UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

CHUGAI PHARMACEUTICAL CO. LTD.,
Patent Owner

Case IPR2017-01358
Patent 7,927,815

PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

LIST OF EXHIBITS

Exhibit	Description
Ex.2001	Excerpt of European Prosecution History of Application No. 03795400.5
Ex.2002	Declaration of Megan Raymond

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REGULATIONS

Pursuant to 37 C.F.R. § 42.107,[1] Patent Owner Chugai Pharmaceutical Co. Ltd. ("Chugai") submits this Preliminary Response to the above-captioned Petition for *Inter Partes* Review of U.S. Patent No. 7,927,815 ("Petition" or "Pet." Paper 2), which should be denied in its entirety for failure to show a reasonable likelihood of prevailing on any asserted ground.

I. Introduction

Petitioner's submission fails to provide the Board with the basic evidence required to institute any *inter partes* review. If the Board nonetheless institutes trial on any of the Challenged Claims,[2] Patent Owner will address in detail in its § 42.120 Response the numerous substantive errors and shortcomings in Petitioner's arguments and its purported evidence. Here, however, where testimonial evidence raising an issue of material fact "will be viewed in the light most favorable to the petitioner" (§ 42.108), Patent Owner addresses only Petitioner's construction of one of the Challenged Claims' pertinent terms and the single issue made pertinent by § 42.107: Petitioner's failure to demonstrate, as to *any* of the Challenged Claims, a reasonable likelihood of success on any asserted

[1] All emphasis/annotations added, and all statutory and regulatory citations are to either 35 U.S.C. or 37 C.F.R., as the context indicates, unless otherwise stated.

[2] Claims 1-7 and 12-13 of U.S. Patent No. 7,927,815 (the "'815").

ground of invalidity. Because of this threshold failure, the Petition should be denied and no *inter partes* review should be instituted under 35 U.S.C. § 314.

To justify institution of an *inter partes* review, Petitioner's papers must make a *prima facie* showing that, as a factual and legal matter for each asserted ground, Petitioner has shown a reasonable likelihood of proving at least one Challenged Claim unpatentable. *See, e.g.*, 35 U.S.C. § 314; 37 C.F.R. § 42.108(c). Petitioner's own arguments and evidence confirm that it cannot meet that burden for *any* asserted ground.

Petitioner relies on a single embodiment of just one reference—Example IA in International Publication No. WO 95/22389 to Shadle, et al. ("Shadle") (Ex.1003)—for both its § 102(b) and § 103(a) grounds. Pet. 5. But Petitioner's § 102 arguments rely on multiple layers of supposed "inherency" in a hand-waving attempt to dismiss several key limitations of the Challenged Claims, and its sparsely-stated obviousness arguments are incomplete and contradict the central teachings of its asserted Shadle reference. Petitioner fails to demonstrate a reasonable likelihood of showing that Shadle discloses or renders obvious all of the elements of independent claim 1 (and thus of the other Challenged Claims 2-7 and 12 which depend from claim 1) and independent claim 13, including, *inter alia*, a "method for removing contaminant DNA in a sample containing physiologically active protein"; "converting the sample containing a physiologically active protein

into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9"; "adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less"; "neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles, wherein the molarity of the neutralized sample is 100 mM or less"; "removing the particles thereby to remove contaminant DNA"; and "filtering the resulting sample from step (2) to remove particles containing contaminant DNA." Petitioners also attempt, but fail, to argue aspects of Shadle based on the Scopes reference (Ex.1009), the Martin reference (Ex.1010), and the '815 Patent itself.

