Trials@uspto.gov
571-272-7822

Paper No. 7
Entered: December 1, 2017

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.*

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

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.") We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we institute an *inter partes* review of claims 1–7, 12, and 13 of the '815 patent.

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 filed a petition for *inter partes* review of related U.S. Patent No. 7,332,289 B2 ("the '289 patent") (IPR2017-01357). Pet. 4; Paper 5, 3.

B. The '815 Patent

The '815 patent, titled "Protein Purification Method," issued April 19, 2011, from U.S. Patent Application No. 12/018,688 ("the '688 application"), 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, 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 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. 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 these particles is a conjugate formed between physiologically active protein and DNA." *Id.* at 6:12–15.

C. Illustrative Claim

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 of1.5 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 prior art reference (Pet. 5):

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

Petitioner also relies on the Declaration of Todd M. Przybycien, Ph.D. (Ex. 1002).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–7, 12 and 13 of the '815 patent on the following grounds (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.

At this stage in the proceeding, we determine that Petitioner's description of the level of ordinary skill in the art is comparable to the level of skill reflected in the asserted prior art. On this record, we find that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). We have reviewed the credentials of Dr. Przybycien (Ex. 1002, Attachment A), and, at this stage in the proceeding, we consider him to be qualified to opine on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). 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). "[W]e need

only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

The parties propose constructions for several claim terms. Pet. 30, 35–36; Prelim. Resp. 11–13. For purposes of this decision, we find it necessary to address only the claim term "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."

> "*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*"

Claims 1 and 13 of the '815 patent recite, in pertinent part, "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." Ex. 1001, 12:41–44, 14:1–5.

In conjunction with its anticipation argument, Petitioner asserts:

> The specification of the '815 patent defines "an acidic aqueous solution of low conductivity" as:
>
> [G]enerally refer[ing] to an aqueous solution of pH 1.5 to pH 3.9, preferably-of [sic] pH 2.0 to pH 3.9, more preferably of pH 2.0 to pH 3.0, which has a molarity of 0 to 100 mM, preferably 0 to 50 mM, more preferably 0 to 30 mM, or has an ionic strength of 0 to 0.2, preferably 0 to 0.12, or has a conductivity of 0 to 300 mS/m, preferably 0 to 200 mS/m, more preferably 0 to 150 mS/m.

Pet. at 35–36 (alterations in original) (quoting Ex. 1001, 5:28–35).

Petitioner additionally contends that the term "[m]olarity" 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." *Id.* at 30. Petitioner appears to recognize, however, 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. *Id.* at 30–31.

Patent Owner responds that the meaning of "molarity" "is not limited to the concentration of a single solute, as the '815 specification and file history make clear in addressing the contributions of multiple solutes to the solution's molarity." Prelim. Resp. 12–13. Patent Owner goes on to point out that Petitioner must recognize that the "molarity" of a solution takes account of the various solutes present in a solution, rather than just a single solute, because Petitioner "adds the concentrations of tris and citrate (*i.e.*, two solutes) in determining [the] molarity" of the neutralized eluate in Shadle. *Id.* at 13. Patent Owner does not address Petitioner's contention that the claim phrase "an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less" excludes the contributions of any protein or contaminant DNA. *See id.* at 10–12. Nor does Patent Owner address Petitioner's assertion that the specification of the '815 patent defines "an acidic aqueous solution of low conductivity."

We agree with Petitioner that the specification of the '815 patent explains that the claim phase "an acidic aqueous solution of low conductivity" generally refers to:

> an aqueous solution of pH 1.5 to pH 3.9, preferably-of [sic] pH 2.0 to pH 3.9, more preferably of pH 2.0 to pH 3.0, which has a molarity of 0 to 100 mM, preferably 0 to 50 mM, more preferably 0 to 30 mM, or has an ionic strength of 0 to 0.2, preferably 0 to 0.12, or has a conductivity of 0 to 300 mS/m, preferably 0 to 200 mS/m, more preferably 0 to 150 mS/m.

Ex. 1001, 5:27–35. We observe that this disclosure broadly provides that a solution of pH 1.5 to pH 3.9 as well as a molarity of 0 to 100 mM *or* an ionic strength of 0 to 0.2, *or* a conductivity of 0 to 300 mS/m qualifies as "an acidic aqueous solution of low conductivity." The greater 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" serves to narrow the scope of claims 1 and 13, however, by requiring that the recited solution have a conductivity of 300 mS/m or less, a molarity of 100 mM or less, and be of pH 1.5 to pH 3.9. *See* Ex. 1005, 107 (Patent Owner representation during prosecution of the parent to the '815 patent that "a molarity of over 0.1 M" is of "higher conductivity" in order to distinguish prior art). Accordingly, we determine, for purposes of this decision, 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.

Turning to the meaning of the term "molarity," as it is used in independent claims 1 and 13, 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. Step (1) of claims 1 and 13 of the ’815 patent requires “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.” Ex. 1001, 12:41–44, 14:1–4. By its plain language, this claim requirement refers to the overall molarity of the solution, and not of any particular solute in the solution.

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)”).

With regard to Petitioner’s further contention that the molarity of the acidic aqueous solution should be calculated without considering any effects

of the contaminant DNA or protein from the sample (Pet. 24–25), we determine that, for purposes of institution, it is not necessary to decide this point. In this regard, we note that Patent Owner does not contend that contributions from the physiologically active protein or contaminant DNA should be included in the molarity calculation. *See* Prelim. Resp. 16–20. And furthermore, Petitioner accounts for contaminant DNA and protein in the eluate produced during step (1) of claims 1 and 13. *See* Pet. 36, n.3 ("To the extent Chugai argues that molarity should be determined by considering contributions from the protein or contaminant DNA, Dr. Przybycien explains that such added contribution would be negligible (*i.e.*[,] less than 1 mM), and certainly not enough to raise the molarity of the ProSep A citrate elution buffer above the claimed 100 mM limit. Ex. 1002 ¶ 87."). Therefore, because there is no controversy to resolve concerning the contribution of protein and contaminant DNA to the molarity of the recited "acidic aqueous solution," for purposes of this decision, we need not decide the issue. *See Nidec*, 868 F.3d at 1017.

