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 7,332,289

PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120

LIST OF EXHIBITS

Patent Owner's Exhibits	Description
2001	Excerpt of European Prosecution History of Application No. 03795400.5
2002	Declaration of Megan Raymond dated August 31, 2017
2003	Todd M Przybycien *et al.*, *Alternative Bioseparation Operation: Life Beyond Packed-bed Chromatography*, Current Opinion in Biotechnology, Vol. 15, pp. 469-478 (Sept. 11, 2004)
2004	Mili Pathak *et al.*, *Re-use of Protein A Resin: Fouling and Economics*, BioPharm Int'l, Vol. 28, No. 3 (Mar. 1, 2015)
2005	M. Roth, *Automated Amino Acid Analysis with Sensitive Fluorescence Detection*, Journal of Clinical Chemistry and Clinical Biochemistry, Vol. 14, No. 7, pp. 361-364 (1976)
2006	Leslie A. Khawli *et al.*, *Charge Variants in IgG1: Isolation, Characterization, In Vitro Binding Properties and Pharmacokinetics in Rats*, MAbs, Vol. 2, No. 6, pp. 613-624 (Nov. 2010)
2007	A. Singla *et al.*, *Aggregation Kinetics for IgG1-Based Monoclonal Antibody Therapeutics*, American Association of Pharmaceutical Scientists, Vol. 18, No. 3, pp.689-702 (May 2016).
2008	Paolo Arosio *et al.*, *Aggregation Mechanism of an IgG2 and two IgG1 Monoclonal Antibodies at low pH: From Oligomers to Larger Aggregates*, Pharmaceutical Research, Vol. 30, No. 3 (Oct. 9, 2012)
2009	CRC Handbook of Chemistry and Physics, 5-72 (Electrical Conductivity of Aqueous Solutions) (W. M. Hayes ed., CRC Press 96th ed., 2015)
2010	Yinges Yigzaw *et al.*, *Exploitation of the Adsorptive Properties of Depth Filters for Host Cell Protein Removal during Monoclonal Antibody Purification*, Biotechnology Progress, Vol. 22, No. 1, pp.288-296 (Jan. 6, 2006)

2011	Ying Hou *et al.*, *Improved Process Analytical Technology for Protein A Chromatography Using Predictive Principal Component Analysis Tools*, Biotechnology and Bioengineering, Vol. 108, No. 1, pp.59-68 (July 29, 2010)
2012	Thomas Skamris *et al.*, *Monoclonal Antibodies Follow Distinct Aggregation Pathways During Production-Relevant Acidic Incubation and Neutralization*, Pharmaceutical Research, Vol. 33, No. 3, pp.716-728 (Nov. 12, 2015)
2013	Maria Vazquez-Rey *et al.*, *Aggregates in Monoclonal Antibody Manufacturing Processes*, Biotechnology and Bioengineering, Vol. 108, No. 7, pp.1494-1508 (Apr. 7, 2011)
2014	Deposition Transcript of Todd M. Przybycien dated January 30, 2018
2015	Declaration of Dr. Steven M. Cramer
2016	Declaration of Dr. Kirston Koths
2017	Declaration of Megan Raymond dated February 26, 2018
2018	Experimental Notebook Pages of Dr. Harry G. Brittain
2019	Declaration of Dr. Harry G. Brittain

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U.S. Patent No. 7,332,289...1

The inventors of U.S. Patent No. 7,332,289 ("'289") developed a surprisingly simple method for removing contaminant DNA during protein purification—a revolutionary invention that allowed those of ordinary skill in the art ("POSITA")[1] to avoid the repeated use of costly, time-consuming, inefficient and complicated column chromatography processes to remove DNA from a single sample, as the prior art had required. Implicitly acknowledging that '289's solution had never before been disclosed in the art, Petitioner Pfizer, Inc. ("Pfizer") rests its attacks on multiple layers of inherency arguments and a nonsensical reading of a single reference in which Pfizer argues the same prior art purification methods the '289 expressly *criticized* and rendered *unnecessary* somehow would have been understood to anticipate the '289 (or, in one limited respect, render it obvious). Chugai now addresses the Petition's ("Pet.," Pap. 2) numerous errors and omissions, supported by the declarations of Drs. Cramer, Koths, and Brittain (EX2015, EX2016, EX2019),[2] and free of §42.108(c)'s institution-only constraints.[3]

[1] Because it does not impact the outcome, it is unnecessary to address the propriety of Petitioner's POSITA definition. *See Genband US LLC v. Metaswitch Networks Ltd.*, IPR2015-01457, Pap. 38, 19 (Dec. 15, 2016).

[2] EX2015, ¶23; EX2016, ¶26; EX2019, ¶¶4-12. Patent Owner's Exhibits 2004-2013 are authentic, and were found where, if authentic, they would likely be. *See*

I. Introduction

The ’289 inventors’ elegantly simple method for removing contaminant DNA builds on their discovery that under certain conditions particles comprising contaminant DNA can be formed and removed from a protein-containing sample—including with basic filtering—thereby removing DNA. This method was a breakthrough: it enabled contaminant DNA to be effectively and simply removed to extremely low concentrations, eliminating the need to use sequential chromatography columns to do so, and giving process designers greater freedom. EX2015, ¶30. As ’289 explains, using these prior-art chromatography steps—both individually and in combination—was time-consuming, expensive, and complicated. *E.g.*, EX1001, 1:57-67, 6:40-46, 1:44-52.

Pfizer relies on a single embodiment of just one reference—Shadle’s Example IA (EX1003)—for §102(b) and §103(a). Pet., 5. The Petition ignores ’289’s surprising result—expressly described in the patent but *absent* from Shadle—of forming particles comprising DNA under the conditions in the

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EX2017; *see also* EX2015, ¶¶11, 93. Further, at least EX2005 is an ancient document under FRE 803(16), and the hearsay exception therefore applies to its content.

[3] Unless noted, all emphasis is added and all section references are to 35 U.S.C. or 37 C.F.R., as context indicates.

Challenged Claims, which allows the claimed step of "removing the particles to thereby remove contaminant DNA" (claim 1))—including to low levels, such as 22.5 pg/ml or less (claim 5). *See, e.g.*, EX1001, 1:57-67, 12:56-58. Instead, in disclosing the same *prior-art methods* of sequential chromatography that '289 expressly criticized, distinguished, and rendered unnecessary (EX1003, 16–18), Pfizer argues Shadle *inherently* disclosed (1) particle formation because (despite Shadle's never saying anything about this) it must necessarily have occurred *every time* Example IA was performed, and (2) removing DNA by removing those (never-mentioned) particles. Petitioner's expert, rather than relying on his own knowledge, instead relied solely on the '289's description itself about conditions under which particles *may* form, to conclude particles *always* form in Shadle.[4]

This is nonsense. As detailed below (along with numerous other shortcomings in Shadle's supposed disclosures), performing Shadle's Example IA did *not* necessarily meet the Challenged Claims'[5] various limitations (such as the molarity limitation), and did *not* necessarily lead to formation of particles, let alone subsequent particle *removal* to remove contaminant DNA. Quite the contrary: to assume away these limitations in the guise of "inherency," Pfizer and

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[4] Tellingly, Pfizer ignores '289's teachings about additional pertinent parameters. *See, e.g.*, §V.C.2, *infra*.

[5] Claims 1-8, 13.

its expert, Dr. Przybycien, ignore numerous factors not disclosed in Shadle and that, when considered, negate this assumption. Perhaps most telling, rather than rely on evidence or analysis based on Shadle, Pfizer and its expert *relied solely and completely on the '289 itself* to argue particle formation and removal of particles must necessarily be occurring in Shadle's Example IA—again ignoring that '289 *does not state this will occur* under Shadle's conditions—highlighting Petitioner's efforts to distort Shadle based on hindsight from '289.

Pfizer's evidence fails to establish anticipation or obviousness for any instituted ground, and every Challenged Claim must be confirmed.

II. Overview of the Art and Challenged Claims

A. Contaminant DNA Removal Before '289 Required Serial Applications of Column Chromatography, Which Was Expensive, Time-Consuming, Complicated and Inefficient

Recombinant gene technology has allowed development of various protein formulations (such as antibodies) for therapy. EX1001, 1:13-17. But before proteins may be administered to humans, contaminants, including DNA, must be removed. *Id.*, 1:18-23. At the time of the '289, "a variety of recombinant antibody drugs, which are more selective than normal-drugs, [had] been developed and entered clinical trial in recent years"; thus, researchers faced increasing pressure for improved purification methods to satisfy the growing demand for such proteins. *E.g, id.*, 1:15-17, 49-53; EX2015, ¶¶24-25.

Before ’289’s invention, DNA was removed from protein preparations using various sequential chromatographic techniques—including serial use of *multiple column chromatography processes* on a single protein-containing volume. *Id.*, 1:23-43:

> [I]n a case where a physiologically active protein is an antibody produced recombinantly in mammalian host cells, the aqueous medium is treated by *affinity column chromatography* on Protein A or Protein G *before purification by various types of chromatography*, based on the binding property of Protein A or Protein G to IgG Fc chain.
>
> By way of example, in JP 5-504579 A, an antibody containing aqueous medium obtained from mammalian cell culture is applied to *Protein A/G column chromatography* to adsorb antibody molecules onto the column, and is then eluted …. The resulting acidic eluate is *sequentially applied* to *ion-exchange column chromatography* and *size exclusion column chromatography* to give the purified antibody molecules.

EX2015, ¶26.

But these repeating chromatographic processes were (1) time-consuming, (2) labor-intensive, and (3) costly, as well as (4) complicated. *Id.*, 1:44-47. They also (5) fail to provide stable results, and (6) could lead to significant loss of the sought-after protein. *Id.* 1:44-52; EX2015, ¶¶26-27.

Indeed, Pfizer's Dr. Przybycien, who today suggests (incorrectly) that Shadle's conventional chromatography discussion disclosed everything in the Challenged Claims *in 1995*,[6] was lamenting *in 2004* (nearly a decade after Shadle's publication) that the cost and efficiency problems with such column chromatography steps *had not yet been solved*:

> *Chromatography* is undoubtedly the workhorse of downstream processes, [but] has the notoriety of being *the single largest cost center* [and] *a low-throughput operation*. Consequently, 'chromatography alternatives' are an attractive proposition, even if only a reduction in the extent of use of packed beds can be realized. This paper reviews the current state of unit operations posing as chromatography alternatives – including . . . precipitation . . .—and their potential to do the unthinkable.
>
> . . .
>
> Bioseparation operations have long been dominated by packed-bed chromatography, despite limitations of *high cost …*, *batch operation*, *low throughput* and *complex scale-up*. . . .[F]or non-therapeutic proteins. . ., the high cost is often enough to rule it out . . .. *Even in the case of therapeutic proteins, there is a downward pressure on the cost of goods*, especially for high volume products such as monoclonal antibodies… and plasma products . . ..

[6] Tellingly, Przybycien did not purport to recognize these disclosures in Shadle until *after* he read the '289. EX2014, 24:6-25:22.

