UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

CHUGAI PHARMACEUTICAL CO., LTD.,
Patent Owner.

Inter Partes Review No. IPR2017-01358
Patent No. 7,927,815 B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

This trial turns on whether the '815 patent's claimed method for removing contaminant DNA is patentably distinct from Shadle—a reference never substantively considered by the Examiner before the '815 patent issued, and which the European Patent Office ("EPO") adopted as novelty-destroying prior art during prosecution of foreign counterparts. This Board instituted review on grounds of anticipation and obviousness after "determin[ing] that Petitioner 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." Dec. Inst. 25–26. Patent Owner's Response does not support a different result.

As an initial matter, Patent Owner admits that its Response is admittedly premised on a host of narrow claim constructions. Resp. 11–22. Regardless of whether these constructions would apply in an infringement action, they are not the "broadest reasonable construction" that governs these proceedings. 37 C.F.R. §42.100(b). When the claims are properly construed under that standard, Patent Owner cannot avoid anticipation. Indeed, Patent Owner does not dispute the calculations of Petitioner's expert, Dr. Przybycien, which show that all of the claimed steps are at least inherently disclosed by Shadle under their proper constructions.

Unable to challenge those calculations, Patent Owner and its experts instead apply a legal standard that contradicts binding precedent. According to Patent Owner, inherency requires proof that any other result is "*impossible*." Resp. 34. But the Federal Circuit has rejected that standard: Petitioner does "not need to prove that it was impossible" to practice Shadle without reading on the claims, "but merely that…the natural result flowing from the operation as taught in the prior art would result in the claimed" invention. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (quotation omitted). When properly applied, the legal standard is easily met here: As Dr. Przybycien's unrebutted testimony shows, the natural result flowing from Shadle's method is the same result claimed in the '815 patent. EX1036 ¶17. Shadle thus anticipates the claims.

At a minimum, the claims would have been obvious. While arguing that Shadle does not "*always*" result in the claimed invention, Patent Owner does not dispute that it "*may*." Resp. 3. Thus, starting from Shadle, a POSA would have arrived at the claimed invention by applying no more than conventional methods and ordinary skill. EX1036 ¶70. No secondary considerations suggest otherwise. While Patent Owner touts the '815 patent as "revolutionary" (Resp. 1), its experts could not cite a single commercial use of the claimed invention. Indeed, they admitted that column chromatography—the same process that the '815 patent allegedly made obsolete—continues to dominate the industry.

In sum, the Board should find the challenged claims anticipated and obvious.

II. ARGUMENT

A. Ground I: Shadle anticipates the challenged claims.

1. Even if the preamble were limiting, and even under Patent Owner's erroneous construction, Shadle would disclose it.

Starting with the independent claims (1 and 13), Patent Owner construes the preamble narrowly as "[a] method comprising the listed steps, wherein in the practice of the listed steps contaminant DNA is removed from a sample containing a physiologically active protein." Resp. 12. Patent Owner's position on the scope of the preamble is unclear, but even accepting Patent Owner's proposed construction, Shadle discloses it.

Throughout its argument that Shadle does not disclose the preamble, Patent Owner characterizes "the heart of the claimed invention as facilitating *elimination* of the[] additional, post-claim steps in Shadle that Petitioner says accomplish DNA removal—the same well-known additional 'complicated chromatographic processes' of the prior art criticized by '815." Resp. 25. But Patent Owner never explains how this alleged characterization is relevant. To the extent Patent Owner

contends the preamble necessitates exclusion of "additional, post-claim steps" (*id*.), that is not the preamble's broadest reasonable interpretation.[1]

Patent Owner does not dispute that the "claims are 'comprising' claims," which means that "'other elements may be added and still form a construct within the scope of the claim.'" Dec. Inst. 26 (quoting *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997)). The same is true for Patent Owner's proposed construction of the preamble, which also uses the term "comprising." Resp. 12. Thus, whether the preamble is construed as limiting or not, it does not exclude "additional chromatography steps beyond those expressly recited in [the] claims." Dec. Inst. 25–26. Indeed, Patent Owner admits that "a practitioner performing the Challenged Claims might *choose* to employ further chromatography." Resp. 13 n.8. Patent Owner's expert agrees. EX1034, 44:13–24 (Dr. Cramer) ("Q. So we look at claim one, would a POSA understand claim one to exclude the use of further purification by column chromatography after step three? A. No.").