Accordingly, we determine, for purposes of this decision, that under the broadest reasonable interpretation, 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, and that molarity refers to the total concentration of solute present in the solution.

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 Ground of Unpatentability Based on Shadle

Petitioner asserts that claims 1–7, 12, and 13 are anticipated under § 102(b) by Shadle. Pet. 33–55. In support of its assertion, Petitioner provides detailed explanations as to how Shadle discloses each claim limitation (*id.*) and relies upon the Przybycien Declaration (Ex. 1002) to support its positions. Patent Owner disagrees that Shadle anticipates the challenged claims. Prelim. Resp. 14–34.

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). Where a reference is silent regarding a given claim requirement, "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." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

> 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.

Id. at 1269 (alteration in original) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

Petitioner asserts that Shadle discloses methods for purifying monoclonal antibody samples that remove "contaminants derived from the host cell, cell culture medium, or other raw materials" (Ex. 1003, 15:7–9) and teaches in particular that the purified antibodies obtained have "low (< 1 pg/mg protein) DNA" (*id.* at 14:21–24). Pet. 34, 53. Petitioner reasons, therefore, that Shadle "discloses that DNA is among the derived contaminants that are removed because the purified antibody product obtained by practicing the disclosed process has a reduced DNA concentration." *Id.* at 34 (citing Ex. 1002 ¶¶ 77–81).

Petitioner also contends that Shadle discloses "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" (Ex. 1001, 12:41–44), as required by independent claims 1 and 13 of the '815 patent. Pet. 34–35, 53. Petitioner explains that Shadle discloses applying an antibody containing sample to an affinity chromatography column, washing the column, and subsequently eluting the antibody "by applying 15–20 liters of ProSep A elution buffer" (Ex. 1003, 21:9–10) Pet. 35; Ex. 1002 ¶¶ 83–84.

With respect to the molarity and pH requirements of step (1), Petitioner explains that Shadle discloses that "the conditions of the ProSep A elution buffer are '25 mM citrate, pH 3.5.'" Pet. 35 (quoting Ex. 1003, 20:10); *id.* at 36. Petitioner additionally argues that to the extent Patent Owner contends the molarity of the "acidic aqueous solution of low conductivity" should account for protein or DNA present in the eluate, any contribution from protein or DNA "would be negligible (*i.e.* less than

1 mM), and certainly not enough to raise the molarity of the ProSep A citrate elution buffer above the claimed 100 mM limit." Pet. 36, n.3 (citing Ex. 1002 ¶ 87).

Concerning the step (1) requirement that the acidic aqueous solution be "of low conductivity of 300 mS/m or less," Petitioner, relying on Dr. Przybycien's declaration testimony, asserts that "the ProSep A buffer solution used and disclosed in Example IA of WO '389 [Shadle] necessarily had a low conductivity of '300 mS/m or less.'" Pet. 37 (citing Ex. 1002 ¶¶ 88–90). In support of this position, Petitioner relies on Dr. Przybycien's testimony that he "prepar[ed] the '25 mM citrate, pH 3.5' ProSep A elution buffer of [Shadle's] Example IA and test[ed] its conductivity at room temperature." *Id.* (citing Ex. 1002 ¶ 88). Dr. Przybycien explains that he performed such testing because "[f]or solutions other than the most dilute solutions of charged species, conductivities are necessarily measured as there are no available theories or models for predicting conductivity that do not include parameters that are estimated from conductivity data." Ex. 1002 ¶ 88.

Specifically, Dr. Przybycien "prepared and tested two ProSep A elution buffer solutions that covered the two different compositions disclosed in WO '389 [Shadle]." Pet. 38 (citing Ex. 1016, 1–3 (describing Dr. Przybycien's testing protocol)); Ex. 1002 ¶ 89. Relying on Dr. Przybycien's declaration testimony, Petitioner asserts that conductivity tests performed using these solutions "show conclusively that the ProSep A elution buffer solution disclosed in WO '389 necessarily had a conductivity of either 194 ± 7 mS/m or 154 ± 7 mS/m . . . , which are both significantly

lower than the claimed conductivity [limit] of '300 mS/m.'" *Id.* (citing Ex. 1002 ¶¶ 88–89; Ex. 1016). Petitioner, relying on Dr. Przybycien's testimony, further contends that to the extent the contributions from the physiologically active protein and contaminant DNA are included in the conductivity analysis, their contribution to conductivity "would certainly not [be] enough to raise the conductivity of the ProSep A citrate elution buffer above the claimed 300 mS/m limit." *Id.* at 38, n.4 (citing Ex. 1002 ¶ 89). Petitioner additionally points out that Dr. Przybycien's testing results are "consistent with the assertions of the third party during the prosecution of EP '149 that, 'when measured at 25°C, 25 mM citrate, pH 3.5 displayed a conductivity of around 150 mS/m.'" *Id.* at 39 (quoting Ex. 1011, 39); Ex. 1002 ¶¶ 88–89.