The Petition also simply ignores the surprising result—expressly described in the '815 but tellingly absent from Shadle—of precipitating particles comprising DNA under the conditions described in the Challenged Claims, which allows the claimed step of "removing the particles thereby to remove contaminant DNA" (claim 1) and "filtering the resulting sample from step (2) to remove particles containing contaminant DNA" (claim 13). *See, e.g.*, Ex.1001 1:61-2:4, 12:48-50, 14:9–10. Indeed, the '815 explains that a particular advantage of its invention over the prior art is the *avoidance* of the need to perform additional column chromatography to remove contaminant DNA, which is "time-, labor- and cost-

consuming, as well as [] complicated." *Id.* 1:40–57. And while the Petition attempts to argue that the '815's claimed invention is disclosed or rendered obvious by Shadle, in fact Shadle teaches doing *precisely what the '815 criticizes and renders unnecessary*. As Petitioner admits, Shadle involves "purifying an IgG (Immunoglobulin) antibody by sequentially subjecting a medium . . . to several purification steps." Pet. 27–28. Further, Shadle is about removing Protein A that leaches during Protein A column chromatography (Ex.1003 at 6), and says nothing about forming or removing of particles comprising contaminant DNA. Rather than avoiding and rendering unnecessary additional column chromatography to remove contaminant DNA later, as taught by the '815 (Ex.1001 1:61–2:4), Shadle instead teaches the opposite: removing DNA *using additional column chromatography steps* (Ex.1003 at 16–18).

Further, Shadle's Example IA—the example on which the Petition relies to satisfy the limitations of the Challenged Claims—says *nothing* about the removal of DNA (let alone, "contaminant DNA") from *any* solution it discloses. Example IA says *nothing* about conductivity. Example IA says *nothing* about the molarity of the Protein A eluate after its pH is adjusted. Example IA says *nothing* about the formation of particles (let alone the formation of particles comprising contaminant DNA). And Example IA says *nothing* about the removal of any such particles

from the eluate. All of these elements are required by the Challenged Claims. But the Petition fails to explain how any of them are disclosed in Shadle.

This is likely why the Petition frequently cites to no particular page or passage from Shadle, relying instead and only on conclusory statements from its expert, who in turn generally fails to cite any particular part of Shadle. *See, e.g.*, Pet. 34 (discussing Shadle's purported disclosure of a method removing contaminant DNA in a sample containing a physiologically active protein), 43–46 (discussing Shadle's purported disclosure of formation of particles) (citing Ex.1002 ¶¶ 100–102), 47–48 (discussing Shadle's purported "express[ ]" disclosure of using its filters to remove particles) (citing Ex.1002 ¶ 105). As the Board has made clear, these sorts of conclusory assertions are not evidence, and cannot meet Petitioner's burden. *See, e.g.*, *Smith & Nephew, Inc. v. Conformis, Inc.*, IPR2017-00487, Paper 7 at 13–14 (July 7, 2017) (denying institution, noting that "the Petition and the Declaration do not offer more than conclusory assertions . . ."); *C.R. Bard, Inc. v. Medline Indus., Inc.*, IPR2015-00511, Paper 9 at 11 (July 15, 2015) (denying institution where petition and expert declaration both lacked "any explanation," beyond "conclusory statement[s]," about how a claim element was disclosed in the prior art). Even an inherency argument must point to some specific passage or passages to prove where and how the reference anticipates, yet Petitioner's inherency arguments, too, are wholly conclusory.

Moreover, Petitioner never cites or distinguishes contradictory statements in the very sections of Shadle on which the Petition relies.

Petitioner's single-reference obviousness arguments fare no better, as Petitioner fails to explain *what* would be modified in Shadle and *why* a POSITA would have been motivated to make such a modification. *See, e.g.*, *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) ("To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on the evidence of record, to support the legal conclusion of obviousness."); *see also Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Paper 10 at 10–11 (July 6, 2017). Indeed, Petitioner and its expert fail to cite to any particular portion of Shadle at all in their obviousness arguments, leaving it to the Board and Patent owner to guess what Petitioner might rely upon. *See* Pet. 55–59; Ex.1002 ¶¶ 130–133. The Rules forbid this (*see* 37 C.F.R. § 42.104(b)(2), (4)–(5)), and Petitioner's failure to articulate a basis for its obviousness arguments compels denial of institution; a Petition is not an invitation for the Board or the Patent Owner to go searching for support for Petitioner's argument. *See Sanofi-Aventis U.S. LLC v. AstraZeneca Pharms. LP*, IPR2016-00348, Paper 10 at 7 (June 28, 2016) (declining to "attempt to fit evidence together into a coherent explanation" or "requir[ing] [p]atent [o]wner to engage in a similar exercise"); *see also John Crane, Inc. v. Finalrod IP,*

LLC, IPR2016-01827, Paper 6 at 14 (Jan. 31, 2017) (finding "the lack of clarity in Petitioner's presentation deprives Patent Owner of an appropriate opportunity to respond to the Petition, and does not lend itself to informed evaluation by the panel").