To be clear, the recited steps 1–3 require and result in the removal of contaminant DNA. *Id*.; EX1036 ¶6. As the Petition explained (and as explained

[1] Nevertheless, by advocating a narrow construction in this proceeding, Patent Owner is estopped from asserting a broader claim scope in any future litigation. *See Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1361 (Fed. Cir. 2017).

below), the same steps of Shadle's process also necessarily result in removing contaminant DNA. Thus, even under Patent Owner's construction, Shadle discloses the preamble's purported requirement of removing contaminant DNA. EX1036 ¶¶18-21. While Shadle also discloses additional chromatography steps, Patent Owner's construction does not exclude them.

Rather than dispute this, Patent Owner contends that the Petition did "not assert [that] Shadle *inherently* discloses the preambles." Resp. 25 n.12. Patent Owner is mistaken. To the extent the preamble requires that "step 3's removing/filtering…actually removes contaminant DNA," (*id*. at 13), Petitioner showed that Shadle "inherently discloses" just that. Pet. 48 ("[Shadle] either expressly *or at least inherently* discloses the final step 3 of the claimed purification process of removing particles to thereby remove contaminant DNA." (emphasis added)).[2] Shadle thus discloses the preamble of claims 1 and 13 even under Patent Owner's construction.

[2] The Petition argued this in the context of step 3 (rather than the preamble), but this makes no difference. Patent Owner's construction of the preamble could just as easily have been a construction of step 3, and Patent Owner could (and did) respond to Petitioner's argument. In any event, the Board's rules do not require Petitioner to anticipate Patent Owner's construction of the preamble. *See Idemitsu Kosan Co. v.*

2. Shadle expressly or inherently discloses each step of the claimed process.

a. Step 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 100mM or less"

Patent Owner and its expert, Dr. Cramer, do not dispute that Shadle discloses converting a sample to an acidic-aqueous solution. *See* Resp. 26–30; EX2015 ¶¶53–61; EX1034, 70:22–71:1; EX1036 ¶23. Nor do they dispute Dr. Przybycien's calculations that, starting with any of four conventional buffer preparations, Shadle meets the claimed conductivity and molarity limitations. *See* Resp. 26–30; EX2015 ¶¶53–61; EX1034, 102:1–23. Instead, unable to challenge the accuracy of Dr. Przybycien's calculations, Patent Owner argues that (i) the calculations should be excluded as improper supplemental information and (ii) Dr. Przybycien should have considered the possibility of a fifth buffer preparation in his calculations, even though a POSA would not have used that buffer preparation to practice Shadle's method. *Id.*

SFC Co., 870 F.3d 1376, 1381 (Fed. Cir. 2017) (patent owners' counterarguments need not be "preemptively addressed by the petition").

i. Dr. Przybycien's updated calculations are admissible and show that the "total molarity" of the solution in step 1 is below 100mM.

Dr. Przybycien's updated calculations (EX1026; EX1027)—which show that the "total molarity" of the solution in step 1 is below 100mM—are admissible.[3] Patent Owner's contrary argument presumes that a petition must contain all evidence that will be raised at trial, and that any additional evidence may be submitted only with "permission from the Board." Resp. 29, n.14. Not so.

The purpose of an instituted trial is to develop the factual record within the contours established by the institution decision. Thus, "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings and, as long as the opposing party is given notice of the evidence and an opportunity to respond to it, the introduction of such evidence is perfectly permissible." *Genzyme Therapeutic Prod. Ltd. v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1366 (Fed. Cir. 2016). That is what happened here.

