UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

CHUGAI PHARMACEUTICAL CO., LTD.,
Patent Owner.

Case IPR2017-01357
Patent No. 7,332,289 B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

This trial turns on whether the '289 patent's claimed method for removing contaminant DNA is patentably distinct from Shadle, a reference never considered by the Examiner before the '289 patent issued and which the European Patent Office ("EPO") later adopted as novelty-destroying prior art during prosecution of foreign counterparts. This Board instituted review on grounds of anticipation and obviousness after "decid[ing] that Shadle supports a reasonable likelihood that at least one of the challenged claims is unpatentable." Dec. Inst. 35. Patent Owner's Response does not support a different result.

As an initial matter, Patent Owner admits that its the Response is premised on a host of narrow claim constructions. Resp. 12–23. 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. 33. 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 '289 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 ¶¶68–70. No secondary considerations suggest otherwise. While Patent Owner touts the '289 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 '289 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 claim 1, 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 an antibody." Resp. 13. 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 '289." Resp. 26. 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]

[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).

Patent Owner does not dispute that the claim "is a 'comprising' claim," which means that "'other elements may be added and still form a construct within the scope of the claim.'" Dec. Inst. 24 (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. 13. 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. 24. 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 [four]? A. No.").

To be clear, the recited steps 1–4 require and result in the removal of contaminant DNA. *Id*.; EX1036 ¶6. As the Petition explained (and as explained 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. 26 n.13. Patent Owner is mistaken. To the extent the preamble requires that "step 4's removing/filtering … actually removes contaminant DNA," (*id*. at 13), Petitioner showed that Shadle "inherently discloses" just that. Pet. 39–40 ("[Shadle] either expressly *or at least inherently* discloses the final step 4 of the claimed purification process of removing particles to thereby remove contaminant DNA." (emphasis added)).[2] Shadle thus discloses the preamble under Patent Owner's construction.

[2] Petitioner argued this in the context of step 4 (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 4, 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. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017) (patent owners' counterarguments need not be "preemptively addressed by the petition").

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

a. Step 1: "applying the antibody-containing sample to affinity chromatography on Protein A or Protein G"

As the Petition explains, Shadle expressly discloses this step (Pet. 28–29) and that is not disputed (*see* Resp. 24–27). EX1036 ¶23

b. Step 2: "eluting the antibody with an acidic aqueous solution of low conductivity having a molarity of 100mM or less"

Patent Owner and its expert, Dr. Cramer, do not dispute that Shadle discloses 'eluting the antibody with an acidic aqueous solution of low conductivity.' *See* Resp. 27–29; EX2015 ¶¶53–55; 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 molarity limitation. *See* Resp. 27–29; EX2015 ¶¶53–55; EX1034 102:1–23. Instead, unable to challenge the calculation's accuracy, Patent Owner argues that the calculations are improper supplemental information.

Dr. Przybycien's unchallenged calculations (EX1026; EX1027)—which show that the "total molarity" of the solution in step 2 is below 100mM—are

admissible.[3] Patent Owner's contrary argument presumes a petition must contain all evidence used at trial, and that additional evidence may be submitted only with "permission from the Board." Resp. 28 n.14. Not so.

The purpose of 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.

The Petition construed the term "molarity" 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. 24. 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

[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.

present in the solution, rather than the concentration of one particular solute." Dec. Inst. 10. 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, 37–38.

Patent Owner's challenge to Dr. Przybycien's updated calculations 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, the 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—before Dr. Przybycien's first deposition and a full month before Patent Owner's Response was due. 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 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 ¶¶37–38; EX1026 1–2; EX1027 1–2. Neither Patent Owner nor its experts contest this. EX1036 ¶37; 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.

c. <u>Step 3</u>: "neutralizing the eluate from step (2) to form particles by addition of a buffer to raise the pH to 4 to 8 to form particles, wherein the molarity of the neutralized eluate is 100mM or less"

As for step three, Patent Owner does not dispute that Shadle discloses "neutralizing the eluate from step (2) . . . by addition of a buffer to raise the pH to 4 to 8." Instead, Patent Owner disputes only the molarity of the neutralized eluate and whether particles are formed. In so doing, Patent Owner (i) applies an erroneous inherency standard in disputing the molarity of the neutralized eluate, and (ii) ignores its admissions in the '289 patent that particles will form under the claimed conditions. Neither argument has merit.

i. Shadle's neutralized eluate inherently has a molarity of 100mM or less.