EX2003, 1 (“column chromatography steps…are the first targets for replacement with lower-cost alternatives”). *See also* EX2004, 1 (“*up to 60% of the downstream costs com[e] from chromatography*.”; “It has been shown that the extended use of a [chromatography] resin results in . . . a *decrease in product recovery*”); EX2015, ¶28.

B. ’289’s Remarkable Invention Eliminated the Need for Serial Chromatography to Remove Contaminant DNA

Long before Przybycien, ’289’s inventors not only *recognized* the “need to develop a simpler and less expensive method for purifying physiologically active proteins … which can ensure removal of contaminant DNA, and which can minimize a loss of physiologically active proteins,” EX1001, 1:48-52; they also *addressed* it: “As a result of extensive and intensive efforts made to overcome these problems, the inventors of the present invention . . . made ***the surprising finding that contaminant DNA can be efficiently removed from a sample containing a physiologically active protein without using complicated chromatographic processes***.” *Id.* 1:57-67; *see also* EX2015, ¶29; EX2016, ¶12; *cf*. EX2003, 1, 3 (in 2004 considering “potential” of “chromatography alternatives”; “there is much left to understand”).

They discovered that under certain conditions, particles comprising contaminant DNA can be formed and removed from a protein-containing sample

by simple filtration/particle removal. EX1001, 1:57-67. This groundbreaking method enabled contaminant DNA to be removed to extremely low concentrations, eliminating the need for sequential chromatography to remove contaminant DNA. *Id.*, 1:57-67, 6:40-46; EX2016, ¶13. The '289 inventors thus achieved what Dr. Przybycien had called "the *unthinkable*" in 2004[7]: enabling replacement and elimination of the requirement of multiple chromatography steps—a process that was time-consuming, labor-intensive, costly, and complicated, failed to provide stable results, and led to significant loss of the target protein. EX1001, 1:44-52l *See also* EX2015, ¶¶30-31; EX2014, 30:6-20.

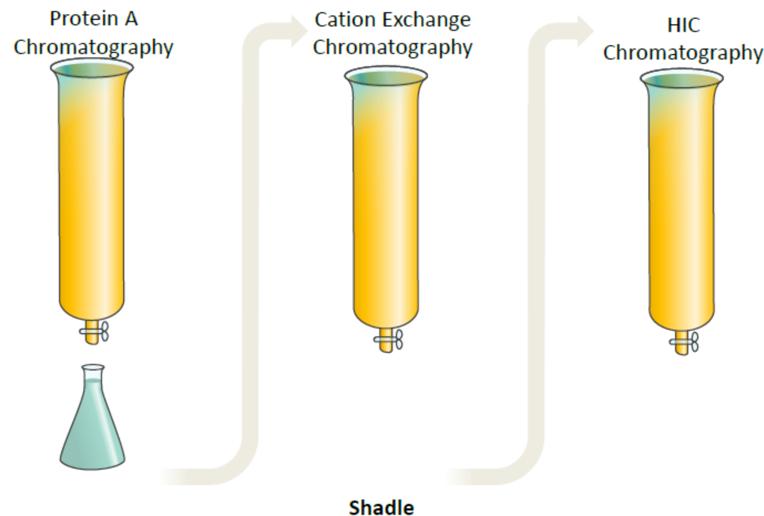
III. Overview of Shadle

Petitioner's sole reference, Shadle, included ordinary, "widely used" Protein A chromatography, but focused on an entirely different problem from '289: Shadle claimed a method for removing contaminating *protein A that leached from the chromatographic column* into the eluted mixture using hydrophobic interaction chromatography ("HIC"). EX1003, 5-6; EX2015, ¶¶32, 41. Shadle addressed this by following Protein A chromatography with a step of cation chromatography to "remove[] protein and non-protein impurities" (EX1003, 17), and then HIC. *E.g.*, *id.*, 22; EX2015, ¶32. Shadle's inventors reported they "surprisingly discovered

[7] *See* (EX2003, 1 (referring, in 2004, to "reduction in the extent of use of packed bed[] [chromatography]")).

that HIC can be usefully employed to remove contaminating Protein A from IgG mixtures eluted from Protein A chromatographic support." EX1003, 6; EX2015, ¶33; EX2016, ¶14.

Shadle's Example IA—the sole embodiment Petitioner relies on—is an "example trial run of the purification of a protein (RSHZ-19, a humanized IgG antibody) at a 1 gram scale using the procedure described generically in Example 1." Pet., 22, n.2; EX2015, ¶34. In this Example, the IgG antibody solution is purified using *three consecutive chromatographic steps*—(1) Protein A affinity chromatography, (2) cation exchange chromatography, and (3) HIC. EX 1003, 21–22; EX2015, ¶34.



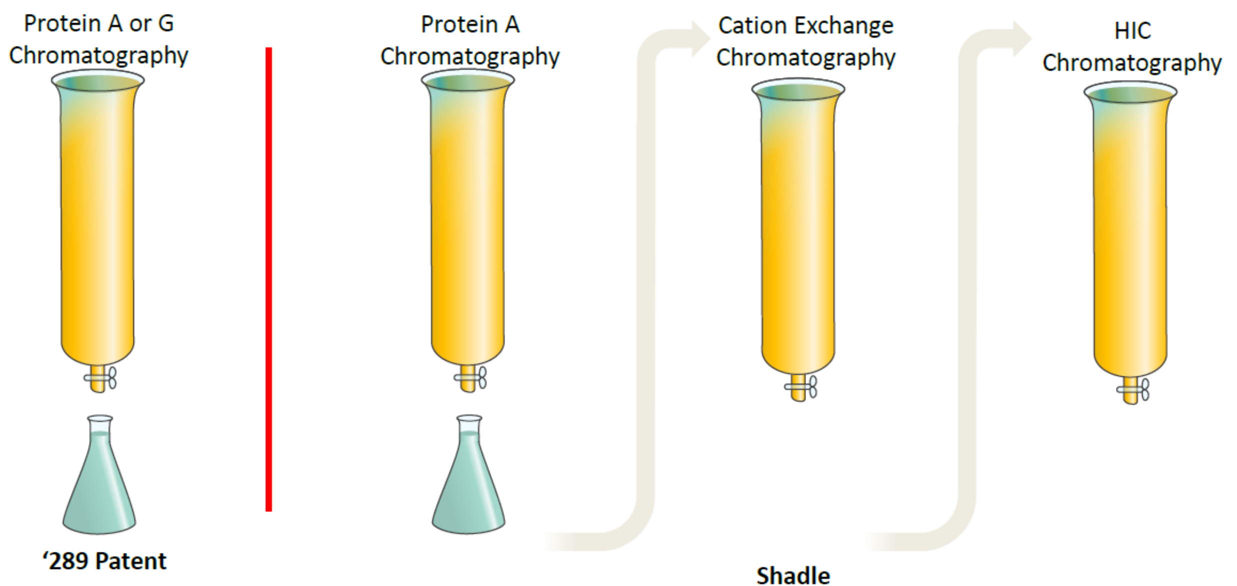
Example IA describes a 5 liter ProSep A affinity loaded with an IgG solution (EX1003, 21), to which approximately 15 liters of PBS/glycine was added. *Id.*; EX2015,¶ 35. The IgG was then eluted by applying 15-20 liters of ProSep A

elution buffer (EX2003, 21), adjusted to pH 3.5 with 2.5 M HCl, and adjusted to pH 5.5 by adding approximately 350 mL of 1 M tris base. *Id.*; EX2015, ¶35. The sample was then filtered and loaded onto the cation exchange chromatography column, and this eluate was loaded onto a HIC column. EX1003, 21-22; EX2015, ¶¶35-36. Although not specifically discussed in Example IA, Shadle elsewhere explains the cation exchange chromatography "removes protein and non-protein impurities," and the HIC chromatography removes additional protein and non-protein impurities, "most notably residual Protein A, IgG aggregates, and host DNA." EX1003, 17-18; EX2015, ¶36. While the Petition argued contaminant DNA was removed by the (unreported) formation and removal of particles following Protein A chromatography that Shadle never mentioned (Pet., 38), Dr. Przybycien conceded that the later cation exchange chromatography step actually results in the removal of contaminant DNA, and Shadle explicitly reports the later HIC chromatography step does, as well. EX2014, 112:4-12; EX2015, ¶37. Thus, Shadle discloses two chromatography steps to remove DNA *after* the steps Petitioner relied on to disclose the Challenged Claims. *Id.* This is unsurprising, as Example IA's focus was reducing the Protein A content of the ProSep A eluate. EX1003, 22; EX2015, ¶37.

Despite extended discussion of its multi-step chromatography process, Shadle says *nothing at all* about observing particle formation following pH

adjustment of the eluate to 5.5 by adding Tris, let alone about particles *always* forming at this step—even though such particle formation would raise concerns about later steps in Shadle. EX2015, ¶38. Example IA is also silent with respect to the conductivity and total molarity of any solution, as well as particle formation and the removal of contaminant DNA from a neutralized eluate. *See, e.g.*, EX2014, 21: 22-23, 22:12-13, 24:15-16; EX2015, ¶39.

Shadle thus represented an entirely different approach of contaminant DNA removal than '289. Far from anticipating the '289—expressly or inherently—Shadle simply described the prior art use of serial chromatography steps '289 criticized. EX2015, ¶¶40-41.



Contrast EX1001, 1:61-2:4 ("the inventors …made the surprising finding that contaminant DNA can be efficiently removed . . . *without using complicated chromatographic processes*"). Instead, Shadle *affirmatively required* using

additional columns to remove "DNA." EX1003, 17-18, 21-22; EX2015, ¶40; *see also, e.g.*, *In re Abbott Diabetes Care, Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (Board's construction of "electrochemical sensor" to include prior art cables and wires unreasonable and inconsistent with claims and specification, which *criticized* prior art external cables and wires); *Alloc, Inc. v. ITC*, 342 F.3d 1361, 1369-70 (Fed. Cir. 2003) (holding asserted claims required a limitation, even though not recited, because specification criticized prior art systems without it).

IV. Claim Construction

In IPRs , "[a] claim in an unexpired patent . . . [is] given its broadest reasonable construction [BRI] in light of the specification of the patent in which it appears." § 42.100(b); *see also* Pet., 24. But "[e]ven under the [BRI], the Board's construction *cannot be divorced from the specification* and the record evidence, and *must be consistent with the one that those skilled in the art would reach*." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (internal quotations/citations omitted).

A. Preamble (Claim 1)

The preamble of claim 1 recites "[a] method for removing contaminant DNA in an antibody-containing sample, which comprises [the listed steps]." The preamble is limiting, and its BRI requires that the completion of the claimed method, by reaching the last of its claimed steps, accomplishes claimed removal of

contaminant DNA. The preamble should be construed 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." EX2015, ¶ 43.