[3] Dr. Pryzbycien prepared EX1027 in response to Patent Owner's arguments in its Response and during his deposition. EX1036 ¶¶8-10. As an exhibit prepared to support arguments in Petitioner's Reply that "respond to arguments raised in the…patent owner response," EX1027 is admissible. 37 C.F.R. §42.23.

The Petition construed the term "molarity" in the challenged claims to mean "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. Dr. Przybycien's opening declaration thus calculated molarity under that construction. In its Institution Decision, the Board construed "the term 'molarity'" differently, as "the total concentration of solute present in the solution, rather than the concentration of one particular solute." Dec. Inst. 10-11. Thus, 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. EX1026; EX1036 ¶¶10, 39.

Patent Owner's challenge to Dr. Przybycien's updated calculations (Resp. 29 n.14) is "a back-door attempt to challenge whether the Board properly instituted review." *Valmont Indus., Inc. v. Lindsay Corp.*, 2018 WL 2130455, at *4 (Fed. Cir. May 9, 2018). If anything, Dr. Przybycien's updated calculations were provided *early*, not late: "[A] petitioner may submit additional evidence in the reply in response to the patent owner response," and thus Petitioner could have (and has) served Dr. Przybycien's updated calculations with this Reply. *Id.* at *3. In an abundance of caution, Petitioner also provided them to Patent Owner three months *before* this Reply—indeed, before Dr. Przybycien's first deposition, and a full month before Patent Owner's Response. Moreover, Patent Owner will get a second

opportunity to examine Dr. Przybycien following this Reply. In short, Patent Owner has had every opportunity to respond to Dr. Przybycien's updated calculations, and has suffered no prejudice by receiving them early. *See id.* at *4 (finding no prejudice where patent owner "cross-examined [the expert], filed observations with the Board, and addressed the evidence at oral argument before the Board").

On the merits, Patent Owner has no response to Dr. Przybycien's updated calculations. They track the Board's claim construction and indisputably show that for each of the four conventional ways of making Shadle's citrate buffer, total molarity remains below 100mM. EX1036 ¶¶39–40; EX1026 1–2; EX1027 1–2. Neither Patent Owner nor its experts contest this. EX1036 ¶39; EX1034 102:1–4 ("Q. Okay. Again, you don't dispute that the four ways for making citrate buffer are among those that a POSA would have considered, right? A. Correct."), 149:8–12 ("Q. You don't dispute that under the four ways that Dr. Przybycien made, proposes making the citrate buffer that each of those total molarities would be under a hundred millimolars, right? A. Correct."); EX1034, 149:1–17.

ii. A POSA would not have used 25mM trisodium citrate and HCl to prepare the citrate buffer, and thus Dr. Przybycien's testing confirms that Shadle's conductivity inherently remains below 300 mS/m.

Instead of disputing that the four conventional methods for preparing Shadle's citrate buffer meet the conductivity limitation, Patent Owner proposes a fifth,

purportedly "known method[]" and says Petitioner must prove this fifth method "*could never have been used*." Resp. 27. But that is not the law. The law looks to the "normal and usual" way a POSA would practice the prior art, and the "normal and usual" practice of a POSA would not have used Patent Owner's fifth method to practice Shadle. *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275–76 (Fed. Cir. 2010); EX1036 ¶26.

When evaluating inherency, the prior art must be understood according to its "normal and usual" practice. *King Pharm.*, 616 F.3d at 1275-76; *accord Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1383 (Fed. Cir. 2005) ("[T]he discovery of a new property of the Pereira composition, when *used in accordance with its normal application*, is not a sufficient basis for avoiding anticipation.") (emphasis added)); *In re King*, 801 F.2d 1324, 1326–27 (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.'") (citation omitted; emphasis added)).

Thus, inherency does not require proof that another result is "impossible." *See SmithKline Beecham*, 403 F.3d at 1343. A result can be inherent even if it theoretically could be avoided. *See Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342,

1349–50 (Fed. Cir. 1999) (finding inherency even though inherent result could be avoided by taking "extraordinary measures"). In assuming that inherency requires proof that another result is "impossible," Patent Owner and its experts thus apply an erroneous legal standard. Resp. 34.