Patent Owner does not dispute Dr. Przybycien's updated calculations on the molarity of the neutralized eluate, which show that the total molarity is necessarily below 100mM. EX1036 ¶41; EX1026 2–3; EX1027 2–3. Nor does Patent Owner acknowledge its previous admission to the EPO that Shadle's neutralized eluate has a calculated total molarity of about 47.2mM—well below the claimed 100mM limit. EX1006 28; EX1034 ¶43 n.2. Instead Patent Owner contends that a POSA could use a fifth buffer preparation yielding a molarity higher than 100mM and that the neutralized eluate would contain so much residual wash buffer that its molarity would exceed 100mM. Both arguments are mistaken and assume that inherency requires proof that any other result is "***impossible***." Resp. 33.

Buffer preparation. Instead of disputing that the four conventional methods for preparing Shadle's citrate buffer result in a neutralized eluate that meets the molarity limitation, Patent Owner proposes a fifth, purportedly "known method[]" that "could" have been used to prepare Shadle's buffer. Resp. 40. 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 ¶26–38.

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" then the application "will be considered to have been anticipated by the former patented device.'" (citation omitted; emphasis added)).

Inherency does not require proof that another result is "impossible." *See SmithKline Beecham*, 403 F.3d at 1343. A result can thus be inherent even if it theoretically could be avoided. *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 "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. 33. 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. 24, 34. But Petitioner has not just shown that a buffer

"may" have met the neutralized eluate limitations (*id.*)—Petitioner showed that *all four* conventional buffer preparations necessarily do. EX1036 ¶41; EX1034 80:15–19, 81:7–17, 84:5–85:6, 102:8–23.

Indeed, the prior art consistently shows that citrate buffers were prepared according to Dr. Przybycien's four conventional methods. EX1036 ¶30; EX1028, 12; EX1037, 4, EX1015, 8; EX1029, 8; EX1038, 24; EX1014, 172; EX1040, 16; EX1041, 5. Dr. Cramer's own publications do too. EX1036 ¶31; 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 in the EPO proceedings when distinguishing Shadle.

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 ¶¶26–38. 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 ¶28; 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 3.5 target—e.g., monosodium citrate, as Dr. Przybycien proposed. EX1036 ¶28.

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 ¶¶31-35; 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 ¶36.

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, ¶29. Roth concerned a field of study and application distinct from the preparative Protein A chromatography of Shadle and the '289 patent. *Id.* ¶29. 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 ¶29.

Wash buffer. Patent Owner's only other response is that the neutralized eluate would contain so much wash buffer that its molarity would exceed 100mM. But as Dr. Przybycien shows, Shadle's neutralized eluate would not contain the large

amounts of wash buffer that Patent Owner presumes. EX1036 ¶¶49–53. Indeed, Shadle does not describe *any* wash buffer collected in the eluate. Instead, it describes the eluate as consisting of concentrated antibody alone. *Id*. ¶¶44–45. 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. EX1036 ¶44.

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. EX1036 ¶48; EX1006 6–7, 38–39; EX1043 6, 9–10, 15, 19, 30, 34.[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. EX1036 ¶¶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 there would be at least 2.1L of wash buffer contamination. *Id*. ¶¶48–49. In response, Dr. Przybycien has prepared

[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 '289 patent, EP '589, and EP '149, and is thus irrelevant. EX1036 ¶48; *compare* EX1042, 1 to EX1001, 1; EX1004, 1; and EX1019, 1.

detailed calculations to demonstrate that any wash buffer contamination in the collected eluate would at most be 0.582L. EX1036 ¶¶50–54; EX1047 5–6. Even that theoretical contamination would not increase the molarity of the neutralized eluate above 100mM. EX1036, ¶50 (explaining preparation no. 1 = 77.93 mM, preparation no. 2 = 65.40 mM, and preparations nos. 3 and 4 = 60.03 mM).

Dr. Przybycien's unrebutted calculations thus confirm that Shadle's neutralized eluate inherently satisfies step 3's molarity requirement.

ii. Shadle's method inherently forms 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. 17, 35. 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. EX1036 ¶¶11–12; *cf.* EX1034 97:10–98:18 (admitting 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 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. EX1036 ¶12. Neither requirement is in the claims. And since the '289 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) (rejecting "a proposed construction" when that "reading of the claim is indefinite").