The preamble is limiting because, *inter alia,* the term "antibody-containing sample" provides antecedent basis for and is necessary to understand a positive limitation in the claim's body. *See Pacing Techs., LLC v. Garmin Int'l, Inc.*, 778 F.3d 1021, 1024 (Fed. Cir. 2015); *Aceto Agric. Chems. Corp. v. Gowan Co., LLC.*, IPR2016-00076, Pap. 51 at 9 (Apr. 28, 2017) (preamble limiting because it provided context antecedent basis); *Fuel Automation Station, LLC, v. Frac Shack Inc.*, IPR2017-01349, Pap. 8 at 9 (Dec. 5, 2017) (use as antecedent basis "strongly supports a conclusion that the phrase limits the claim."). EX1001, Table 3-6, 9:40-10:6, 10:44-11:2. The preamble's plain language additionally breathes life and meaning into the claims by making clear they conclude with step 4, and that it is step 4's removing/filtering (not additional steps that might be performed *after* claim 1) that actually removes contaminant DNA as the preamble recites.[8] This

[8] As '289 makes clear, its invention surprisingly enabled removal of contaminant DNA without *requiring* further chromatography. EX1001, 1:57-67, 6:4-8. While a practitioner performing the Challenged Claims might *choose* to employ further chromatography, the Claims' steps must remove contaminant DNA through the claimed particle formation and removal.

construction is required by the claim and specification. *See, e.g.*, *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260-61 (Fed. Cir. 2010) (reversing "unreasonable construction"; "[BRI] coupled with the term 'comprising' does not give the PTO unfettered license to interpret claims to embrace anything remotely related. . . . Rather, claims should always be read in light of the specification and teachings in the underlying patent"; material in prior art alleged to be "*finishing* the top surface of the floor" cannot be "*finishing* any surface unless it is the *final layer*"); *Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1407-09 (Fed. Cir. 2004) ("contacting . .. to form [an] interface," was – despite use of "comprising" – limited to physical contact: "While the 'contacting' requirement may be satisfied with either physical or electrical contact, we do not see how electrical contact alone can form the 'necessary physical' junction required for the interface. 'Comprising,' while permitting additional elements not required by a claim, does not remove the limitations that are present."). *See also BASF Agro B.V. v. Makhteshim Agan of N. Am., Inc.*, 519 Fed. App'x 1008, 1014, 1017 (Fed. Cir. 2013) (rejecting argument that "comprising" claim infringed by method combining disclaimed prior art method with other steps) (internal quotations/citations omitted); *Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1379–80 (Fed. Cir. 1998) (rejecting argument that "'comprising' permits the addition of any elements to those listed in the claims" and thus could restore subject matter otherwise

excluded; "'Comprising' is not a weasel word with which to abrogate claim limitations"); *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc*., 242 F.3d 1337, 1340-41 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the [comprising] language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature"). '289's specification explains it is the formation and removal of particles that accomplishes the claimed contaminant DNA removal, not the additional purification processes in the prior art, such as chromatography. EX1001, 1:57-67, 6:4-8. Indeed, the invention's purpose is to remove contaminant DNA *without* requiring additional chromatography (*see id.*, 1:44-52), and reading the preamble (and step 4) to the contrary would not be reasonable or consistent with the specification. EX2015, ¶43; *e.g.*, *In re Suitco*, 603 F.3d at 1260-61; *In re Abbott*, 696 F.3d at 1149; *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings,* 370 F.3d 1354, 1362 (Fed. Cir. 2004) ("A preamble may provide context for claim construction, particularly, where as here, that preamble's statement of intended use forms the basis for distinguishing the prior art in the patent's prosecution history"); *Proveris Sci. Corp. v. Innovasystems, Inc.*, 739 F.3d 1367, 1372-73 (Fed. Cir. 2014) (claim preamble limiting because it recited aspect specification touted as important and provided antecedent basis).

B. "molarity" (Claim 1)

The Board correctly construed "molarity" at institution as the "total concentration of solute present in the solution, rather than the concentration of one particular solute." Paper 7, 10. "Molarity" is not limited to the concentration of a single solute, as the '289 claims, specification, and file history make clear in addressing the contributions of *multiple* solutes to the solution's molarity. *See, e.g.*, EX1001, claim 1 ("solution . . . having a molarity . . ." and "molarity of the adjusted sample"); claim 13 ("molarity of the neutralized sample"); 4:61-67 ("As used herein, a 'neutral aqueous solution . . .' generally refers to an aqueous solution . . . which has a molarity of 0 to 100mM . . ."); 5:27-35, 59–62; *see also, e.g.*, EX1005, 36 (considering contributions to molarity from 1M Tris with 0.1M acetic acid results in "molarity of the [neutralized solution] [] <u>over</u> 100mM" (emphasis original)), 11 ("[A]n important feature of the present invention is to adjust pH value of the solution, the eluate, to from 4 to 8 [by the addition of a buffer] while maintaining the molarity of the solution at 100mM or less."), 37 (considering molarity contributions from more than one solute to conclude solution's molarity is at least 0.1M: "in this example, 0.1M buffer was used as an eluent, and 1M Tris-HCl was used to adjust the pH of the eluted fraction, that is, *the fact that 0.1M and 1M solutions were used means that the molarity of the eluted fration [sic] must be over 0.1 M (100 mM)*"), 40 (molarity of eluted fraction

over 0.1M when 0.1M sodium citrate used as eluent and 1M Trizma used to adjust pH). While Petitioner limited "molarity" to one solute's concentration (Pet., 24), this was contradicted by Dr. Przybycien's analysis of the molarity of Shadle's adjusted eluate (EX1002 ¶79-82), and indeed Dr. Przybycien later admitted some of his molarity calculations failed to account for additional substances, such as hydrochloric acid and sodium hydroxide (EX2014, 91:24-92:3).

C. "to form particles" (Claim 1)

The BRI of "to form particles" is "to produce particles comprising DNA causing the solution to become clouded." The specification explains producing particles is synonymous with becoming clouded. EX1001, 6:4-6 ("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*)."); *Abbott Labs. v. Novopharm Ltd*., 323 F.3d 1324, 1327–28, 1330 (Fed. Cir. 2003) (term "explicitly defined" by specification's use of "*i.e.*"). Petitioner and its expert also recognize and apply this same definition. *See, e.g.,* Pet., 36-39 (citing, *inter alia*, EX1001, 6:4-6 ("*produces particles* (i.e., becomes clouded)" (emphasis original)), EX1002, ¶100 (same)); EX1002, ¶¶41, 83; EX2014, 21:13-19 ("Because we don't have a description of, say, the size distribution, [the particles] may be suspension of precipitants. It may be a suspension of colloidal particles. Either would scatter light or become clouded.").

D. "the treated sample containing an antibody" (Claim 5)

Claim 5 depends from claim 1, and recites: "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*." While Petitioner offered no explicit construction, *cf.* §42.104(b)(3)-(4), the Petition *implicitly* applied one[9] in which "the treated sample containing an antibody" had no antecedent basis, but was instead the result of steps entirely outside those recited in independent claim 1. *See* §VI.C, *infra*. This is, of course, improper. The BRI of this term, consistent with the specification, is "the sample resulting from performing the method of claim 1, which concludes with removing particles in step 4." *See, e.g.*, EX2015, ¶46; *Suitco*, 603 F.3d at 1260-61; *Power Mosfet*, 378 F.3d at 1407-09. *See also BASF*, 519 Fed. App'x at 1014, 1017; *Spectrum*, 164 F.3d at 1379–80; *SciMed.*, 242 F.3d at 1340-41.

It is a fundamental construction principle that terms beginning with "the" refer to an earlier portion of the claim for antecedent basis. *See, e.g.*,

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[9] *See, e.g.*, *Synopsys, Inc. v. Mentor Graphics Corp.*, IPR2012-00041, Pap. 16, 5-7 (Feb. 22, 2013) (rejecting implicit construction); *Securus Technologies, Inc. v. Global Tel*Link Corp.*, IPR2016-00996, Pap. 32, 21 (Oct. 30, 2017) (same); *Macronix Int'l Co. v. Spansion LLC*, IPR2014-00106, Pap. 13, 8-13 (Apr. 24, 2014) (same).

Microprocessor Enhancement Corp. v. Texas Instruments Inc., 520 F.3d 1367, 1379-80 (Fed. Cir. 2008). This is basic logic in reading a dependent claim like claim 5, which adds a specific purity limitation to claim 1's result: no POSITA would understand "*the treated sample* containing an antibody" to refer to a treated sample originating *outside* claim 1, as this would render claim 5 meaningless.[10] EX2015, ¶46 Nor would any POSITA mistake what the "the treated sample" in claim 1 is: "a sample" appears in claim 1's preamble as the subject of treatment, by the claim's method steps, to "remov[e] contaminant DNA." *Id.* ¶47. The claim's steps recite *how* that same sample (now referred to as "*the*" sample) is then "appl[ied] " to affinity chromatography (step 1), and subject to "remov[al of] particles" (step 4) to become the treated sample from which "contaminant DNA" has been removed, as the preamble explains for the claimed method. *See* EX1001, Claim 1, step 4 ("to thereby remove contaminant DNA from *the antibody-*

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[10] For example, this would allow the ridiculous reading that claim 5 could be met by (1) performing claim 1, (2) discarding the result, and (3) obtaining a new "treated sample" elsewhere with impurities below the 22.5 pg/ml limit. No POSITA would read claim 5 this way. EX2015, ¶47; *e.g.*, *In re Suitco*, 603 F.3d at 1260; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1363 (Fed. Cir. 2008) (declining to apply dictionary meaning producing nonsensical result and rendering dependent claims meaningless).

containing sample" identified in the preamble). As any POSITA would recognize, the "treated sample" is certainly not the pre-treatment sample introduced in preamble, nor the "appl[ied]" sample partway through the claim (in steps 1-3) before the method of the claim for treating the sample has been completed. EX2015, ¶¶47-49. Petitioner agrees: the Petition and Dr. Przybycien argue this limitation is disclosed by a sample in Shadle that (according to Petitioner) has already gone through steps 1, 2 3, and 4. *See* Pet., 41-42 (mapping this limitation to results "obtained by practicing [entire] process of [Shadle's] invention"); EX1002, ¶97; EX1003, 14, 22; EX2015, ¶48. Thus, although the words "treated sample" do not appear *in haec verba* in claim 1, the claim itself makes clear "the treated sample containing an antibody" is the sample after particles have been removed in claim 1's step 4, where the claimed treatment of claim 1's method has been completed (in step 4). *See Energizer Holdings, Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366, 1370–71 (Fed. Cir. 2006) (reversing indefiniteness finding because term without identical antecedent basis "can be construed"; 'anode gel' is by implication the antecedent basis for 'said zinc anode'"); EX2015, ¶49.

The specification also confirms this construction, explaining the formation and removal of particles *recited in claim 1* (the "method of the present invention") is what accomplishes removal of contaminant DNA to the low DNA concentration

of 22.5 pg/mL or less—not additional prior-art purification processes (*outside* the claim) that ’289 renders unnecessary:

> The *method of the present invention* enables contaminant DNA to be efficiently removed in a very simple manner up to an extremely low DNA concentration (e.g., 22.5 pg/ml). . . The method of the present invention also enables cost reduction and has great significance in this technical field.