The very purpose of the § 314 threshold is to avoid the empty, wasteful exercise Petitioner asks this Board to commence: because it is clear that Petitioner has failed to make out even a threshold case for anticipation or obviousness and the Petition on its face fails to show a reasonable likelihood of success as to *any* asserted ground, Petitioner's request for a trial should be denied.

II. The Challenged Claims of the '815 Are Directed to a Novel Invention, and Claim a Surprising Result

Using recombinant gene technology, it is possible to develop various protein formulations for therapeutic use in humans. Ex.1001 1:19–23. Before the proteins may be administered to humans, however, contaminants must be removed, including DNA. *Id.* 1:24–29. Prior to the invention of the '815, DNA was removed from protein preparations using various chromatographic techniques. *Id.* 1:29–48. But these chromatographic processes are time-consuming, labor-intensive, and costly, as well as complicated. *Id.* 1:49–52. They also fail to provide stable results, and can lead to significant loss of the sought-after protein. *Id.* 1:49–57.

The inventors of the ’815 recognized the “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.” *Id.* 1:53–57. “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: 61–67.

The ’815 issued on April 19, 2011, with two independent claims reciting:

> 1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps:
>
> 1) converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9;
>
> 2) adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less; and
>
> 3) removing the particles thereby to remove contaminant DNA in the sample.
>
> 13. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises:
>
> 1) converting the sample containing a physiologically active protein into an acidic aqueous solution of low

conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9;

2) neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles, wherein the molarity of the neutralized sample is 100 mM or less; and

3) filtering the resulting sample from step (2) to remove particles containing contaminant DNA.

III. Shadle Purports to Disclose a Method for Removing Residual Protein A from an Antibody Solution After Protein A Chromatography

Petitioner's sole reference, Shadle, is an international patent application proffering an entirely different invention about hydrophobic interaction chromatography, or "HIC," a chromatographic process that separates compounds based on their relative degrees of hydrophobicity. Ex.1003 at 5. Shadle addresses "the application of hydrophobic interaction chromatography combination chromatography to the purification of antibody molecule proteins," specifically immunoglobulin G ("IgG"), a type of antibody. *Id.* at 1, 3. More specifically, Shadle relates to the combined use of HIC with affinity chromatography. *Id.* at 4. "Affinity chromatography relies on the specific interaction of the protein with an immobilized ligand." *Id.* One common type of affinity chromatography uses as its ligand immobilized Protein A, a protein for which IgG antibodies have a very strong affinity. *Id.* at 4–6.

According to Shadle, "[a]lthough Protein A affinity column chromatography is widely used," a problem associated with the use of Protein A is that the "elution of antibody from such columns can result in leaching of residual Protein A from the support," resulting in contamination by Protein A itself. *Id.* at 6. According to Shadle's named inventors, they "surprisingly discovered that HIC can be usefully employed to remove contaminating Protein A from IgG mixtures eluted from Protein A chromatographic support," thus addressing the problem of leached Protein A. *Id.*

Shadle's Example IA—the sole embodiment relied on by the Petition to meet the limitations of the Challenged Claims—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. 28 n.2. 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 at 21–22. Example IA describes a 5 liter ProSep A affinity column (a type of Protein A chromatography) loaded with a solution of IgG (*id.* at 21), to which approximately 15 liters of PBS/glycine was then added. *Id.* The IgG was then eluted by applying 15-20 liters of ProSep A elution buffer. *Id.* After elution, the eluate of the Protein A column was adjusted to pH 3.5 by the addition of 2.5 M HCl, and then adjusted to pH 5.5