Step (2) of 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." Ex. 1001, 12:45–47. Step (2) of claim 13 is similar, but narrower, and recites "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 14:5–8. Petitioner asserts that Shadle expressly describes neutralizing the eluate by addition of a buffer to raise the pH to 5.5, and inherently teaches particle formation and that the molarity of the neutralized eluate is 100 mM or less. Pet. 40–46 (citing Ex. 1002 ¶¶ 91–99), 53–55 (Ex. 1002 ¶¶ 124–126).

Petitioner identifies the following excerpt of Shadle as disclosing the adjusting/neutralizing aspect of step (2) of claims 1 and 13:

> The eluate was approximately 15 liters in volume, and contained approximately 5 milligrams protein per milliliter.
>
> Immediately *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 l 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.

Pet. 40 (quoting Ex. 1003, 21:11–19), 53–54.

Petitioner acknowledges that Shadle does not expressly describe the formation of particles upon eluate neutralization, or identify the molarity of the neutralized eluate, but contends that these claim requirements are inherently disclosed. Pet. 41, 54–55. With respect to the requirement that the molarity of the eluate be 100 mM or less, Petitioner explains, relying on Dr. Przybycien's declaration testimony, that the molarity of the neutralized eluate in Shadle can be calculated based on other disclosures in Shadle. Pet. 41 (citing Ex. 1002 ¶ 94). In particular, Petitioner asserts that the molarity of citrate and Tris base in the neutralized elute of Shadle is 47.2 mM. *Id.* at 41–42(citing Ex. 1002 ¶ 96).

Concerning the contribution of HCl to the molarity of the neutralized eluate, again relying on the testimony of Dr. Przybycien, Petitioner explains:

> Example IA discloses that eluate of 15 L in volume is produced using 15–20 liters of the 25mM Citrate elution buffer with a pH of 3.5. Ex. 1003, 21. As such, the volume of 2.5 M HCl needed to adjust the pH of the eluate to 3.5 is minimal. Ex. 1002 ¶¶ 95–99; Ex. 1007, 1–3. In fact, WO '389 [Shadle] explicitly states that the HCl addition step can be omitted. Ex. 1003, 17 ("The pH 3.5 treatment can be omitted if desired.").

Id. at 41. Petitioner, therefore, contends that "even if the minimal effect of the HCl solution on the molarity of the neutralized eluate were included, the overall effect would be insignificant and the molarity of the neutralized eluate in Example IA would still be well below the required [limit of] 100 mM." *Id.* at 43 (citing Ex. 1002 ¶ 99). Furthermore, Dr. Przybycien provides a molarity calculation that expressly accounts for the contribution of HCl to the molarity of the neutralized eluate, and determines that "the total molarity of the neutralized eluate" would be "50.8 mM." Ex. 1002 ¶ 99.

In support of this conclusion, Petitioner and Dr. Przybycien point out that during prosecution of the '289 patent, which is the parent to the '815 patent, in order to secure allowance, Patent Owner represented to the examiner that because the amount of buffer used to adjust the pH of the solution "is very small compared with that of the solution to which the buffer is added, *the effect of the molarity of the buffer to the molarity of the whole solution is extremely small*" (Ex. 1005, 13), and further that "use of a small amount of a buffer solution to modulate a pH value of a solution of a relatively large volume is well known in this technical field" (*id.*). Pet. 43 (citing Ex. 1002 ¶ 97). Petitioner and Dr. Przybycien additionally identify Patent Owner's representation during prosecution of a European counterpart to the '815 patent that the molarity of the neutralized eluate in Shadle "can be calculated to at least (375 + 350)/15.35 = 47.2 mM" (Ex. 1006, 27–28) as consistent with Petitioner's understanding of Shadle. *Id.* (citing Ex. 1002 ¶ 98).

As for the contribution of protein and contaminant DNA to the molarity of the eluate, Petitioner asserts that such contributions should not be considered. *See* Pet. 42, n.5; Ex. 1002 ¶ 96. Nevertheless, relying on Dr. Przybycien's testimony, Petitioner asserts that to the extent protein and contaminant DNA are included in the molarity determination, "such added contribution would be negligible (*i.e.* less than 1 mM), and certainly not enough to raise the molarity of the adjusted ProSep A citrate elution buffer above the claimed 100 mM limit." Pet. 36 n.3 (citing Ex. 1002 ¶ 96). Specifically, Dr. Przybycien calculates that the contribution of the RSHZ-19 antibody, the purification of which is the subject of Shadle, to the molarity of the neutralized eluate is 0.03 mM. Ex. 1002 ¶ 96; Ex. 1007, 1.

With respect to the particle formation requirement of claims 1 and 13, Petitioner contends, relying on D. Przybycien, that neutralization of the eluate under the conditions described in Shadle would inherently result in the recited particle formation, and further, that the particles so formed would necessarily contain contaminant DNA. Pet. 43–46 (citing Ex. 1002 ¶¶ 100–102).

In particular, Petitioner asserts that "[t]he conditions from [Shadle's] Example IA fall within the same range of conditions (pH of 4–8 and molarity less than 100 mM) recited in step 2 of the claimed process that the '815 patent claims is sufficient to form particles." *Id.* at 44 (citing Ex. 1002 ¶¶ 100–102). Petitioner also identifies the disclosure in the '815 patent specification stating "[a]ccording to the present invention, the solution neutralized to a neutral pH level in the above stage, in turn, produces particles (i.e., becomes clouded)" (Ex. 1001, 6:4–6) as indicating that

particle formation necessarily follows from eluate neutralization under the conditions set forth in claims 1 and 13. Pet. 44–45 (citing Ex. 1002 ¶ 100); *see also id.* (explaining that the '815 patent specification discloses after neutralization, the solution is "then filtered through a filter to remove the resulting particles" (Ex. 1001, 1:62–67)).