EX1001, 6:40-46; *see id.*, 1:57-67, 6:4-8. Similarly, in ’289’s Example 2, DNA concentration is measured just after filtration—*i.e.*, after claim 1’s step 4 particle removal. *Id.*, 9:42-53. And Table 3 shows how, in this embodiment, DNA concentration after step 4 may be reduced from 25,110 pg/mL (*prior to* filtration) to 22.5 pg/mL or less (*after* filtration). *Id.*, Table 3.

While the Petition’s brief discussion of claim 5 confirms Petitioner’s agreement that POSITA would understand claim 5 is performed on the sample after all steps of claim 1 have been performed, a closer examination reveals Petitioner argues far more happens between claim 1 and claim 5—indeed, far more than the claims or specification would permit. Petitioner asserts that *after* what Petitioner argues is Shadle’s express or inherent disclosure of step 4 (the use of 0.1 and 0.2µ filters (Pet., 38-40; EX1002, ¶¶90-91)), it is Shadle’s disclosure of a later sample containing “approximately 2.4 milligrams protein per milliliter” (EX1003, 22) that supposedly disclosures this limitation. Pet., 41-42; EX1002, ¶97. But this

sample is not the result of step 4 of claim 1, because, *inter alia*, it has *also* been subjected to two further column chromatography steps and numerous other processes. *See* EX1003, 17-18 ((1) cation exchange chromatography, (2) viral inactivation with guanidine, (3) hydrophobic interaction chromatography, (4) ultrafiltration, (5) diafiltration, and (6) filtration).

Petitioner's implicit construction is, thus, that "*the* treated sample containing an antibody" is actually *a different* treated sample that has been further changed by additional steps not recited in claim 1, including two additional column chromatography steps and other alterations. This cannot be the BRI—or, indeed, *any* construction—of "*the* treated sample containing an antibody" because it contradicts not only the plain language of the claim, but also the express teachings of the specification. *In re Smith Int'l, Inc.*, 871 F.3d 1375, 1382 (Fed. Cir. 2017) Even when giving claim terms their BRI, the Board cannot construe the claims so broadly that its constructions are unreasonable"). As discussed above, the specification expressly confirms the claimed invention *eliminates* the need for these very steps of additional chromatography to remove contaminant DNA that would need to be *added* (with the result still being called the *same* "sample") to meet the claim. EX1001, 1:57-67, 6:4-8, 1:44-1:52. Indeed, to accept Petitioner's view would permit claim 5's impurity target to be met by (1) performing the steps of claim 1 to create "the treated sample," then (2) adding 500 liters of purified

water, but still calling this the *same* "treated sample" of claim 1, and (3) measuring the impurities in the wildly-altered result. This is not even close to a reasonable construction (*see, e.g.*, *Suitco*, 603 F.3d at 1260)—which is likely the reason Petitioner was unwilling to spell out this argument in the Petition. *See, e.g.*, n.9, *supra*.

V. The Challenged Claims Are Not Anticipated

To prove anticipation, Petitioner must show Shadle discloses each and every element of the Challenged Claims. *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00653, Pap. 12, 9–11, 13–14 (Sept. 29, 2014) (reference lacking element cannot anticipate claim or dependents). Petitioner argues inherency, and inherency *within* inherency, for many of these limitations. But inherency fails unless Petitioner presents "persuasive technical reasoning to explain" that a limitation *must necessarily* be present. *E.g.*, *Albaad Massuot Yitzhak, Ltd. v. Edgewell Pers. Care Brands, LLC*, IPR2017-00693, Pap. 11, 9–10 (July 17, 2017). A conclusory statement of inherency is entitled to no weight.[11] *Id.* Further, inherency may not

[11] *Motorola Mobility, LLC v. ITC*, 737 F.3d 1345, 1349-1350 (Fed. Cir. 2013) (expert's single-sentence argument not clear and convincing evidence of inherency); *TCL Corp. v. Telefonaktiebolaget LM Ericsson*, IPR2015-01584, Pap. 74, 47 (Jan. 24, 2017) (conclusory assertion insufficient to demonstrate express or inherent disclosure); *Pungkuk Wire Mfg. Co. v. Seong, Ki Chul*, IPR2016-00762,

be established by "probabilities or possibilities." *See, e.g.*, *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002). "The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Id.*

Petitioner fails to establish Claim 1's or Claim 13's limitations are disclosed—expressly or inherently—by Shadle. For these reasons, and the additional reasons discussed in §VI for Claims 2-5 and 13, Petitioner has also not established that the challenged dependent claims are unpatentable. *E.g.*, EX2015, ¶93; EX2016, ¶55.

A. "A method for removing contaminant DNA in an antibody-containing sample, which comprises the following[] steps" (Claim 1)

The Petition argues only that the preamble is "explicitly" disclosed by Shadle. *See* Pet., 28. But Petitioner fails to explain where, in the portions the Petition relies on to meet the remainder of the claim elements, Shadle discloses a method for removing contaminant DNA that has been performed when the last recited step has been performed, as claim 1 requires. Nothing in the Petition links the step in Shadle that Petitioner asserts discloses the conclusion of claim 1 (*i.e.*, pH adjustment and filtration using 0.1 micron Polygard and 0.2 micron Millipak

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Pap. 63, 10-11 (Aug. 16, 2017) (conclusory expert testimony entitled to little weight).

filters) to removing contaminant DNA.[12] Shadle discloses ***only*** that *later* chromatography steps (after Petitioner argues the claimed steps have already been completed) remove DNA. EX1003, 16-18; EX2014, 112:4-12; EX2015, ¶50. And Petitioner's mapping to Shadle *concedes* Petitioner is not relying on these adjustment/filtering steps to satisfy the preamble's requirement of a method removing contaminant DNA. Instead, Petitioner relies on Shadle's entire "procedure outlined below . . . for the *isolation and purification of a monoclonal antibody*," which does not stop with the adjustment/filtering Petitioner cites to disclose the last step of claim 1 (*see* Pet., 27 (emphasis original) (citing EX1003, 15); EX2015, ¶50), including, *inter alia*, two additional chromatography steps *after* what Petitioner argues is the method of claim 1—including the HIC chromatography step Shadle explicitly describes as removing unwanted DNA

[12] Nowhere does Shadle say or suggest these filters are meant to remove contaminant DNA. EX1003, 16-17, 21. Instead, Shadle says "[t]he pH 3.5 treatment provides viral inactivation, and the pH 5.5 adjustment *prepares the solution for cation exchange chromatography (CEC)*"—additional chromatography of the sort criticized and rendered unnecessary by '289. EX1003, 17; EX2015, ¶50. Petitioner's expert admitted such filtration before loading onto a chromatography column was standard practice (and would be present whether or not particles formed). EX2014, 27:19-28:9; EX2015, ¶50.

(EX1003, 15-18), and Shadle's cation chromatography step Dr. Przybycien concedes would remove DNA. EX2014, 112:4-12. And it is this series of *additional* chromatography steps that is referred to in Shadle's statement (*see* Pet., 27) that "the process of this invention" yields "low (<1 pg/mg protein) DNA." *See* EX1003, 14; EX2015, ¶51. Petitioner is actually arguing this preamble, requiring a "method for removing contaminant DNA" comprised of steps concluding with the last recited step of each claim, are met by steps in Shadle that *do not* remove contaminant DNA, because removal happens somewhere outside the claims. This is not what the claim requires, and accepting Petitioner's argument would render nonsensical results: this limitation requiring a method with a series of steps for removing contaminant DNA cannot be satisfied by a disclosure in which those steps *do not* remove contaminant DNA. *See, e.g.*, *Suitco*, 603 F.3d at 1260-61; *see also BASF*, 519 Fed. App'x at 1014, 1017. This is confirmed by '289 itself, which makes clear the heart of the claimed invention is facilitating *elimination* of these 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 as "time-, labor- and cost-consuming" and "fail[ing] to provide stable results." EX1001, 1:35-67; EX2015, ¶52.[13]

[13] Further, even if DNA-containing particles were shown to be inherently removed in Shadle (they have not, as explained below), Petitioner does not assert Shadle

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

Claim 1 requires the acidic aqueous solution have a molarity of 100 mM or less. Petitioner asserts Shadle's Table 1 listing for "ProSep Elution Buffer" ***expressly*** discloses the ProSep A buffer has a molarity of 100 mM or less. Pet., 29. But what Petitioner claims is the molarity of Shadle's ProSep A elution buffer is simply wrong. EX2015, ¶53. Petitioner's expert admitted at deposition that his molarity calculations were incomplete. EX2014, 90:23-92:23. He now untimely seeks to "update" them, *see id.*, apparently hopes to switch not only his opinion on

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inherently discloses the claims' preambles, but only that they are *explicitly* disclosed. Petitioner is not permitted to switch theories now. *E.g., Dell Inc. v. Acceleron, LLC*, IPR2013-00440, Pap. 49, 13 (Aug. 22, 2016) (declining to analyze inherency where the petition only argued express disclosure); *Colas Sols. Inc. v. Blacklidge Emulsions, Inc.*, IPR2016-01031, Pap. 38, 26 (Nov. 2, 2017) ("It is of the utmost importance that petitioners…adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds . . .'").

molarity but also his express-disclosure theory to one of inherency; both are improper.[14]

[14] Petitioner waited more than eight months after filing its Petition and did not seek permission from the Board to supplement. *Cf.* §42.123. EX2014, 90:23-92:23. Dr. Przybycien now claims the molarity of Shadle's ProSep A buffer could be 44 mM (*id.*)—*more than 75% above his original opinion* Shadle expressly disclosed 25 mM. EX1002, ¶ 73. Petitioner's untimely attempt to "update" should be rejected, as should any future attempt to switch to yet another inherency argument. *Intelligent Bio-Sys. v. Illumina Cambridge Ltd.,* 821 F.3d 1362, 1369–70 (Fed. Cir. 2016) (affirming Board's rejection of Petitioner's new invalidity theory referencing new evidence not in the Petition; *citing* Trial Practice Guide, 77 Fed.Reg. at 48,767); *Wasica Finance GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) ("Rather than explaining how its original petition was correct, Continental's subsequent arguments amount to an entirely new theory of prima facie obviousness absent from the petition. Shifting arguments in this fashion is foreclosed by statute, our precedent, and Board guidelines."); *In re NuVasive, Inc.*, 841 F.3d 966, 971-73 (Fed. Cir. 2016) (vacating and remanding final written decision where PTO relied on prior art figure first argued by petitioner in reply); *Dell*, IPR2013-00440, Pap. 49, 13 (Aug. 22, 2016) (declining to analyze inherency argument where petition argued express disclosure).

Petitioner failed to address other solutes in the "ProSep Elution Buffer" that would affect total molarity. EX2015, ¶¶54-55. Shadle's Table 1, the sole support relied on by Petitioner, addresses only the concentration of the ***citrate.*** EX1003, 20 ("25 mM citrate, pH 3.5."); EX2015, ¶55EX2015, ¶. Without any explanation, Petitioner and its expert simply *omitted* those same solutes when discussing the solution's *molarity*. This is unsupportable, because (as Petitioner's expert conceded at deposition) "molarity" includes the contributions from other solutes in the buffer (not just the citrate). Paper 7, 10; EX2014, 91:24-92:3; EX2015, ¶55.