Patent Owner's cited cases do not hold otherwise. They simply say that "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient [for inherency]." *E.g.*, Resp. 23, 27, 35. But Petitioner has not just shown that a buffer "may" have met the 300 mS/m conductivity limitation (*id.*)—Petitioner showed that *all four* conventional buffer preparations necessarily do. EX1036 ¶25; EX1034, 80:15–19, 81:7–17, 84:5–85:6, 102:8–23. Nor does Patent Owner even address the testing results submitted to the EPO, which similarly measured conductivity at less than 300 mS/m. EX1011, 39; EX1036 ¶25.

Indeed, the prior art consistently shows that citrate buffers were prepared according to Dr. Przybycien's four conventional methods. EX1036 ¶29; EX1028, 12; EX1037, 4, EX1015, 8; EX1029, 8; EX1038, 24; EX1014, 172; EX1040, 16; EX1041, 5. Dr. Cramer's own publications do too. EX1036 ¶30; EX1030, 3; EX1031, 3; EX1032, 3; EX1034, 133:6–12, 134:7–15, 135:25–136:5. Tellingly, none of those publications teach that a 25mM citrate buffer, pH 3.5 should be prepared using Patent Owner's fifth preparation (25mM trisodium citrate and HCl). *See id.* Nor did Patent Owner even suggest the possibility of that preparation when

distinguishing Shadle in the EPO proceedings, where test results similarly confirmed that the conductivity of Shadle's buffer is below 300mS/m. EX1011, 39.

Consistent with the prior art, a POSA practicing Shadle would not have used Patent Owner's fifth preparation (25mM trisodium citrate and HCl) to prepare Shadle's ProSep A citrate buffer. EX1036 ¶¶27–28, 31–35. Even Dr. Cramer refused to opine that a POSA "would" have used it, insisting only that a POSA "could." EX1034 104:7–105:2. Dr. Cramer's reluctance is unsurprising. As Dr. Przybycien shows, the starting pH for trisodium citrate is far higher than the target pH for Shadle's buffer, and would require an impractical excess of hydrochloric acid to titrate the pH to Shadle's target of 3.5. EX1036 ¶27; EX1034 110:7–18 (admitting "the pH is high and that you need more acid to bring it down to pH 3.5"). A POSA would instead use a starting solution that was closer in pH to the desired 3.5 target—e.g., monosodium citrate, as Dr. Przybycien proposed. EX1036 ¶27.

A POSA also would have understood from the cation exchange chromatography step in Examples 1 and 1A of Shadle that the conductivity of the citrate buffer solution should be kept as low as possible. EX1036 ¶¶31–34; EX1033, 12-13; EX1046 532; EX1045 4–5. This also would have directed a POSA to prepare the Shadle citrate buffer according to one of the four conventional preparations—not with 25mM trisodium citrate and HCl. EX1036 ¶35.

Dr. Cramer cites only a single reference that allegedly taught preparing a citrate buffer as he proposed. Resp. 28 (citing Roth, EX2005). But as Dr. Przybycien explains, a POSA practicing Shadle would not rely on Roth. EX1036 ¶28. Roth concerned a field of study and application distinct from the preparative Protein A chromatography of Shadle and the '815 patent. *Id.* ¶28. Roth is therefore not an analogous prior art reference. *Cf. In re Kahn,* 441 F.3d 977, 986–87 (Fed. Cir. 2006). And using Roth's citrate buffer, which included other excipients, would denature the very antibodies Shadle sought to purify. EX1036 ¶28.

Dr. Przybycien's unrebutted calculations thus confirms that Shadle's buffer inherently satisfies the conductivity and molarity requirements of step 1.

b. <u>Step 2</u>: "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 100mM or less"

As for step two, Patent Owner does not dispute that Shadle discloses "adjusting the pH of the resulting sample from step (1) to pH 4 to 8." EX1036 ¶41. Instead, Patent Owner (i) repeats the same mistakes in disputing the molarity of the adjusted sample, and (ii) ignores its own admissions in the '815 patent that particles form under the claimed conditions. Neither argument has merit.

i. Shadle's adjusted sample inherently has a molarity of 100mM or less.