Petitioner further contends, relying on the declaration testimony of Dr. Przybycien, that "[t]he '815 patent specification further describes that the formed particles will contain contaminant DNA." Pet. 45 (citing Ex. 1002 ¶ 100). Specifically, Petitioner points to disclosure by the '815 patent that

> [w]ithout being bound by any particular theory, the inventors of the present invention estimate that *each of these particles is a conjugate formed between physiologically active protein and DNA*. Particle removal by filtration results in a small loss of physiologically active protein because it is removed in the form of *DNA-physiologically active protein conjugates*.

Id. (quoting Ex. 1001, 6:12–19); Ex. 1002 ¶ 100.

Petitioner additionally explains that "[t]he inherent formation of particles under the recited eluate solution conditions and those particles containing contaminant DNA is also consistent with the teachings in the prior art," as evidenced by Scopes (Ex. 1009).[1] Pet. 45 (citing Ex. 1002 ¶ 101). Specifically, Petitioner contends, relying on Dr. Przybycien's testimony, that an ordinarily skilled artisan would have understood from Scopes "[i]n many cases isoelectric precipitates can be formed in a tissue

[1] Robert K. Scopes, *Protein Purification: Principles and Practice* (Charles R. Cantor ed., 2nd ed. 1987) (Ex. 1009).

extract by lowering the pH to between 6.0 and 5.0" (Ex. 1009, 28), and further that "[m]ost isoelectric precipitates are aggregates of many different proteins and may include particulate fragments and *protein-nucleic acid complexes*" (*id.* at 29 (emphasis added)). Pet. 45–46 (citing Ex. 1002 ¶ 101)).

Step (3) of claim 1 requires "removing the particles thereby to remove contaminant DNA in the sample." Ex. 1001, 12:48–49. Step (3) of claim 13 is similar, but narrower, requiring "filtering the resulting sample from step (2) to remove particles containing contaminant DNA." *Id.* at 14:9–10. Petitioner contends that these claim steps are taught, either expressly or inherently, by Shadle. Pet. 46–48 (citing Ex. 1002 ¶¶ 104–109), 55. In particular, Petitioner asserts that "[a]fter neutralizing the eluate to pH 5.5, the next step of Example IA discloses that '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.'" Pet. 46 (quoting Ex. 1003, 21:17–19). Petitioner argues, relying on Dr. Przybycien's testimony, that "the particles that formed according to the steps of Example IA, including those containing contaminant DNA, would inevitably and necessarily be removed by the disclosed filters, because the purpose of such filters is to remove all particles above a certain size through filtration." Pet. 46–47 (citing Ex. 1002 ¶¶ 104–106; Ex. 1010, 27, 30). Petitioner, therefore, asserts that Shadle "expressly disclosed using its two filters to remove particles, including those formed in step 2 and containing contaminant DNA." *Id.* (citing Ex. 1002 ¶¶ 104–107).

Petitioner further argues, relying on Dr. Przybycien's declaration testimony, that "the particles that formed according to the steps of Example IA, including those containing contaminant DNA, would inevitably and necessarily be removed by the disclosed filters, because the purpose of such filters is to remove all particles above a certain size through filtration." *Id*. at 46–47 (citing Ex. 1002 ¶¶ 104–106). In this regard, Dr. Przybycien testifies that "[a]lthough Example IA does not describe what is removed using these two filters, a POSA would understand that the purpose of such filters is to remove all particles above a certain size through filtration." Ex. 1002 ¶ 105. Dr. Przybycien explains that an ordinarily skilled artisan would have understood, as disclosed by Martin,[2] that "[a]bsolute removal of particulate solids from the process stream, including sterile filtration, serves as an essential prefiltration/protection step for downstream chromatography and ultrafiltration systems" (Ex. 1010, 27). Ex. 1002 ¶ 106; *see also* Pet. 46–47. Dr. Przybycien also opines that such an artisan would have further understood that "[i]n most cases, a 0.2-µm-rated sterilizing-grade membrane filter is employed as the fluid filter" (Ex. 1010, 30). Ex. 1002 ¶ 106; *see also* Pet. 46–47.

Based upon our review of the current record, and in light of our preliminary claim construction, we discern no deficiency in Petitioner's characterization of Shadle and the knowledge in the art, or in Petitioner's

[2] Jerry M. Martin et al., "Cartridge Filtration for Biotechnology," in *Bioprocessing Engineering: Systems, Equipment and Facilities*, 317–370 (Bjorn K. Lydersen et al., eds. 1994) (Exhibit 1010).

assertions as to the reasonable inferences an ordinary artisan would make from that reference. In addition, for purposes of this decision only, we accept Dr. Przybycien's testimony concerning the express and inherent teachings of Shadle.

Patent Owner contends that Petitioner fails to explain where in the portions of Shadle asserted as disclosing the steps of claims 1 and 13 that reference teaches a method for removing contaminant DNA, as recited in the preamble. Prelim. Resp. 15. Specifically, Patent Owner argues that the Petition fails to establish a link between Shadle's disclosure of "the pH adjustment and filtration step using Polygard and Millipak filters" and the removal of contaminant DNA. *Id.* In this regard, Patent Owner observes that Shadle identifies the Protein A and hydrophobic interaction chromatography as removing DNA from the sample, but does not expressly describe the filtration step as so doing. *Id.* Patent Owner additionally contends that the cation exchange and hydrophobic interaction chromatography steps taught by Shadle are "precisely of the sort criticized and rendered unnecessary by the '815—a step that Shadle would have no reason to perform if DNA were removed earlier." *Id.* at 16. Patent Owner further asserts that Petitioner fails to explain how Shadle teaches a "physiologically active protein," as required by the claims. *Id.*