C. "neutralizing the eluate from step (2) to form paticles by addition of a buffer to raise the pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less"

1. Shadle's Adjusted Eluate Does Not Inherently Have a Molarity of 100 mM or Less

Petitioner argues this limitation is disclosed because Shadle's eluate, after its pH is raised to 5.5, *inherently* has a molarity of 100 mM or less. Pet., 32. But Petitioner's inherency arguments fail because this ignores that Shadle does not specify how its ProSep A elution buffer was prepared, and ignores the wash buffer's contribution to molarity. EX2015, ¶¶56-58, 65-77.

In particular, purporting to calculate this solution's molarity, Petitioner and its expert add (a) the concentration of citrate in Shadle's ProSep elution buffer and (b) the molarity of 1 M Tris used by Shadle to raise the pH, to get a total molarity of 47.2 mM. *Id.*, 41-42; EX1002, ¶79. Petitioner's expert also considers (c) the

molarity contribution from an amount of 2.5 M hydrochloric acid he says would lower the pH of the pre-adjusted eluate from 3.7 to 3.5. EX1002, ¶82. Petitioner and its expert then summarily conclude Shadle's adjusted eluate is "necessarily" 100 mM or less. Pet., 32-34; EX1002, ¶79. But the molarity of this solution in Shadle also depends on at least two unknowns: (d) how Shadle's ProSep A elution buffer was prepared, and (e) the amount of PBS/glycine wash buffer that was collected in Shadle's eluate. EX2015, ¶57. The Petition ignores these issues, quietly making assumptions to try to avoid both. Pet., 32-34. But a review of these assumptions reveals the molarity of the sample adjusted to pH 5.5 in Shadle was certainly not *necessarily* 100 mM or less, and in fact may have been *well over 100 mM*. EX2015, ¶57. Petitioner's expert, realizing his failure more than eight months after signing his declaration, improperly attempted, on January 24, 2018, to "update" his molarity calculations to account for the first unknown. EX2014, 96:22-97:19, 123:17-126:6, 129:21-130:8. But his improper attempts to change the record and Petitioner's arguments are too little, too late. *See* n.14, *supra*.

First, in their molarity calculations, Petitioner and its expert assume Shadle's ProSep A elution buffer had a molarity of only 25 mM, omitting, as explained above, molarity contributions from other solutes—including those Dr. Pryzbycien later conceded should have been included, trying to "update" his

original testimony. Paper 7, 10; Pet., 32-34; EX1002, ¶79; EX1007; EX2014, 90:23-92:19, 82:22-83:18, 84:15-85:5; EX2015, ¶58.

And (even in Przybycien's improperly "updated" calculations) they fail to consider, as detailed below in §V.C.2(b), that Shadle's ProSep A elution buffer may have been prepared using, *e.g.*, 25 mM trisodium citrate and hydrochloric acid. The molarity of such a buffer is at least 77.1 mM. EX2015, ¶¶59-60. Dr. Cramer calculated the molarity contribution of a 25 mM citrate buffer at a pH of 3.5 that is prepared with trisodium citrate and hydrochloric acid in two ways: one using experimental values generated in the Karow reference (EX1012, EX1007, 2), also relied on by Dr. Przybycien (EX1002, ¶¶78, 79, 82), and another using Dr. Przybycien's method for calculating ionic strength in Pfizer's co-pending IPR challenging the ''815 (IPR2017-01358, EX1007, 3-8). EX2015, ¶¶61-63. Using either method, when this molarity contribution is added to the molarity contributions from the 1 M Tris base and hydrochloric acid (even using the amount of hydrochloric acid assumed by Petitioner's Dr. Przybycien (EX1007, 2-3)), the total molarity is at least 102 mM, and thus greater than 100 mM. EX2015, ¶¶ 61-63. In addition, Dr. Brittain actually prepared a 25 mM citrate buffer at a pH of 3.5, and measured the amount of hydrochloric acid added to trisodium citrate. EX2019 ¶21. Using Dr. Brittain's actual values, Dr. Cramer calculated the molarity of Dr. Brittain's buffer (about 78.5 mM), and of Shadle's eluate after

adjusting to 5.5 (103 mM)—confirming Dr. Cramer's molarity calculations, and a molarity exceeding 100mM. EX2015, ¶64.

Second, as to the amount of PBS/glycine collected in Shadle's eluate, the Petition simply assumes (without saying) that *no* PBS/glycine is collected in Shadle's eluate. *See* Pet., 31-34; EX1002, ¶¶76-82; EX2014, 58:21-60:7; EX2015, ¶¶65-73. But there is no reasonable basis for this assumption (*id.*), and Petitioner does not attempt to explain it.

Shadle describes applying approximately 15 liters of PBS/glycine wash buffer to the five-liter column after loading it with the RSHZ-19 solution. EX1003, 21. Then, after the column is washed with PBS/glycine, the ProSep A elution buffer is applied. *Id.*; EX2015, ¶66.

Shadle reports that the eluate from the ProSep A column was "pooled based on the UV tracing on the chromatogram" and the entire peak was collected. EX1003, 19; EX2015, ¶66. Ultraviolet (UV) tracing is a method of detecting protein exiting a chromatography column. EX2015, ¶66. Once the UV meter detects any protein, the UV trace rises, and eluate collection begins. EX2015, ¶66. The solution will be collected *as soon as the UV trace increases*, so that no antibody of interest (typically extremely valuable) is discarded. EX2015, ¶66. Thus, when collection began in Shadle depends on the conditions under which the antibody started eluting from the ProSep A chromatographic material, as well as

the sensitivity of the UV meter. EX2015, ¶¶66-67. As explained by Dr. Cramer, it is common for protein to begin to elute *before all of the wash buffer exits the column*. EX2015, ¶66; EX2011, 3. Thus, some PBS/glycine wash buffer was very likely collected in Shadle's Protein A eluate, although the exact amount cannot be known with certainty simply from reviewing Shadle (as Petitioner did here). EX2015, ¶¶66-69.

To prove Shadle's adjusted eluate is *necessarily*, and thus inherently, 100 mM or less, it was Petitioner's burden to show, *inter alia*, that it was ***impossible*** for the contribution of the wash buffer in Shadle's adjusted eluate to result in a molarity greater than 100 mM. *Harmonic Inc. v. Avid Tech., Inc.*, 289 F.3d 1356, 1363 (Fed. Cir. 2016) (petition must identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"); *Pungkuk*, IPR2016-00762, Pap. 63, 10-11. But Petitioner failed to do so, relying simply on an unstated and unsupported assumption that the wash buffer made no contribution. For example, Petitioner simply ignored the European Patent Office examining division's finding that Shadle's eluate adjusted to pH 3.5 contained 3.75-4.5 L PBS/glycine wash buffer, resulting in a molarity of 109 mM to 122 mM. EX2001, 5-6; EX2015, ¶70.

Indeed, as explained by Dr. Cramer, even setting aside the outer boundaries of what was *possible* (*Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356,

1367 (Fed. Cir. 2017) ("fact that a certain thing *may* result" insufficient)), even as a *conservative* estimate at least about 1 L of Shadle's 15 L eluate was likely PBS/glycine wash buffer. EX2015, ¶71. If Shadle's buffer was prepared using trisodium citrate and hydrochloric acid, as discussed above, the molarity of Shadle's adjusted sample was about 114 mM—above the claimed limit. EX2015, ¶71.

Petitioner and Dr. Przybycien failed to show Shadle's adjusted eluate is 100 mM or less even assuming Shadle used one of Dr. Przybycien's hand-picked buffer preparations (discussed in his deposition, EX2014). For example, according to Dr. Przybycien, his buffer no. 1 (prepared using 25 mM citric acid adjusted to pH 3.5 with NaOH) is 44 mM. EX2014, 92:12-13. If Shadle used such a buffer, as Dr. Przybycien hypothesized, Shadle's adjusted eluate would have been greater than 100 mM if at least 2.1 L of PBS/glycine wash solution was collected in Shadle's eluate—certainly a possibility, and far less than the amount assumed by the examiner in the European Patent Office, as discussed above. EX2001, 6; EX2015, ¶72.

2. Shadle's pH Adjustment Does Not Inherently Result in the Formation of Particles

(a) Petitioner fails to consider factors important to particle formation, and its expert admitted particles may not form in Shadle

Dr. Przybycien admitted that the solution in Shadle's Example IA *may not be clouded* after adjustment of the pH to 5.5. EX2014, 27:4-18. Thus, under the proper construction of "to form particles," Petitioner's expert admits this does not *necessarily* occur. *See supra* §IV.C.

In addition, Petitioner and its expert failed to consider numerous factors that are important to particle formation, but which cannot be determined from Shadle's disclosure. EX2016, ¶¶31-41. For example, particles take time to form, and Shadle provides no information as to how long the adjusted eluate was held in Example IA before subsequent filtering. EX2016, ¶43; EX2014, 107:4-16, EX1009, 54. But even if particles were assumed to eventually form, it would take time for this to occur, particularly under the correct construction of "to form particles," which requires clouding. EX2016, ¶43. Thus, even if, *arguendo*, clouding might *eventually* occur in Shadle's pH adjusted mixture, Petitioner failed to prove the adjusted eluate was held long enough for any clouding to have *necessarily* occurred in Shadle. EX2016, ¶¶43-44

Moreover, POSITA would have known there are other process compositions and conditions that affect whether and to what extent protein forms particles.

EX2014, 119:12-121:4. As POSITA would know, these factors include "pH, temperature, salt concentration, buffer type, protein concentration, ionic strength, mixing, shear, metal ions, pressure,…" as well as cavitation and concentrations of components. EX2016, ¶42; EX2007, 1; EX1009, 54, EX2013, 1; EX2014, 44:1-57:3. Petitioner and its expert fail even to consider most of these variables, and have thus failed to show that particles would necessarily have formed. EX2016, ¶¶42, 44.

Finally, if particles formed every time Shadle's procedure was followed (as Petitioner argues) and resulted in a clouded solution (as required under the correct construction), Shadle would certainly have reported it. POSITA would have understood that, given the value of the product being purified and the sensitivity and cost of column chromatography equipment, if particles formed every time Shadle performed these steps before cation chromatography (as is *required* for Petitioner's argument), Shadle would certainly have remarked on this, as it would have raised fundamental concerns both about the potential loss of the antibody being purified and its quality, and potential impacts on later steps in Shadle's process. EX2015, ¶38. Instead, Shadle says nothing of clouding. And Petitioner's expert acknowledges that Shadle's filtering, relied on in the Petition, is simply standard procedure before storing a solution or applying a solution to a

chromatography column, and would be done whether or not any particles formed. EX2014, 27:19-28:9; EX2015, ¶50.