Patent Owner does not dispute Dr. Przybycien's updated calculations on the molarity of the adjusted sample, which show that the total molarity is necessarily below 100mM. EX1036 ¶43; EX1026 2–3; EX1027 2–3. Nor does Patent Owner acknowledge its previous admission to the EPO that the adjusted sample of Shadle has a calculated total molarity of about 47.2mM—well below the claimed 100mM limit. EX1006 28; EX1036 ¶42 n.2. Instead, Patent Owner again contends that a POSA could use its fifth preparation (25mM trisodium citrate and HCl), and that it would yield a molarity higher than 100mM. Resp. 32–33. This argument lacks merit for the same reasons discussed above for Step 1. *Supra* II.A.2.a.i.

Patent Owner's only other response is to speculate that the adjusted sample would contain so much residual wash buffer that its molarity would exceed 100mM. But as Dr. Przybycien shows, Shadle's adjusted sample would not contain the large amounts of wash buffer that Patent Owner presumes. EX1036 ¶52. Indeed, Shadle does not describe *any* wash buffer collected in the eluate. Instead, it describes the eluate as consisting of concentrated antibody alone. *Id*. ¶¶47–48. Moreover, a POSA would take steps to minimize the amount of wash buffer in the collected eluate, which a POSA would have viewed as undesirable contamination. *Id.* ¶46.

Related EPO proceedings for the EP ’589 and EP ’149 foreign counterpart patents confirm that Patent Owner’s wash buffer argument, which the EPO rejected, lacks merit. *Id.* ¶48; EX1006 6–7, 38–39; EX1011 7–8, 34–35; EX1043 6, 9–10, 15, 19, 30, 34; EX1044 9, 14–15.[4]

Even if some wash buffer could contaminate the eluate—contamination a POSA would avoid (EX1036 ¶46)—Patent Owner exaggerates its impact. Any contribution of residual wash buffer to the molarity would be minimal, and would not increase molarity above 100mM. *Id.* ¶¶49, 52. As Dr. Przybycien explains, Dr. Cramer’s speculation to the contrary is improperly based on either his fifth buffer preparation theory, or an unsupported presumption that there would be at least 2.1L of wash buffer contamination. *Id*. ¶¶50-51. In response, Dr. Przybycien has prepared detailed calculations to demonstrate that any wash buffer contamination in the collected eluate would at most be 0.582 L. *Id.* ¶¶52–56; EX1047 5–6. Even that theoretical contamination would not increase the molarity of the adjusted sample

[4] The different proceeding cited by Patent Owner (Resp. 35) is for an unrelated European application that claims priority to a different Japanese application than do the ’815 patent, EP ’589, and EP ’149, and is thus irrelevant. EX1036 ¶48; *compare* EX1042 1 *with* EX1001 1; EX1004 1; EX1019 1.

above 100mM. EX1036 ¶52 (explaining preparation no. 1 = 77.93 mM, preparation no. 2 = 65.40 mM, and preparations nos. 3 and 4 = 60.03 mM).

ii. Shadle's method inherently produces particles.

Recognizing that particles will form whenever the claimed conditions are met, Patent Owner again resorts to claim construction to avoid anticipation. According to Patent Owner, "to form particles" means "becomes clouded." Resp. 16. Again, however, Patent Owner's construction is not the broadest reasonable interpretation. Under the proper standard, Shadle discloses the claimed particle formation.

First, the broadest reasonable interpretation of "to form particles" does not require the solution to become "clouded," because a POSA would not equate forming particles with clouding. EX1036 ¶12. To be sure, a clouded solution *might* indicate that particles have formed, but particles can form in a non-clouded solution too. *Id.* ¶¶11–12; *cf.* EX1034 97:10–98:18 (admitting that clouding can occur without particle formation); EX1035 58:20–59:17 (same). This is especially true when only a few particles form in solution, which a POSA would understand to be covered by either the plain or broadest reasonable meaning of "to form particles." EX1036 ¶13.