As an initial matter, even assuming, for purposes of this decision, that the preambles of claims 1 and 13 are limiting,[3] we determine that Petitioner

[3] We note that Petitioner does not assert that the preambles of claims 1 and 13 are non-limiting, but rather states that "[t]o the extent that the preamble is

has established a reasonable likelihood of showing that Shadle discloses "[a] method for removing contaminant DNA in a sample containing a physiologically active protein" comprising the recited steps. Ex. 1001, 12:38–40, 13:11–12. Claims 1 and 13 are "comprising" claims, which recite a series of steps. Ex. 1001, 12:38–40, 13:11–12. As such, we determine, for purposes of institution, the fact that Shadle discloses additional chromatography steps beyond those expressly recited in claims 1 and 13 does not preclude that reference from anticipating those claims. Moreover, at this juncture, the identification of the purported drawbacks of prior art antibody purification methods in description of the "Background Art" in the specification of the '815 patent does not persuade us otherwise, because claims 1 and 13 are not commensurate in scope with that description in the specification. Rather, because those claims are "comprising" claims, "the named [claim] elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997).

Nor do we agree with Patent Owner's assertion that Petitioner has not adequately shown how the neutralization and filtration steps of Shadle remove contaminant DNA. As discussed in greater detail below, we determine, for purposes of this decision, that Petitioner has established a reasonable likelihood of showing that neutralization of the eluate of Shadle to pH 5.5 with Tris base, and subsequent filtration of that eluate, as

---

a limitation—a matter that the Board need not reach—WO '389 [Shadle] discloses it." Pet. 33, 52.

expressly disclosed by Shadle (Ex. 1003, 21:15–19), would necessarily remove DNA containing particles from the eluate (*see* Pet. 35–40; Ex. 1002 ¶¶ 82–91).

We are likewise unpersuaded by the assertion that Petitioner has not adequately established that Shadle discloses a "physiologically active protein" (Prelim. Resp. 16). To the contrary, we agree with Petitioner that Shadle's disclosure of "a process for purifying antibodies" satisfies this claim requirement because antibodies are physiologically active proteins. Pet. 34 (citing Ex. 1002 ¶¶ 77–81).

Patent Owner also asserts that the Petition fails to show that Shadle discloses step (1) of claims 1 and 13. Prelim. Resp. 16. Specifically, Patent Owner contends that Petitioner has not established that the elution buffer of Shadle is of "low conductivity of 300 mS/m or less," or that it has a "molarity of 100 mM or less." *Id.* at 16–20.

Turning first to Patent Owner's contention that the Petition fails to demonstrate that the acidic aqueous solution of claims 1 and 13 (*id.* at 17–19), has a molarity of less than 100 mM, Patent Owner asserts that the molarity calculation proffered by Petitioner fails to account for the contributions of all of the solutes present in Shadle's elution buffer. *Id.* at 17. Specifically, Patent Owner contends that Petitioner acknowledges, in conjunction with its conductivity calculations, that solutes beyond those included in Petitioner's molarity calculations would be present in the claimed acidic aqueous solution. *Id.* at 17–18.

We are mindful of the high bar for proving inherency; however, in view of the record before us, and solely for purposes of this decision, based

on the particular facts and circumstances of this case, we credit Dr. Przybycien's testimony that the molarity of Shadle's ProSep A buffer would be less than 100 mM. In making this determination, we note that Dr. Przybycien's molarity calculation is consistent with Patent Owner's representation to the European Patent Office during prosecution of claims similar to those presently challenged that the "ProSep A elution buffer" of Shadle is "25 mM citrate at pH 3.5" (Ex. 1006, 27), and inclusion only of a citrate contribution from that elution buffer in its calculation of the molarity of the neutralized eluate (*id.*, 28). We remain cognizant, however, of the purported disparities between Petitioner's molarity and conductivity calculations identified by Patent Owner, and anticipate that this issue will be further fleshed out during trial.

We are likewise unpersuaded by Patent Owner's argument that "Petitioner never asserts, let alone explains, where, how, or why Shadle teaches that the eluting solution of Example IA (*i.e.*, '*ProSep A* elution buffer') is the same as the buffer listed in Table 1 (*i.e.*, '*ProSep* Elution Buffer')" (*id.* at 18). As an initial matter, we note that Patent Owner does not contend in its Preliminary Response that ProSep Elution Buffer and ProSep A elution buffer are in fact distinct solutions. Moreover, solely for purposes of this decision, we credit the unrebutted testimony by Dr. Przybycien that "Table 1 of WO '389 further discloses that the conditions of the ProSep A Elution Buffer are '25 mM citrate, pH 3.5'" (Ex. 1002 ¶ 84).

As for Patent Owner's contention that Petitioner has not demonstrated sufficiently that the elution buffer employed by Shadle is of "low

conductivity of 300 mS/m or less" (Prelim. Resp. 19–20), we do not agree. Rather, on the current record, we determine that Petitioner has demonstrated a reasonable likelihood of establishing that Shadle inherently discloses "converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/s or less" (Ex. 1001, 12:41–43, 14:1–3), as required by claims 1 and 13 of the '815 patent. Specifically, based on the particular facts and circumstances in this case, we credit, solely for purposes of this decision, Dr. Przybycien's testimony that he tested "the two different [ProSep A buffer] compositions disclosed in WO '389 [Shadle]," and that his results "show conclusively that the ProSep A elution buffer solution disclosed in WO '389 necessarily had a conductivity of either 194 ± 7 mS/m (buffer preparation method 2) or 154 ± 7 mS/m (buffer preparation method 3), which are both significantly lower than the claimed conductivity [limit] of "300 mS/m." Ex. 1002 ¶ 89; Ex. 1016. We are mindful of Patent Owner's concerns pertaining to the sufficiency of Dr. Przybycien's conductivity testing, and the extent of any conclusions that may be drawn therefrom, and expect that the parties will address any weaknesses in Petitioner's inherency argument during trial.