(b) Petitioner's reliance on '289's disclosure fails to support their position that particles are necessarily formed in Shadle

Petitioner's expert makes clear that his conclusion that particles containing contaminant DNA inherently formed in Example IA of Shadle is based solely on '289's disclosures. *See, e.g.*, EX1002, ¶¶41-43, 83 ("as to the formation of particles in the neutralized and adjusted eluate, the conditions disclosed in 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, and I rely on the '289 patent's claims (which I understand are presumed to be enabled) that such conditions are sufficient for and result in the formation of particles. I also rely on the '289 patent specification's descriptions that these claimed conditions of the neutralized eluate 'produce[] particles.'"). Indeed, at deposition he was repeatedly asked the basis for his opinion regarding particle formation in Shadle, and each time he conceded he was relying solely on what the '289 (and its child '815) disclosed, referring back in every instance to the patent rather than to any independent knowledge or expertise. EX2014, 7:10-9:24, 15:3-16:3, 22:14-27:18, 44:1-57:16, 61:19-69:25, 72:10-77:17, 103:11-105:23; 106:16-107:10. But such "expert" testimony (mere reading) should be given no weight, and Petitioner

cannot rely on hindsight from ’289 to provide the missing support for Petitioner’s contention that particles will ***necessarily*** form in Shadle’s Example IA. *E.g.*, *Crown Operations*, 289 F.3d at 1377 (rejecting “the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property . . . should be assumed”); *see Zoltek Corp. v. United States*, 815 F.3d 1302, 1312–13 (Fed. Cir. 2016) (reversing decision resting on “insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher”).

Further, ’289’s disclosures do not support Petitioner’s contention that particles *necessarily* formed in Shadle’s Example 1A, regardless of whether the term “to form particles” requires clouding. Petitioner says the conditions in Example IA “fall within the same range of conditions” recited in step 4 of claim 1 of ’289, and thus, Petitioner argues, the eluate in Example IA necessarily produced particles. Pet., 36; EX1002, ¶¶83-85; EX2014, 32:10-33:3, 36:2-20, 37:3-38:17, 39:4-40:25, 63:1-64:25, 85:25-86:13, 88:18-89:16, 103:11-107:10. But as an initial matter, Petitioner failed to show the conditions in Example IA actually “fall within the same range of conditions.” EX2015, ¶74. As discussed in §V.C.1, *supra*, Petitioner failed to show the molarity limitations of the ’289 were

necessarily present in Shadle.[15] In addition, as discussed below, Petitioner failed to show that the conductivity of the acidic aqueous solution was within the range disclosed in Shadle—indeed, Petitioner ignored this entirely, despite its assertion that particles form if the conditions of the '289 are satisfied.

Dr. Pryzbycien said at deposition that the '289 patent requires, separate and apart from molarity and ionic strength requirements, the conductivity of the acidic aqueous solution be low for particles to necessarily form. EX2014, 32:10-33:3, 36:2-20, 37:3-38:17, 39:4-40:25; 85:25-86:13, 88:18-89:16. The '289 patent provides an example of low conductivity as "conductivity of 0 to 300 mS/m, preferably 0 to 200 mS/m, more preferably 0 to 150 mS/m." EX1001, 5:34-35. But, as discussed below, the conductivity of Shadle's ProSep A buffer, which Petitioner maps to the acidic aqueous solution, is *not* necessarily low. ¶74-76.

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[15] Thus, Petitioner's reliance (*e.g.,* Pet., 39) on cases like *Knauf Insulation, Inc. v. Rockwool Int'l,* 680 Fed. App'x. 956 (Fed. Cir. Feb. 27, 2017) (unpub'd), is, *inter alia*, inapposite. *Cf. id*., 960-61 (citing "*identity* of reactants and process steps" between prior art and challenged patent); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (relying on "express[] disclos[ure]" of *overlapping concentrations* with patent claims, and patent's "defin[ition of] mast cell stabilization as a property that is *necessarily present* at those concentrations").

Shadle does not specify how this buffer was prepared; it merely lists a ProSep buffer of 25 mM citrate at a pH of 3.5. EX1003, 20. For example, Shadle's buffer (25 mM citrate, pH 3.5) could very well have been prepared using 25 mM trisodium citrate and hydrochloric acid—a well-known and reasonable choice at the time for forming Shadle's buffer. EX2015, ¶59; EX2005 (preparing elution buffers by adjusting trisodium citrate pH to 3.07 and 4.25, respectively, using hydrochloric acid); EX2014, 88:22-24. The conductivity of such a buffer is not low—it is well above 600 mS/m. EX2015, ¶¶77-79. Dr. Brittain experimentally determined the conductivity of a 25 mM citrate buffer at a pH of 3.5, prepared using trisodium citrate and hydrochloric acid. EX2019, ¶¶2, 21-24. He prepared the buffer three times, and measured the conductivity of each. *Id.* ¶¶18-21. The conductivity exceeded 600 mS/m each time. *Id.* ¶21. Dr. Brittain's experimental results are also consistent with Dr. Cramer's expectation that the conductivity of such a buffer would exceed 300 mS/m. EX2015, ¶¶77-79; EX2009, 4. Thus, it cannot be proven that the conductivity of the ProSep A in Shadle is low, and it cannot be shown that Shadle is in the range of conductivity described in the '289, and which Dr. Przybycien stated is required for particle formation. EX2015, ¶80.

Even if Petitioner's (and its expert's) premise that two conditions in Example IA "fall within the same range of conditions (pH of 4-8 and molarity less

than 100mM)" as '289 (Pet., 36; EX1002, ¶¶83-85; EX2014, 103:11-106:15) had been proven true (it hasn't), Petitioner's assertion that '289 teaches these two conditions alone are "sufficient to form particles" (*id.*) is false. Petitioner's and Dr. Przybycien's attempt to stitch together a hindsight disclosure of the claimed invention using isolated statements from '289 (*e.g.,* Pet., 36-37; EX1002, ¶83) misrepresents '289's actual teachings. For example, while '289 notes the adjustment step of the claimed invention produces particles (EX1001, 6:4-8 ("According to the present invention…") (cited in Pet., 36)), '289 *also* explains that the "a neutral [pH] level" and the "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.***" EX1001, 5:37-40, 5:54-56. And the inventors further confirmed "those skilled in the art will readily determine optimal conditions for these parameters in preliminary experiments as described [in the specification]." *E.g.*, EX1001, 5:40-42, 5:56-60; EX2016, ¶36. Petitioner and Dr. Przybycien simply ignore these disclosures, offering no analysis of what parameters would lead to particle formation *for the particular antibody Shadle was purifying* (RSHZ-19), which is not among the examples the '289 discusses. EX2016, ¶¶33-34, 40-41; EX2014, 15:3-25, 22:14-28:9, 44:1-57:16, 61:19-69:25, 72:10-75:18, 103:11-105:23.

As Dr. Koths explains, trying to analyze whether particles would necessarily have formed in Shadle's Example IA in the absence of experimental results and without the many parameters Shadle's description simply left unknown is a *necessarily uncertain* enterprise. EX2016, ¶¶33-34. As '289 teaches and POSITA well understood,[16] particle formation depends on the properties of the particular antibody and a number of other process compositions and conditions. EX2016, ¶¶36-44; EX2006, 2. Different antibodies—even closely related antibodies—behave differently with respect to particle formation under different conditions.[17] EX2016, ¶¶40-41. Petitioner's simplistic analysis failed even to *attempt* to account for these variables and complexities, and certainly failed to show that particles *necessarily* formed in Shadle's Example IA. EX2016, ¶41; EX2014, 71:12-14.

In addition, with respect to the impact of temperature on particle formation, Shadle says only that the steps of Example 1 were carried out at the widely-varying temperature range of 18-25°C. EX1003, 15. But when asked at deposition about

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[16] *See Hybritech Inc. v. Moncolonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art").

[17] For example, even "subtle variations" in an antibody's amino acid sequence "greatly affect responses towards low-pH incubation and subsequent neutralization." EX2012, 1-2; EX2016, ¶40; *see also* EX2008, 1-2.

temperature conditions and whether this would affect particle formation, Dr. Przybycien—ignoring what POSITA reading '289's specification would know (*e.g.*, EX2016, ¶42)—failed to provide any understanding of the temperature range at which particles would form other than to refer to "ambient temperature," which he could not concretely define. EX2014, 44:1-57:3. Tellingly, Dr. Przybycien was *unable to answer whether particles would form at 20°C*—well within the range of Shadle's Example IA reported conditions. *Id.* 47:22-57:3 ("Q: Will particles form at 20 degrees?...A: Again, this is laid out as being practiced at ambient temperature, so if you were practicing this at ambient temperature, caccording to these conditions, you would expect to find particles…Q: Is 20 degrees at ambient temperature? A: It's not clear. It's not laid out what their expectation for temperature is. . . Q: Do you know whether particles would necessarily form at 20 degrees Celsius? . . . A: Again, I have no [not] considered temperature dependence, and it has not been explicitly called out.").

(c) Neither Scopes nor the patent's prosecution history supports inherency; indeed, Scopes underscores that the formation of particles is not inherent.

The only purported support Petitioner offers for its assertion that formation of particles under Shadle's recited eluate solution conditions is "inherent" other than the '289 and its prosecution, is Dr. Przybycien's citation to Scopes (EX1009). Pet., 37 (citing EX1002, ¶¶83-85); EX1002, ¶84.

But Dr. Przybycien now claims not to have relied on Scopes for anticipation (EX2014, 109:6-14, 110:11-20) and, moreover, provides no explanation for such inherency—his assertion is merely the conclusory statement that particle formation is "consistent with" Scopes' disclosures. *See, e.g.*, *Albaad Massuot Yitzhak,* IPR2017-00693, Pap. 11, 9-10 (July 17, 2017) (establishing inherency requires more than conclusory statement). And Scopes does not teach that particle formation *necessarily occurs* under Shadle's conditions. EX2016, ¶35, 45. Quite the contrary: Scopes says only that "some proteins form particles," and goes on to say (as Petitioner's expert quotes) that "[m]ost" isoelectric precipitates are aggregates of many different proteins and "may include…protein-nucleic acid complexes." EX1009, 28; EX1002, ¶84; EX2016, ¶45. Petitioner does not address how the mere possibilities mentioned in Scopes—for conditions that are not demonstrated to match those of Shadle to begin with—provide a basis for proving that particles *necessarily* form *every time* in Shadle's Example IA. Petitioner's omission is particularly telling given that Scopes expressly concedes that particles *do not* always form: it states that "some" proteins form particles and "may" do so under certain conditions, thus expressly confirming this is *not always what occurs*. *White v. H.J. Heinz Co*., 640 Fed. App'x 930, 933, 2016 U.S. App. LEXIS 2867, *4-6, 2016 WL 683822 (Fed. Cir. Feb. 19, 2016); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (claimed invention not

inherent when allegedly inherent compound was not produced every time by following the teachings of the reference even though validity challenger's expert performed prior-art example 13 times and obtained claimed material); EX2014, 109:6-14, 110:11-20; EX2016, ¶¶35, 45-46. That particles do not *necessarily* form when an antibody solution is neutralized was not only the understanding at the time of Scopes and the ’289 patent, but also remained the understanding in, *e.g.*, 2011. EX2013, 5 (“***[s]ome*** mAb [monoclonal antibody] solutions ***might*** exhibit a turbid appearance following neutralization [with, for example, Tris].”); *id.* 2; EX2016, 46.