by the addition of approximately 350 mL of 1 M tris base. *Id*. After the pH adjustments, the sample was filtered and then loaded onto the cation exchange chromatography column. *Id.* Although not specifically mentioned in Example IA, elsewhere Shadle generally states that the "cation exchange chromatography step removes protein and non-protein impurities." *Id.* at 17. The eluate from the cation exchange chromatography column was then loaded onto a HIC column. *Id.* at 22. Although not specifically mentioned in Example IA, elsewhere Shadle generally states that the HIC chromatography step removes additional protein and non-protein impurities, "most notably residual Protein A, IgG aggregates, and host DNA." *Id.* at 18. Thus, Shadle discloses the use of at least one chromatography step to remove host DNA *after* the steps relied on by Petitioner to satisfy the Challenged Claims. The process of Example IA, according to Shadle, reduced the Protein A content of the ProSep A eluate. *Id.* at 22.

IV. Petitioner's Improper Construction of "Molarity"

For purposes of *inter partes* review, "[a] claim in an unexpired patent . . . shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see also* Pet. 29. However, "[e]ven under the broadest reasonable interpretation, 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 and citations omitted). While reserving further discussion of claim construction as may be appropriate for its § 42.120 Patent Owner Response if any trial is instituted, or as may arise in another proceeding, *see, e.g.*, *T-Mobile US, Inc. v. Huawei Techs. Co.*, IPR2017-00674, Paper 9 at 10 (Aug. 7, 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)) (declining to address constructions not necessary for purposes of deciding institution), Patent Owner notes here as a preliminary matter Petitioner's improper construction of "molarity."

Petitioner improperly attempts to limit "molarity" to the concentration of one particular solute within a solution. Pet. 29–30 (defining "molarity" as a "measure of the concentration of a *given solute* within a solution in terms of the moles of that solute contained per liter of solution"). But neither the claims nor the specification support limiting the term "molarity" to the concentration of one solute. *See, e.g.*, Ex.1001 2:30–32, 5:23–35, 5:59–65. Nor does Petitioner explain, under its construction, *which* solute in a solution would be used to determine molarity.

Petitioner's construction is inconsistent with the broadest reasonable interpretation of "molarity," which is not limited to the concentration of a single solute, as the '815 specification and file history make clear in addressing the

contributions of multiple solutes to the solution's molarity. *See, e.g.*, Ex.1001 claim 1 ("solution . . . having a molarity . . ." and "molarity of the adjusted sample"); claim 13 ("molarity of the neutralized sample"); 4:61–66 ("As used herein, a 'neutral aqueous solution . . .' generally refers to an aqueous solution . . . which has a molarity of 0 to 100mM . . ."); 5:27–33, 59–62; *see also, e.g.*, Ex.1005 at 36 (considering contributions to molarity from 1M Tris with 100mM glycine results in "molarity of the neutralized solution [] over 100mM" (emphasis original)), 82 ("[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."), 107 (considering contributions to molarity from more than one solute in a solution to conclude that its 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)*"), 110 (molarity of eluted fraction over 0.1M when 0.1M sodium citrate used as eluent and 1M Trizma used to adjust pH). Indeed, Petitioner itself recognizes the mistake in its own construction, when (in attempting to map Shadle to Claim 1) it adds the concentrations of tris and citrate (*i.e.*, two solutes) in determining molarity. Pet. 41–42.

V. The Petition Fails to Establish that Shadle Anticipates Any Challenged Claim

Because the Petition fails to establish that Shadle discloses—explicitly or inherently—each and every limitation of the Challenged Claims, Petitioner has failed to meet its burden for institution on its anticipation-based ground. *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00653, Paper 12 at 9–11, 13–14 (Sept. 29, 2014) (prior art reference lacking one or more elements of a claim cannot anticipate that claim or any of its dependent claims).

A. Shadle Does Not Disclose Every Limitation of Claim 1 and 13 and, Thus, of the Other Challenged Claims (2–7 and 12), Which Depend from Claim 1

1. The Petition Fails to Demonstrate that Shadle Discloses the Preamble of Claims 1 and 13: A Method for Removing Contaminant DNA in a Sample Containing a Physiologically Active Protein

To establish anticipation, Petitioner must demonstrate either that the preamble of the Challenged Claims (found in independent Claims 1 and 13) is not limiting, or that it is disclosed in the relied-upon portion of Shadle. *See, e.g.*, *Unified Patents Inc. v. Olivistar, LLC*, IPR2015-01217, Paper 15 at 15 (Nov. 20, 2015) ("Because the Petition fails either to demonstrate that the preamble of claim 17 is not limiting, or to persuasively show that [the prior art discloses the limitations of the preamble], Petitioner has not shown a reasonable likelihood that it would prevail on its anticipation challenge.").