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]

[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. 36. For anticipation,

Second, particles necessarily form in Shadle because Shadle discloses the same conditions (*i.e.*, pH, molarity) that the '289 patent admits are sufficient to form particles. EX1036 ¶55. As the Board recognized, there is "no meaningful difference between the conditions sufficient for particle formation set forth in claim 1 and the specification of the '289 patent, and the conditions disclosed by Shadle in conjunction with the eluate neutralization step." Dec. Inst. 30. Patent Owner condemns this logic as "hindsight" (Resp. 38), 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. 38), either the challenger made an unsupported "assumption" about inherency, *Crown Operations Int'l, Ltd. v.*

Shadle does not need to expressly note the presence of particles, or even clouding. Anticipation "does not require that a [POSA] at the time would have recognized the inherent disclosure." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

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.

Patent Owner next disputes whether Shadle is necessarily "in the range of conductivity described in the '289 [patent]," but its sole support for this point is its speculation that a POSA would use its fifth buffer preparation (trisodium citrate and hydrochloric acid). Resp. 40. Preliminarily, there is no conductivity limitation in any of the claims of the '289 patent, let alone as a requisite to particle formation. Nevertheless, and as explained above, this fifth preparation is not the "normal and usual" manner of preparation Shadle's buffer (*King Pharm.*, 616 F.3d at 1275–76)—a POSA would have used one of four conventional preparations. Moreover, Patent Owner does not dispute the testing results submitted to the EPO or Dr. Przybycien's testing that confirmed for all of the four conventional preparations of 25mM citrate buffer that the conductivity is necessarily in the range described in the '289 patent (*e.g.*, below 300 mS/m). *E.g.*, EX1001 5:27–35; EX1036 ¶57; EX1053.

The fact that Shadle's example involved an antibody (RSHZ-19) "not among the examples the '289 [patent] discusses" is immaterial. Resp. 41. The claims of the '289 patent are not limited to its examples, and if enabled to their full scope, presumptively work for all antibodies. EX1036 ¶59. Nothing in the '289 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 '[289] patent's written description discloses [some of the alleged] conditions" for particle formation, "its claims only recite [molarity and pH limits]. It would be improper to limit the broad terms used in the ['289] 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 ¶55.

d. Step 4: "removing the particles thereby to remove contaminant DNA in the sample"

The '289 patent admits that when particles form, they contain contaminant DNA that "may be removed by filtration." EX1001 6:1–18; EX1034 ¶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. 48. These arguments lack merit.

As Patent Owner's experts admit, the claims of the '289 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 as (or even finer than) those disclosed in the '289 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 '289 specification itself teaches that particles formed during the claimed process—the same process that Shadle teaches—contain contaminant DNA. EX1036 ¶64; EX1001 6:17–19 ("[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 expressly and/or inherently discloses each of the claimed limitations and anticipates claim 1.

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* 10–13; *King Pharm.*, 616 F.3d at 1275–76.

b. <u>Claim 3 (and dependent claim 4)</u>: The method according to claim 1, wherein the acidic aqueous solution of low conductivity is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid, and acetic acid.

Patent Owner asserts that the term "consisting of" in the recited Markush group excludes components other than citric acid. Resp. 51. 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 "25 mM 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 ¶67. 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.*

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

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: Claim 1, from which claim 5 depends, uses open "comprising" language, and thus permits "additional chromatography steps beyond those expressly recited." Dec. Inst. 26; *see* EX1036 ¶¶15, 68; *supra* 4.

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. EX1036 ¶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 n.5.

d. Claim 13: The method according to claim 1, wherein the particles are removed by filtration through a filter.

Patent Owner's only response to claim 13 is that Petitioner "failed to establish that the filtration process achieves the removal of particles." Resp. 53. But as explained above, the filters used in Shadle—which are the same as or finer than the filters in the '289 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. 44–48. 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 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." *In re 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 '289 patent purportedly eliminated. EX1036 ¶¶70–71; 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 regularly attending

conferences and consulting 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 column 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 confirms it did not satisfy any long-felt need.

III. CONCLUSION

For all these reasons and those in the Petition, Petitioner respectfully requests that the Board cancel claims 1–8 and 13 of the '289 patent.

Dated: May 24, 2018

Respectfully submitted,

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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 5,582 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).

Dated: May 24, 2018

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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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