If the claims required some greater degree of particle formation, a POSA would expect that requirement to be expressly recited, either as a concentration of particles or an appearance of cloudiness. *Id.* ¶12. Neither requirement is in the

claims. And since the '815 patent does not describe how "cloudy" the sample must become (or how to measure its "cloudiness"), Patent Owner's construction would render the claims indefinite. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003) ("This reading of the claim is indefinite…. This court therefore rejects this proposed construction.").

The actual language of the claims simply says "to form particles," which a POSA would not equate with clouding. EX1036 ¶12. Patent Owner's expert, Dr. Koths, admits this. EX1035 53:24–54:4 ("Q. If a POSA were to see the phrase 'to form particles,' would that POSA understand that phrase to mean to produce particles containing DNA to cause the solution to become clouded? A. No.").[5]

Second, particles necessarily form in Shadle because Shadle discloses the same conditions (*i.e.*, pH, molarity, conductivity) that the '815 patent admits are sufficient to form particles. EX1036 ¶57. Patent Owner condemns this logic as

[5] Even if clouding were required, Shadle discloses it. Particles form in Shadle, so if Patent Owner is right that particles cause clouding, there is clouding in Shadle. That Shadle "says nothing of clouding" misses the point. Resp. 37. Anticipation "does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

"hindsight" (Resp. 39), but hindsight is irrelevant to anticipation. Indeed, the Federal Circuit has repeatedly relied on a challenged patent's disclosure to establish the inherency of a property. *See In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("the [inventors'] application itself instructs that [the claimed] … property [is] necessarily present"); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (patentee's own "specification…confirms that the claimed [stability] is an inherent property").

In the two cases cited by Patent Owner (Resp. 39), either the challenger made an unsupported "assumption" about inherency, *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1378 (Fed. Cir. 2002), or the invalidity ground was obviousness, not anticipation, *Zoltek Corp. v. United States*, 815 F.3d 1302, 1313 (Fed. Cir. 2016). Neither case applies here.

The fact that Shadle's example involved an antibody (RSHZ-19) "not among the examples the '815 [patent] discusses" is immaterial. Resp. 41. The claims of the '815 patent are not limited to its examples, and if enabled to their full scope, presumptively work for all antibodies. EX1036 ¶59. Nothing in the '815 patent suggests otherwise. And Patent Owner's experts admit that a POSA would understand Shadle's RSHZ-19 to fall within the category of antibodies covered by the claims. EX1034, 19:1–8; 20:5–13, 63:1–5; EX1035, 22:10–24, 72:22–73:9.

Equally misguided is Patent Owner's reliance on unclaimed "parameters" that supposedly affect when particles will form. Resp. 3 n.4, 41. While "the '[815]

patent's written description discloses [some of the alleged] conditions" for particle formation, "its claims only recite [molarity and conductivity limits]. It would be improper to limit the broad terms used in the ['815] patent's claims to the specific [] conditions disclosed in the written description." *King Pharm.*, 616 F.3d at 1275. "To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *Id*. at 1276. Thus, "to the extent such a method [forms particles], the identical prior art method does as well." *Id*.; EX1036 ¶60.

c. Step 3: "removing the particles thereby to remove contaminant DNA in the sample"

The '815 patent admits that when particles form, they contain contaminant DNA that "may be removed by filtration." EX1001, 6:1–18; EX1036 ¶63. Patent Owner complains that Shadle does not meet this limitation because it does not speak to the "size of [the] putative particles," or "why they would be understood to comprise contaminant DNA." Resp. 47–48. These arguments lack merit.

As Patent Owner's experts admit, the claims of the '815 patent do not require particles to reach a certain size—only that they be removed. EX1034, 37:6–9; EX1035, 38:23–39:7, 39:19–40:4; 40:15–20, 40:22–41:5. Patent Owner suggests that Shadle's filters might not remove the particles. Resp. 48. But Shadle's filters are the same (or even finer than) those disclosed in the '815 patent—and thus would necessarily remove the particles that are formed. EX1036 ¶¶62-63; EX1003, 21. As

Patent Owners' experts admit, Shadle's filters will remove particles. EX1034 75:16–76:23; 77:13–24; EX1035, 30:23–31:12, 32:5–10.