With regard to step (2) of claims 1 and 13, Patent Owner contends that the Petition fails to establish either that the molarity of the neutralized eluate of Shadle is 100 mM or less, or that particle formation necessarily follows from the neutralization of that eluate. Prelim. Resp. 20–28.

Concerning the molarity requirement of step (2) of claims 1 and 13, Patent Owner argues that "[t]he Petition fails to establish that the molarity of the adjusted or neutralized sample in Example IA is 100 mM or less."

Prelim. Resp. 20. In this respect, Patent Owner asserts that the molarity calculation proffered by Petitioner accounts for the contributions of citrate and Tris base, while "arbitrarily excluding other solutes." *Id.* at 21. Specifically, Patent Owner contends that Petitioner should have accounted for the wash buffer employed prior to elution in its molarity calculation (*id.* at 22–23), as well as "the molarity contribution from the undisclosed solution that raised the pH of the elution buffer in the eluate" (*id.* at 23 (emphasis omitted)). Patent Owner additionally asserts that its representation to the European Patent Office that the molarity of the eluate described in Example IA of Shadle was "at least" 47.2 mM (Ex. 1006, 27–28) does not "imply that the molarity of the neutralized eluate in Example IA was less than 100mM" (Prelim. Resp. 23–24).

We do not find Patent Owner's arguments persuasive on this record. Dr. Przybycien testifies that in addition to protein and DNA, the neutralized eluate of Shadle would include citrate, HCl, and Tris base. Ex. 1002, ¶¶ 94–96, 99; Ex. 1007, 1–3. This testimony is consistent with Shadle's disclosure that "Protein A chromatography removes a large proportion of cell and media derived impurities (particularly protein and DNA in the flow-through and wash fractions), and concentrates RSHZ-19 in the elution buffer for further processing" (Ex. 1003, 16:25–27), which suggests that the wash and eluate fractions are distinct. *See also id.* at 21:9–13 ("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."),

19:3–5 ("The eluate fractions from the Protein A capture and cation exchange steps are pooled based on the UV tracing on the chromatogram, and the entire peak is collected.").

With regard to the purported contribution to eluate molarity of an "undisclosed solution," we note that this assertion by Patent Owner is attorney argument, which, at this stage of the proceeding, is unsupported by objective evidence suggesting the presence of an "undisclosed solution" in the neutralized eluate of Shadle. For purposes of determining whether to institute a trial, we are sufficiently persuaded by Shadle's indication that, in addition to antibody and DNA, the neutralized eluate includes citrate, Tris base, and optionally, HCl. Ex. 1003, 20:10, 21:9–19; Ex. 1002 ¶¶ 92, 125.

This determination is consistent with Patent Owner's representation, below, to the European Patent Office during prosecution of claims similar to those presently challenged that Shadle's eluent includes citrate, HCl, and Tris base and has a molarity of "at least" 47.2 mM:

> Thus, the eluent before the filtration has:
>
> 375 mmol (25 mM • 15 l) of citrate
>
> "x" mmol (2.5 M • "Y" l (unknown)) of HCl
>
> 350 mmol (1 M • 0.35 l) of Tris base
>
> at least 15.35 1(15 l + "Y" l +0.351) in total volume.
>
> Based thereon, the molarity of the eluent can be calculated to at least: (375 + 350)/15.35 = 47.2 mM.

Ex. 1006, 28. Accordingly, at this stage in the proceeding, and solely for purposes of this decision, we accept Dr. Przybycien's testimony that the neutralized eluate of Shadle includes citrate, HCl, and Tris base, but not wash buffer constituents, such as PBS and glycine.

As to the particle formation requirement of step (2) of claims 1 and 13, Patent Owner contends that "the disclosures in the '815 and its prosecution history do not support Petitioner's contention that particles *necessarily* formed *in Example IA of Shadle*." Prelim. Resp. 26. In particular, Patent Owner argues that Petitioner has not established that the conditions described in Example IA of Shadle fall within the same range of conditions required by claim 1. *Id.* Patent Owner asserts that Petitioner fails to account for statements in the '815 patent specification that the type, conductivity, and neutral pH level of the acidic aqueous solution of low conductivity "will vary depending on the type of physiologically active protein or antibody to be purified" (Ex. 1001, 5:37–40, 5:53–59). Prelim. Resp. 26–27. In addition, Patent Owner argues that its representations to the Patent Office during prosecution of the '815 patent that "it is recognized that no DNA particle was precipitated in this [prior art] example because of its higher conductivity, i.e.[,] of a molarity of over 0.1M" (Ex. 1005, 107) and that "no such particles are formed during the procedure of [that reference] because the conditions described in the disclosure and carried out in the examples are fundamentally different from those stipulated in applicants' claims" (*id.* at 108) do not support Petitioner's position. Prelim. Resp. 28.

Patent Owner further asserts that Petitioner's reliance on teachings by Scopes as evidencing that an ordinarily skilled artisan would have understood "that proteins will aggregate by isoelectric precipitation under the conditions recited in the claims of the '815 patent" (Ex. 1002 ¶ 101) is misplaced. Prelim. Resp. 25–26. Patent Owner reasons that Scopes' discussion of mere possibilities is insufficient to establish inherency. *Id.*

Patent Owner additionally points out that Scopes describes lowering pH to obtain a pH of between 5.0 and 6.0, rather than raising it, as described by Shadle. *Id.* at 26.