Further, contrary to Petitioner’s arguments that Chugai’s statements during prosecution support Petitioner’s inherency theory (Pet., 37), Chugai never told the Patent Office that particles would necessarily form under Shadle’s Example IA conditions. During prosecution, to overcome a *different* reference, Tsuchiya, Chugai argued particles were *not* inherently formed in Tsuchiya because the “conditions described in the disclosure and carried out in the examples are fundamentally different from those stipulated in applicants’ claims and required according to the present invention.” EX1005, 38. Chugai argued Tsuchiya could not be a basis for anticipation or obviousness because Tsuchiya “is silent about the formation of particles containing DNA contaminants.” *Id.* Chugai also pointed out that DNA particles were not formed in Tsuchiya because of the neutralized

eluate's high molarity, *i.e.*, over 100 mM. *Id.*, 37. Nowhere did Chugai suggest the inverse. And Chugai certainly never suggested that *any* protein eluate having its pH raised to *any* level between 4 and 8 would *necessarily* form particles without regard to other conditions. Nor would any POSITA have believed this to be the case. *See, e.g.*, EX2016, ¶¶36-41.

(d) The Law Does Not Support Inherency Under the Circumstances Petitioner Admits Exist

Petitioner's expert admitted he did not recognize that particles formed in Shadle *before he reviewed the '815 and '289* patents. EX2014, 24:6-24. And, in Shadle, even if particles formed, it would have been an accidental (and, in fact, undesirable (*see, e.g.*, EX2015, ¶38)) result of Shadle's process. If a result is unintended and unappreciated when first achieved, and only later recognized, then such so-called "accidental" achievements do not anticipate subsequent inventions. *Tilghman v. Proctor*, 102 U.S. 707, 711-12 (1881); *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923); *In re Seaborg*, 328 F.2d 996, 998-99 (CCPA 1964). Although the Federal Circuit has in some more recent instances not required that POSITA would have recognized the inherent property, the prior precedential cases requiring such recognition have not been reversed, are still good law, and should be applied here. *Schering Corp. v. Geneva Pharm., Inc.*, 348 F.3d 992, 995 (Fed. Cir. 2003) (Newman, J., dissent) ("The panel now contradicts this body of precedent, stating that it "rejects the contention that inherent anticipation

requires recognition in the prior art." A rejection of precedent requires en banc action, not panel disruption"); *EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342 (Fed. Cir. 2001) ("Such recognition by one of ordinary skill may be important for establishing that the descriptive matter would inherently exist for every combination of a claim's limitation"); *Elan Pharm., Inc. v. Mayo Found.*, 304 F.3d 1221 (Fed. Cir. 2002), *vacated* 314 F.3d 1299 (Fed. Cir. 2002) (en banc), *aff'd on other grounds*, 346 F.3d 1051 (Fed. Cir. 2003); *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). Further, the Federal Circuit has recognized that the requirement that POSITA recognize the missing but inherent matter "may be sensible for claims that recite … compositions of matter, and method steps," as contrasted with laws of nature. *EMI Grp.*, 268 F.3d at 1350-51. Here, the claims require a method step, and particle formation is not a law of nature. Thus, even if particles formed in Shadle (by accident and, as Dr. Przybycien testified, with no recognition until the '289 and ''815 (EX2014, 24:6-25:22)), such formation should not be deemed anticipatory.[18]

[18] Petitioner's citations to *Teleflex, Inc. v, Fisosa N. Am. Corp*, 299 F.3d 1313, 1335 (Fed. Cir. 2002), MPEP §2124, and *In re Wilson*, 311 F.2d 266, 269 (C.C.P.A. 1962) are also inapposite. *Teleflex* relied on additional references to show the claimed subject matter was "in the public's possession," *Teleflex*, 299 F.3d at 1335—not the situation here. And MPEP §2124 and *In re Wilson* address

D. “removing the particles to thereby remove contaminant DNA in the antibody-containing sample”

Petitioner has also failed to establish that the filters used Shadle’s Example expressly or inherently remove any contaminant DNA from the Example IA eluate. First, Petitioner has not proven particles form; therefore they cannot be removed. EX2015, ¶¶81-82. And, neither Petitioner nor its expert provides any information about the size of the particles allegedly formed in Shadle or whether and why they would be understood to comprise contaminant DNA. Moreover, neither explains why, if particles comprising contaminant DNA *did* form in Shadle, they would be the same size as the particles disclosed in examples of the ’289. Indeed, even if particles were to form in Shadle (regardless of whether this is construed to require clouding or not), Petitioner has not addressed the size of such putative particles, nor can such information be determined without more information. EX2016, ¶48.

Petitioner cites Martin in attempt to support its argument that Shadle’s Polygard and Millipak filters remove particles with contaminant DNA. But Martin (EX1010, cited in Pet., 38) does not address the removal of particles comprising contaminant DNA. Rather, it discusses using a membrane filter before other

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the exception to the rule that a reference date precedes the filing date of the patent at issue when it relates to “characteristics of a material or a scientific truism” (MPEP §2124)—an argument that fails to solve Petitioner’s lack of proof.

filtration steps such as column chromatography in order to "prevent premature plugging." EX1010, 30. And even in this context, Martin merely says that "[i]n ***most*** cases, a 0.2-µm-rate sterilizing grade membrane filter is employed as the fluid filter," and the '289 specification merely states that "particles may be removed by filtration through a filter" and that "***[e]xamples*** 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." *See* EX1002, ¶¶89-90 (quoting EX1010, 30 and EX1001, 6:6-11); EX2015, ¶¶83-84. But Petitioner does not demonstrate that Shadle's contaminant DNA is identical to the '289's, or why these filters would be expected to remove contaminant DNA in Shadle, which expressly refers to later HIC chromatography as performing this role. EX1003, 18; EX2014, 112:4-12; EX2015, ¶¶84-85.

Petitioner and its expert also fail to explain why Shadle's additional cation chromatography column and HIC column are needed to remove DNA *after the steps they argue satisfy the Challenged Claims* if, as Petitioner contends, the DNA has necessarily already been removed by the prior filtration steps. EX2015, ¶¶85-92.

Furthermore, even if it were assumed that particles were formed and were removed in Shadle's Example IA, removing those particles would not necessarily have removed contaminant DNA. EX2016, ¶¶47-48. For example, Petitioner's

expert apparently takes the position that clouding is not required for particles to form. EX2014, 27:9-18, 104:5-105:9. And, as discussed above (§V.C.2(a)), Shadle does not disclose how long, if at all, the pH-adjusted solution sat in Example IA before being filtered. Thus, even if it were assumed that some sort of particles were eventually "formed" in Shadle (with or without the clouding required by the Challenged Claims, §IV.C), it is not necessarily the case that any were formed by the time of Shadle's filtering and thus even present to be removed, let alone that any such particles contained DNA. EX2016, ¶¶49-51; EX2010, 1, 7. Again, Petitioner has failed to establish inherency for this limitation.

VI. Dependent Claims 2-5 and 13Are Not Anticipated For Additional Reasons

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

As discussed in §V.C.1, *supra* Petitioner fails to show that the molarity of Shadle's ProSep A elution buffer necessarily has a molarity of 50 mM or less. Indeed, if Shadle's ProSep A buffer was prepared using trisodium citrate and hydrochloric acid, its molarity would have been at least 77.1 mM. EX2015, ¶86.

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

Petitioner asserts this limitation is met because the 25mM Citrate buffer solution "contains" citric acid. But Petitioner failed to address the claims "consisting of" language, which is strongly presumed to be a closed term. *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016) (holding that "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" and "presumption that a claim term set off by the transitional phrase 'consisting of' is closed to unrecited elements is at least a century old"). The ProSep A buffer, which includes the 25mM citrate buffer, includes more than just citric acid (EX2014, 90:23-92:19), and therefore does not "consist of" (and is not the claimed aqueous solution of) citric acid. For this same additional reason, Petitioner has failed to address Claim 4, which depends from Claim 3.

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

Petitioner asserts Shadle disclosed this claim because it discloses a DNA concentration of <1pg/mg and a protein concentration of 2.4mg/ml. Pet., 42. But this DNA concentration is only achieved "by practicing the process of [Shadle's

entire] invention" (Pet., 41-42; EX1003, 14), which requires ion exchange and HIC column chromatography steps. *See* §III, *infra*; EX1003, 6. As Shadle expressly describes, and POSITA would have understood, the DNA concentration relied on by Petitioner as being achieved by practicing Shadle, is the concentration *after* those prior art ion exchange and HIC column chromatography steps. EX1003, 14. EX2015, ¶¶87-88.

Petitioner failed to address how Shadle meets this limitation under the proper construction of "the treated sample . . .," which requires that the concentration of DNA be below 22.5pg/ml *in the sample resulting from performing the method of claim 1*, which concludes with removing particles in step 4. *See* §IV.D; EX2015, ¶89; EX2014, 114:7-24. Not surprisingly, Shadle discloses nothing about the concentration of DNA at this point in the process, which by Petitioner's argument is filtering by Polycard and Millipak filters—a point before any HIC or ion exchange chromatography (which remove DNA).[19] *Id.* Therefore, Shadle cannot anticipate this additional limitation of claim 5.

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[19] Nor does Shadle describe how long, if at all, the adjusted eluate is held before filtering—a variable that would impact DNA concentration even if particles formed. *See supra* §V.C.2(a).

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

Petitioner asserts this limitation is met explicitly or inherently through filtration through a Polygard and Millipak filter. Pet., 43. But Petitioner failed to establish that the filtration process achieves removal of particles. *Supra* §V.D.

VII. The Challenged Claims Are Not Obvious

Petitioner's brief and conclusory obviousness arguments (Pet., 44-48) are limited only to step 4 of claim 1, which requires "removing the particles to thereby remove contaminant DNA from the antibody-containing sample." EX1001, 12:57-58. Petitioner states a "POSA would have been motivated to remove particles or aggregates containing DNA …" Pet., 46.

But as to that particle removal step (step 4), Petitioner provides ***no*** explanation of how Shadle would be modified, even though Petitioner's expert concedes this analysis is necessary (*see* EX1002, ¶¶21-22). *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) (holding that the "differences between the prior art and the claims at issue are to be ascertained" under a proper obviousness inquiry). In fact, Petitioner insists there "is no patentable difference between the prior art antibody purification process of Example IA in [sic, Shadle] and the claimed invention" but provided no explanation as to what that difference there might be if the Board does not find anticipation. Pet., 46. This violates the Board's rules and the Federal Circuit's minimum requirements for any showing of

obviousness (*see, e.g.*, 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.104(b)(4); *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016)), improperly leaving it to the Board and Chugai to guess how Petitioner might argue to modify Shadle. *E.g.*, *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap. 6, 14 (Jan. 31, 2017) (confirming Petitioner's responsibility "to explain specific evidence that support[s] its arguments, not the Board's responsibility to search the record and piece together what may support Petitioner's arguments"); *Kingston Tech. Co. v. Polaris Innovations Ltd.*, IPR2016-01623, Pap. 33 at 14-16 (Feb. 9, 2018) (citing *Intelligent Bio-Sys.*, 821 F.3d at 1369) (refusing to consider new arguments supporting obviousness not originally articulated in petition).

