '815 patent. *Id.* ¶ 131. There is no patentable difference between the prior art antibody purification process of Example IA in and the claimed invention. *Id.* In light of these circumstances, the single prior art reference WO '389 renders the claims obvious. In particular, a POSA would understand from the teachings of WO '389 that DNA contaminants would be removed from an antibody sample by converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9, and then adjusting or neutralizing the pH of the resulting sample from 4 to 8 or a neutral level, wherein the molarity of the adjusted sample is 100 mM or less. *Id.* The resulting neutralized and adjusted pH buffer solution is then filtered using a 0.1 micron and a 0.2 micron filter. *Id.*

Pet. 57–58. The Petition does not further elaborate on its assertion that Shadle teaches or suggests these claim requirements. *See id.* at 55–59. Indeed, the only claim step specifically addressed in the obviousness analysis set forth in the Petition is the removal of particles to remove contaminant DNA. *Id.* 58–59. Petitioner's Reply is likewise superficial in its obviousness analysis, simply stating that "[e]ven if any limitation were not disclosed by Shadle at least inherently, it would have been obvious to a POSA" (Reply 23), without explaining why that would be the case for the

initial antibody-containing eluate conductivity or molarity requirements, the pH-adjusted eluate molarity requirement, or the particle formation requirement of the challenged claims (*see id.* at 23–25).

Accordingly, in view of the deficiencies in Petitioner's obviousness analysis, and for the reasons set forth above concerning anticipation by Shadle, we determine that Petitioner has not established, by a preponderance of the evidence, that claims 1–7, 12m and 13 of the '815 patent would have been obvious Shadle.[4]

III. MOTION TO EXCLUDE

Petitioner moves to exclude Patent Owner's Exhibits 2201–2207. Paper 36, 1. Patent Owner opposes the motion. Paper 44. As the moving party, Petitioner has the burden of proof to establish that it is entitled to the requested relief.

Petitioner asserts that Patent Owner untimely introduced Exhibits 2201–2207 for the first time during the deposition of Petitioner's Reply declarant, Dr. Przybycien. Paper 36, 4. Petitioner additionally asserts that the challenged exhibits are inadmissible because they are irrelevant. *Id.* Patent Owner responds that the objected-to exhibits were timely introduced because they were used to challenge opinions presented by Dr. Przybycien for the first time in conjunction with Petitioner's Reply. Paper 44, 2. Patent

[4] In light of the above described shortcomings in Petitioner's obviousness analysis, we do not address Patent Owner's objective evidence of nonobviousness. *See* PO Resp. 56–62.

Owner further asserts that the exhibits are relevant because they illuminate gaps in Dr. Przybycien's Reply testimony. *Id.* at 3.

Because we have not relied on Exhibits 2201–2207, or Dr. Przybycien's testimony regarding those exhibits in this Final Written Decision, we dismiss Petitioner's Motion to Exclude Exhibits 2201–2207 as moot.

IV. CONCLUSION

For the foregoing reasons, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–7, 12, and 13 of the '815 patent are unpatentable.

V. ORDER

It is

ORDERED that claims 1–7, 12, and 13 of the '815 patent are not held unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *dismissed* as moot; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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