In turn, those particles admittedly contain contaminant DNA: The '815 specification itself teaches that particles formed during the claimed process—the same process that Shadle teaches—contain contaminant DNA. EX1036 ¶64; EX1001 6:1–18 ("[E]ach of these particles is a conjugate formed between physiologically active protein and DNA."). Shadle thus discloses removing particles with contaminant DNA. In sum, Shadle anticipates claims 1 and 13.

3. The dependent claims are not separately patentable.

a. Claim 2: The method according to claim 1, wherein the acidic aqueous solution of low conductivity has a molarity of 50mM or less.

Claim 2 merely lowers the molarity limit of claim 1 to 50mM, and is also anticipated. As discussed above, the acidic-aqueous solution of step 1 inherently has a total molarity of 50mM or less. EX1036 ¶66; EX1026 1–2; EX1027 1–2. A POSA would not have prepared the solution using Patent Owner's alleged fifth method, which is not the "normal and usual" practice of Shadle. *Supra* II.A.2.a.ii.

b. Claim 3: The method according to claim 1, wherein the acidic aqueous solution of low conductivity has an ionic strength of 0.2 or less.

Patent Owner does not dispute Dr. Przybycien's calculations showing that Shadle's buffer inherently meets claim 3's ionic strength limitation. EX1036 ¶67;

EX1026, 4–8; EX1027, 4–8. Nor does Patent Owner dispute the third-party observations in the related EPO proceeding that "the elution buffer of [Shadle] exhibits an ionic strength of 0.01959 M." EX1011, 52. There is no dispute that Shadle discloses this limitation, and thus claim 3 is anticipated.

c. Claim 4: The method according to claim 1, wherein the acidic aqueous solution is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid, and acetic acid.

As to claim 4, Patent Owner asserts that the term "consisting of" in the recited Markush group excludes components other than citric acid. Resp. 50. But "consisting of" only limits the selection from the Markush group choices (here, acidic-aqueous solutions of HCl, citric acid, and acetic acid)—it does not exclude components outside that group of possible acid solutions, as Patent Owner's own case makes clear. *See Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016) ("Thus, if a patent claim recites '*a member* selected from the group consisting of A, B, and C,' *the* '*member*' is presumed to be closed to alternative ingredients D, E, and F." (emphasis added)).

Here, Shadle's buffer is "25mM citrate, pH 3.5," which a POSA would understand would be made using either citric acid or hydrochloric acid as the only acidic aqueous solution in the buffer. EX1036 ¶68. It makes no sense to say that

other non-acid solution components—e.g., the antibody itself—removes Shadle's citrate buffer from the scope of the claims. *Id.*

d. Claim 5: The method according to claim 1, wherein the contaminant DNA is present at a DNA concentration of 22.5pg/ml or less in the treated sample containing a physiologically active protein.

Patent Owner does not dispute that practicing Shadle yields a sample with "a DNA concentration of 22.5 pg/ml or less." Instead, Patent Owner relies on a narrow claim construction (based on the preamble and the term "treated sample") to require that the claimed purity (≤22.5pg/ml) results from the recited steps, not any additional steps. Yet the plain language of the claim belies that construction: Independent claim 1, from which claim 5 depends, uses open "comprising" language, and thus permits "additional chromatography steps beyond those expressly recited." Inst. Dec. 26; *see* EX1036 ¶¶15, 69; *supra* II.A.1.

Moreover, the plain meaning of "treated sample" is simply a "sample" that has been "treated," and thus contains less DNA contamination than it started with before the treatment. EX1036 ¶15. If claim 5 were limited in the manner Patent Owner suggests, a POSA would have expected the claim to expressly require as much. *Id.* ¶16. And if Patent Owner wished to add that limitation to claim 5, it should have moved to amend it. *See* 37 C.F.R. §42.121.