We are not persuaded at this preliminary stage of the proceeding. On the limited record before us, and solely for purposes of this decision, we determine that Petitioner has demonstrated a reasonable likelihood of establishing that the process of Shadle necessarily results in the formation of particles that contain contaminant DNA. As an initial matter we determine that Petitioner has established a reasonable likelihood of showing that Shadle discloses neutralizing the eluate by addition of a buffer to raise the pH to 5.5. *See* Ex. 1003, 21:15–19 ("Immediately 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"). Likewise, for the reasons set forth above, and solely for purposes of this decision, we determine that Petitioner has demonstrated a reasonable likelihood of establishing that the molarity of the eluate taught by Shadle is 100 mM or less.

Moreover, based on the current record, and the particular facts and circumstances of this case, we discern no meaningful difference between the conditions sufficient for particle formation set forth in claims 1 and 13 and the specification of the '815 patent on the one hand, and the conditions disclosed by Shadle in conjunction with the eluate neutralization step on the

other. In particular, we observe that step (2) of 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" (Ex. 1001, 12:45–47 (emphasis added)), and claim 13 similarly recites "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 14:5–8 (emphasis added)). The specification likewise states that "[a]ccording to the present invention, *the solution neutralized to a neutral pH level in the above stage, 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 (emphasis added); *see also id.* at 1:66–2:3 ("[T]he sample is 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."). On the current record, we discern no meaningful difference between the conditions set forth in the '815 patent, and Shadle's disclosure of neutralization of the eluate to pH 5.5 with Tris base (Ex. 1003, 21:15–19).

We further observe that the disclosures of Scopes that "isoelectric precipitates can be formed in a tissue extract by lowering the pH to between 6.0 and 5.0" (Ex. 1009, 28), and that "[m]ost isoelectric precipitates are aggregates of many different proteins and may include particulate fragments and protein-nucleic acid complexes" (*id.* at 29) are consistent with Dr. Przybycien's testimony that an ordinarily skilled artisan would have understood from Scopes "that proteins will aggregate by isoelectric

precipitation under the conditions recited in the claims of the ’815 patent” (Ex. 1002 ¶ 101).

Accordingly, for the limited purposes of this decision, in view of the record before us, we credit Dr. Przybycien’s testimony, and conclude that Petitioner has established a reasonable likelihood of showing that Shadle discloses step (2) of claims 1 and 13.

Lastly, Patent Owner contends “[e]ven if Example IA of Shadle inherently disclosed the formation of particles—and it does not—Petitioner fails to explain how Shadle discloses, explicitly or inherently, that (1) those particles were removed; and (2) removing those particles removed contaminant DNA.” Prelim. Resp. 29. Patent Owner asserts that exemplification of “using a 0.2 μm or a 0.22 μm cellulose acetate filter to remove contaminant DNA from the neutralized solutions of hPM-1 antibody, anti-PTHrP antibody, anti-HM1.24 antibody, erythropoietin, and G-CSF *involved in those examples*” does not support Petitioner’s assertion that the filtration steps disclosed by Shadle would necessarily remove particles comprising contaminant DNA “while still allowing the purified protein or antibody to pass through.” *Id.* at 29. Patent Owner likewise argues that Dr. Przybycien’s testimony that a 0.1 μm filter would necessarily remove contaminant DNA from the neutralized eluate described by Shadle is conclusory, and contends that the Petition does not address the size of the particles purportedly formed in Shadle, including whether they would be the same size as those disclosed in the ’815 patent, or whether such particles would include contaminant DNA. *Id.* at 30.

Patent Owner further asserts that Petitioner does not reconcile Shadle's description of the filtration step that Petitioner contends removes contaminant DNA as relating to viral inactivation and preparation for cation exchange chromatography with Shadle's subsequent discussion of hydrophobic interaction chromatography as removing "host DNA" (Ex. 1003, 18:18–19). *Id.*at 30–31. Patent Owner also argues that Petitioner's reliance on Martin as indicating that an ordinarily skilled artisan would have recognized that Shadle's filtration step necessarily would have removed contaminant DNA-containing particles is misplaced, because Martin merely states that "[i]n *most* cases, a 0.2-μm-rate sterilizing grade membrane filter is employed as the fluid filter." *Id.* at 31 (quoting Ex. 1010, 30). Similarly, Patent Owner asserts that the '815 patent specification identifies "a 1.0–0.2 μm Cellulose Acetate Filter System (Corning) or TFF" as an exemplary filter (Ex. 1001, 6:3–7), and not one that would necessarily remove the particles of Shadle. Prelim. Resp. 31.

Patent Owner also reiterates its argument, described above in the discussion of step (2), that "Petitioner does not explain why any formed particles in Example IA would necessarily comprise contaminant DNA." Prelim. Resp. 32. In addition to its previously addressed arguments concerning the insufficiency of Petitioner's reliance on Scopes and the '815 patent as supporting its contention that Shadle necessarily discloses contaminant DNA-containing particles, Patent Owner asserts that Petitioner fails to explain how Shadle itself discloses the formation and removal of particles including contaminant DNA. *Id.* at 32–33. Patent Owner also reasserts its contention that the Petition fails to explain why hydrophobic

interaction chromatography, which is identified by Shadle as removing host DNA, would be performed if Shadle's filtration step removes contaminant DNA. *Id.* at 33–34. Patent Owner also reiterates its contention that Shadle does not anticipate claim 1 because it discloses precisely the additional chromatography steps that the '815 patent specification criticizes. *Id.* at 34.