Further, Petitioner never explains why POSITA would be motivated to modify Shadle to achieve the claimed invention. *See, e.g.*, *Elec. Arts Inc. v. Terminal Reality, Inc.*, IPR2016-00928, Pap. 48, 42 (Oct. 23, 2017). For instance, Petitioner does not say (let alone explain why) POSITA would appreciate that, according to Petitioner, particles formed in Shadle to begin with. *Cf.* EX2014, 24:6-25:22. Indeed, Shadle mentions nothing about particle formation after adjustment of the pH to 5.5. Petitioner's expert stated that the alleged particle formation in Shadle may not result in clouding. *Id.* 21:7-22:24, 27:4-19, 104:2-105:9. Setting aside the proper construction of "to form particles," if particles had formed in Shadle but not clouded, POSITA would not have been able to *see* any

particle formation. EX2014, 27:4-18; *contrast* EX1002, ¶83; *see* §IV.C, *supra*. Thus, because there is no proof that POSITA would even have appreciated that particles formed in Shadle, POSITA would have had no reason to *modify* Shadle to remove any alleged particles. EX2015, ¶¶90-91. Nor has Petitioner demonstrated POSITA know to hold the solution at a pH of 5.5 for long enough such that particles could form (let alone particles that result in clouding), and such that particles containing DNA could be filtered out. EX2016, ¶¶52-53. In fact, POSITA would have wanted to avoid such particle formation. EX2015, ¶38. For these same reasons, contrary to Petitioner's conclusory assertions about reasonable expectation of success (Pet., 47), POSITA would not have expected the filter would remove particles, because POSITA would not have known there were any particles to begin with and would not have had reason to wait to filter in hopes that particles would eventually form. EX2015, ¶¶90-92; EX2016, ¶¶53-55.

Similarly Petitioner fails to explain why POSITA would modify Shadle when *Shadle already purports to accomplish DNA purification* (without need for any modification) using the very prior-art chromatography techniques that the '289 sought to *avoid*. *See* EX1001, 1:57-67; EX1003, 16, 18; *see, e.g.*, *Arris Int'l Plc. v. Sony Corp.*, IPR2016-00828, Pap. 10 at 13–18 (Oct. 7, 2016) (no motivation where prior art already addressed alleged problem/need). Accordingly, Petitioner fails to

explain why POSITA would have been motivated to make whatever modification(s) to Shadle Petitioner might imagine.

Even if Petitioner now recognizes the palpable weaknesses in its obviousness arguments, Petitioner may not now attempt to add new arguments in Reply to address them. Moreover, Petitioner may not now attempt to expand its obviousness arguments beyond the single particle removal limitation it argued was obvious in the Petition. *See* Pet., 46 ("In view of the disclosures of WO '389 as discussed above, the conditions of the neutralized and pH adjusted eluate of Example IA in WO '389 would inherently have formed particles, and *a POSA would have been motivated to remove particles or aggregates containing DNA* formed in the neutralized and adjusted pH buffer solution of Example IA as part of the purification process. . . . As such, a POSA would have had *a reasonable expectation of success* that the 0.1 micron and 0.2 micron filters would work as intended to remove any particles that are formed."). Petitioner is only permitted to rely on—and Chugai can only be expected to respond to—the arguments Petitioner actually made in its Petition. *See* n.18, *supra*.

A. Secondary Indicia Support Nonobviousness of the Challenged Claims

The surprising and beneficial results achieved by the '289 in eliminating the need for successive chromatography steps to remove DNA in protein purification—and thus the associated costs, delays, complications and

inefficiencies that had made reduced reliance on chromatography a long-standing focus in the field—constitute objective evidence of nonobviousness that *must* be considered in any obviousness analysis. *See, e.g.*, *Graham,* 383 U.S. at 17-18 (such objective indicia, referred to as "secondary considerations," "give light to the circumstances surrounding the origin of the subject matter sought to be patented."); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) ("Objective indicia … play a critical role in the obviousness analysis."); *Circuit Check Inc. v. QXQ Inc.*, 795 F3d 1331, 1337 (Fed. Cir. 2015); EX2015, ¶30. This *mandatory* consideration is required to avoid precisely the sort of improper hindsight Petitioner employed here, using the '289 itself as a hindsight road-map to try to piece together the '289's invention. These material facts are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness…[that] enable[] the court to avert the trap of hindsight." *Leo Pharm.*, 726 F.3d at 1358 (citations omitted). When present, such "objective evidence *must be 'considered* as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

Although Petitioner ignored these secondary indicia altogether, it was certainly aware of them—indeed, they are described in the very first column of the ’289, where the patent explained that:

> these individual chromatographic processes and a combination thereof are time-, labor- and cost-consuming, as well as being complicated. Moreover, they fail to provide stable results.
>
> Thus, there is a need to develop a simpler and less expensive method for purifying physiologically active proteins, especially antibodies, which can ensure removal of contaminant DNA, and which can minimize a loss of physiologically active proteins.

EX1001, 1:13-57.

As a result of extensive efforts to overcome these problems, the ’289 inventors made the surprising finding that contaminant DNA can be efficiently removed from a sample containing an antibody without using complicated chromatographic processes by converting the sample into an acidic aqueous solution of low conductivity, neutralizing by addition of a buffer to raise the pH to a neutral level, and then removing the resulting particles (*e.g.*, with a filter) to remove contaminant DNA in the sample. *See, e.g.*, EX1001, 1:57-67, 12:56-58. This finding led to the completion of the present invention—a discovery clearly

solving a problem in the prior art with results the inventors recognized and described to the art at the time as "surprising."[20] *Id.*

After arguing at length that this breakthrough was somehow in the art already in the form of a reference (Shadle) that, as detailed above, neither recognized nor inherently yielded these surprising results—and, instead, simply taught the same prior art processes the '289 inventors were affirmatively criticizing and replacing—Petitioner and its expert briefly try to portray these results as an obvious commonplace that would have been apparent to any POSITA. EX1002, ¶¶103-105; Pet., 45-47. But their own words many years *after* the invention of the '289 reveal this is not the case.

For example, in 2004—well *after* the 2002 priority date of the '289 patent, but years before it issued in 2011—Petitioner's expert, Dr. Przybycien, wrote about "*Alternative Bioseparation Operations: Life Beyond Packed-Bed*

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[20] This long felt need and the surprising results have a clear nexus to the asserted claims: It is the formation and removal of particles, as explicitly claimed, that eliminates the need for these costly, time-consuming and inefficient extra chromatography steps to remove contaminant DNA and resolve the long felt need for such elimination. Likewise, the formation of particles using this technique, as in the claims, is the surprising result described above that permits removal of contaminant DNA by simple filtering/particle removal.

Chromatography." EX2003, 1. In that article (years before he was given his present mission to invalidate the '289), Dr. Przybycien stressed the importance to POSITA of finding "chromatography alternatives" because chromatography "ha[d] the notoriety of being the *single largest cost center in downstream processing* and of being a *low-throughput operation*." EX2003, 1.[21] And, far from his assertion *today* that it would have been "obvious," Dr. Przybycien *in 2004* described the use of precipitation of particles (including "subtractive precipitation") to "reduc[e]"

[21] Packed-bed chromatography includes size-exchange, HIC and ion-exchange chromatography. EX2015, ¶28. Despite making these statements about the expense of packed-bed chromatography before being retained by Pfizer, Dr. Przybycien now asserts such chromatography steps are *not* expensive. EX2014, 112:13-113:18. His shifting opinions within this case (*see, e.g.*, *supra* §V.C.1) and between 2004 and now, combined with his evasiveness at deposition (*see, e.g.*, EX2014, 44:1-54:11 and 66:12-69:25 (refusing to answer questions regarding what he meant by "ambient temperature"), 103:15-105:9 (refusing to explain his understanding of "to form particles"), 106:4-107:16 (admitting inability to figure out how long argued particles in Shadle would take to form), 63:1-65:23 and 74:5-75:18 (refusing to explain whether he would have concluded particles are formed without relying on the disclosure of the '289 and '815), indicate Dr. Przybycien's testimony is not credible and should be given little to no weight.

chromatography steps as "unthinkable" at the time. EX2003, 1 ("This paper reviews the current state of unit operations *posing as chromatography alternatives*—including . . . precipitation…—and their potential to *do the unthinkable*"), 3 (discussing, *inter alia*, "subtractive precipitation mode to remove nucleic acids during or after cell lysis using polycationic compaction agents such as spermine"; "Despite its relative maturity, there is much left to understand about precipitation"). *See also* §II, *supra*; *Circuit Check*, 795 F3d at 1337 (considering "[w]ith respect to long-felt need . . . that the industry tried multiple prior art [] methods preceding [patented] invention").

Dr. Przybycien's praise for the kind of results achieved by the '289 inventors, eliminating costly serial chromatography steps to remove contaminant DNA, and his frank assessment years *after* the '289 invention (but before its issuance) that POSITA had not yet solved this problem are powerful evidence that their obviousness arguments (flawed in many other respects, *see supra*), are meritless. *See, e.g.*, *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir 2016) ("Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious."); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed.

Cir. 2012) ("Evidence that others were going in different ways is strong evidence that the inventor's way would not have been obvious.")

This independent evidence of nonobviousness, *Leo Pharm.*, 726 F.3d at 1358, provides yet another reason the Board should deny the Petition's instituted obviousness challenge. *See, e.g.*, *Millenium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017) (reversing invalidity determination; "unexpected properties" of new compound and "ensuing pharmaceutical efficacy and benefit, negate the district court's ruling of obviousness").

Respectfully submitted by: Dated: February 26, 2018

/J. Steven Baughman/
J. Steven Baughman (Reg. No. 47,414)
Paul, Weiss, Rifkind, Wharton &
Garrison LLP
2001 K Street, NW
Washington, DC 20006-1047
P: 202-223-7340/F: 202-403-3740
sbaughman@paulweiss.com

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton &
Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

Attorneys For Patent Owner

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120 complies with the type-volume limitation in 37 C.F.R. § 42.24(b)(2). According to the word-processing system's word count, the brief contains 13,575 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(c).

Dated: February 26, 2018

Respectfully Submitted,

By: */Megan Raymond/*

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Petitioner's Counsel of Record:

Jovial Wong (Reg. No. 60,115)
Charles B. Klein
Eimeric Reig-Plessis
WINSTON & STRAWN, LLP
1700 K St. NW
Washington, DC 20006
jwong@winston.com
cklein@winston.com
ereigplessis@winston.com
rituximabIPR@winston.com

Sharick Naqi
WINSTON & STRAWN, LLP
35 W. Wacker Drive
Chicago, IL 60601
snaqi@winston.com

Dated: February 26, 2018

Respectfully Submitted,

By: */Megan Raymond/*

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com