In any event, even under Patent Owner's construction, whenever the claimed steps are performed, the claimed level of purity will inherently be met. *See* EX1036 ¶43 n.5. Claim 5 is thus anticipated.

e. Claim 12: The method according to claim 1, wherein the particles are removed by filtration through a filter.

Patent Owner's only response to claim 12 is that Petitioner "failed to establish that the filtration process achieves the removal of particles." Resp. 52. But as explained above, the filters used in Shadle—which are the same as or finer than the filters in the '815 patent—necessarily remove particles. EX1036 ¶62.

Shadle thus anticipates every challenged claim.

B. Ground II: At a minimum, the challenged claims would have been obvious.

1. All claims are prima facie obvious over Shadle.

As explained in the Petition, the challenged claims are at least obvious over Shadle. Pet. 55–59. Even if any limitation were not disclosed by Shadle at least inherently, it would have been obvious to a POSA. Patent Owner's attorney arguments to the contrary lack merit.

First, Patent Owner says Petitioner did not explain "how Shadle would be modified" (Resp. 53), but that misses the point: Shadle requires no modification. Shadle either anticipates the claims (because practicing Shadle necessarily practices the invention) or renders them obvious, because Shadle at least "sometimes, [if] not

always, embodies [the] claimed method [and thus] teaches that aspect of the invention." *Hewlett-Packard Co. v. Mustek Sys.*, 340 F.3d 1314, 1326 (Fed. Cir. 2003) (internal quotations and citation omitted).

Second, Patent Owner ignores Dr. Przybycien's (unrebutted) testimony that particles inherently form in Shadle, and a POSA would have been motivated to remove any particles containing DNA "to protect the subsequent chromatography columns," with a reasonable expectation that filtration would accomplish that. EX1002 ¶¶ 131–33; EX1010 27 ("Absolute removal of particulate solids from the process stream, including sterile filtration, serves as an essential prefiltration/protection step for downstream chromatography…."). Thus, the challenged claims are prima facie obvious over Shadle.

2. There is no evidence of secondary considerations.

Federal Circuit "precedent requires that the [patentee] submit actual evidence of long-felt need, as opposed to argument." *Kahn*, 441 F.3d at 990. Patent Owner presents no such "actual evidence." *Id.* And its marketing puffery—about a long-felt need and the invention's "surprising and beneficial results" (Resp. 56)—is belied by the invention's failure in the market.

As Dr. Przybycien explains, the industry still relies on platform processes, which include successive chromatography that the '815 patent purportedly eliminated. EX1036 ¶¶71–72; EX1052 2, Fig. 1. Indeed, Patent Owner's own

experts testified that they had never practiced the invention. EX1035 89:21–90:5 ("Q. Okay. Dr. Koths, have you ever practiced the method of Claim 1 that is described in the Chugai patents? A. No."). And despite the fact that they regularly attend conferences and consult in the industry, Patent Owner's experts were not aware of any commercial use of the claimed invention. *See* EX1034 173:23–174:5, 175:1–7 (admitting he was "not aware" of "any commercial process that purifies antibodies by forming and filtering particles according to the Chugai method without further columnar chromatography"); EX1035 90:17–24, 93:12–94:3 (admitting he was "not aware of" "any commercial scale process that purifies an antibody-containing sample by forming and filtering out particles so that there is no further need for purification by column chromatography."). The fact that Patent Owner's experts had never heard of the alleged invention being used before this proceeding confirms that it did not satisfy any long-felt need.

III. CONCLUSION

The Board should find claims 1–7 and 12–13 of the '815 patent unpatentable.

Dated: May 24, 2018

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. §42.24, I certify that the foregoing PETITIONER'S REPLY TO PATENT OWNER RESPONSE contains 5,579 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), I certify that, on May 24, 2018, I caused to be served true and correct copies of the foregoing "PETITIONER'S REPLY TO PATENT OWNER RESPONSE," by electronic mail on the following attorneys:

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