In view of the current record, we do not find Patent Owner's position persuasive. Based on the record as it exists before us, as well as the particular facts and circumstances of this case, we discern no meaningful difference between the conditions set forth in the claims and specification of the '815 patent, and the eluate filtration step disclosed by Shadle. Shadle teaches the use of a "0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200" for eluate filtration. Ex. 1003, 21:18–19. Step (3) of claim 1 of the '815 patent recites "removing the particles *thereby to remove contaminant DNA*" (Ex. 1001, 12:48–49 (emphasis added)), indicating that removal of the particles formed upon eluate pH adjustment in accordance with step (2) necessarily removes contaminant DNA. Claim 13 likewise recites "filtering the resulting sample from step (2) *to remove particles containing contaminant DNA*" (*id.* at 14:9–10 (emphasis added)), indicating that filtration achieves removal of contaminant DNA-containing particles.

In addition, the '815 patent specification expressly identifies filtration of the neutralized eluate through 1.0–0.2 μm filters as sufficient to remove contaminant DNA:

> According to the present invention, the solution neutralized to a neutral pH level in the above stage, 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. Examples of a filter available for filtration include, but are not limited to, a 1.0–0.2 µm Cellulose Acetate Filter System (Corning) or TFF.

Ex. 1001, 6:1–7. The disclosures of Martin on which Petitioner and Dr. Przybycien rely are consistent with these teachings of the '815 patent. Pet. 47; Ex. 1002 ¶ 105; Ex. 1010, 27, 30.

In view of the above determination, we do not find it persuasive, for purposes of this decision, that Shadle does not expressly disclose the removal of contaminant DNA. Similarly, the fact that Shadle describes a method for viral inactivation subsequent to cation exchange chromatography, and identifies hydrophobic interaction chromatography as removing "additional protein and non-protein impurities, most notably residual Protein A, IgG aggregates, and host DNA" (Ex. 1003, 18:18–19), on this record, does not overcome Petitioner's demonstration of a reasonable likelihood of showing that the neutralization and filtration steps of Shadle would necessarily remove contaminant DNA. In this respect, we note that Patent Owner does not contend, at this stage of the proceeding, that claims 1 and 13 specify the extent to which contaminant DNA must be removed through the performance of step (3) (*See* Ex. 1001, 12:48–49, 14:9–10), or preclude the performance further chromatography steps (*see id.* 12:38–40 ("[a] method . . . , which comprises the following steps"), 13:11–12 ("[a] method . . . , which comprises").

With regard to Shadle's hydrophobic interaction chromatography step, in particular, we observe that the '815 patent specification distinguishes

between "host DNA"—*i.e.*, the DNA Shadle purports to remove through hydrophobic interaction chromatography (Ex. 1003, 18:18–19)—and "contaminant DNA associated with viral contamination" (Ex. 1001, 1:20–21), further suggesting that the removal of "host DNA" by hydrophobic interaction chromatography is immaterial to the instant analysis.

In sum, based on the current record, Petitioner has demonstrated a reasonable likelihood of prevailing at trial in showing that at least claims 1 and 13 of the '815 patent are anticipated by Shadle. Having decided that Shadle supports a reasonable likelihood that at least two of the challenged claims are unpatentable, we exercise our discretion under 37 C.F.R. § 42.108 to have the review proceed on all of the claims on which Shadle is the basis for anticipation. In doing so, we seek to achieve finality of review at the Board and avoid parallel or serial review in the district court, at least with respect to the petitioner in this proceeding and the Fast reference. *See Synopsys, Inc. v. Mentor Graphics Corp.*, 814 F.3d 1309, 1316 (Fed. Cir. 2016) (stating that "[t]he validity of claims for which the Board did not institute *inter partes* review can still be litigated in district court").

E. Obviousness Ground of Unpatentability 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. 44. We are "cognizant of the ramifications of partial institution where the grounds are in different statutory classes." *Amendments to the Rules of Practice for Trials Before the Patent Trial and*

Appeal Board, 80 Fed. Reg. 50720, 50739 (Aug. 20, 2015) (Response to Comment 12). Concerns of fairness and efficiency in this case, therefore, persuade us to institute on the ground of anticipation by Shadle, as well as on the ground of obviousness over Shadle. *See HP Inc. v. MPHJ Tech. Inv., LLC*, 817 F.3d 1339, 1347 (Fed. Cir. 2016) (holding that petitioner was "not estopped from raising the obviousness of claim 13 in a subsequent court or Board proceeding" where Board instituted only on grounds of anticipation of claim 13). Thus, we exercise our discretion to institute *inter partes* review on Petitioner's second ground, namely, that claims 1–7, 12, and 13 would have been obvious over Shadle.

III. CONCLUSION

After considering the evidence and arguments of record, we conclude that Petitioner has demonstrated a reasonable likelihood of succeeding in challenging the patentability of at least independent claim 1 of the '815 patent. And, in keeping with our mission of "the just, speedy, and inexpensive resolution" of patentability disputes, we exercise our discretion to institute *inter partes* review of all of the claims and grounds specified in the Petition. 37 C.F.R. §§ 42.1(b), 42.108.

At this stage in the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is instituted as to claims 1–7, 12, and 13 of the '815 patent on the following grounds of unpatentability:

A. Claims 1–7, 12, and 13 under 35 U.S.C. § 102(b) as anticipated by Shadle;

B. Claims 1–7, 12, and 13 under 35 U.S.C. § 103(a) as obvious over Shadle; and

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that 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 commencing on the entry date of this Decision.

PETITIONERS:

Jovial Wong
WINSTON & STRAWN LLP
jwong@winston.com

PATENT OWNER:

J. Steven Baughman
Megan Raymond
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
sbaughman@paulweiss.com
mraymond@paulweiss.com