Petitioner fails to do either. To begin with, Petitioner fails to take a position as to whether the preambles of claims 1 and 13 are limiting or not, offering no rationale one way or the other. *See* Pet. 33, 52. And while Petitioner suggests the Board need not reach that question because Shadle explicitly discloses the limitations of the preamble (*id.* at 33–34, 52), Petitioner fails to explain where, in the portions the Petition relies on to meet the remainder of the claims, Shadle discloses a method for removing contaminant DNA.

Further, nothing in the Petition links the step in Shadle that Petitioner asserts discloses the elements of claim 1 and 13 (*i.e.*, the pH adjustment and filtration step using Polygard and Millipak filters) to removing contaminant DNA. Shadle discloses ***only*** that the Protein A and HIC chromatography steps remove DNA, not that the .1 micron Polygard or .2 micron Millipak 200 filters remove DNA. Ex.1003 at 16–18. Further, steps such as Shadle's additional HIC chromatography step are the well-known additional "complicated chromatographic processes" of the prior art identified and criticized by the '815 as "time-, labor- and cost-consuming" and "fail[ing] to provide stable results." Ex.1001 1:40-67. Shadle does not say that the pH adjustment and filtration step on which Petitioner relies to disclose the elements of claims 1 and 13 removes DNA. Instead, Shadle says that "[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 the claimed invention of the ’815. Ex.1003 at 17.

Moreover, Petitioner fails to address why, if Shadle teaches removing contaminant DNA through particle formation, it teaches subsequently performing a conventional, complicated chromatographic process to remove DNA precisely of the sort criticized and rendered unnecessary by the ’815—a step that Shadle would have no reason to perform if DNA were removed earlier, as Petitioner asserts. Ex.1001 at 1:40–52.

Finally, the preambles require that the sample contain “physiologically active protein,” but the Petition fails to explain which disclosure(s) in Shadle allegedly teach this limitation. Pet. 33–34, 52–53.

2. The Petition Fails to Establish that Shadle Discloses Converting the Sample Containing a Physiologically Active Protein Into an Acidic Aqueous Solution of Low Conductivity of 300 mS/m or Less and Having a Molarity of 100 mM or Less at pH of 1.5 to 3.9

The Petition (at 34-39, 53) fails to demonstrate that Shadle discloses “converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9,” as required by claims 1 and 13.

(a) Molarity of 100 mM or Less

Claims 1 and 13 of the ’815 require converting the sample containing a physiologically active protein into an acidic aqueous solution of a molarity of 100 mM or less. Ex.1001, claims 1 and 13. The Petition argues this is disclosed by Shadle, asserting that elution of a protein sample using an affinity chromatography column loaded with that sample converts the sample “into an acidic aqueous solution” (Pet. 35), and apparently mapping the “eluting solution,” which it identifies as an elution buffer that is added to elute protein in Shadle’s column, as the solution whose molarity is addressed in step 1 of ’815 claims 1 and 13. Pet. 36. Among other problems, Petitioner’s argument provides no explanation as to why any contribution to molarity from other solutes in the elution buffer it points to should be ignored.

Petitioner contends that the “ProSep Elution Buffer” in Table 1 has a “molarity” of 25 mM. *See* Pet. 36–37. But Petitioner does not address other solutes in the “ProSep Elution Buffer” that would affect the total molarity of the acidic aqueous solution. Shadle’s Table 1, the sole support relied on by Petitioner, addresses only the concentration of the citrate, stating simply that “ProSep Elution Buffer” has “25 mM citrate, pH 3.5.” Ex.1003 at 20. Indeed, Petitioner and its expert admit that the elution buffer they are mapping as the solution whose molarity and conductivity are addressed in step 1 contains other solutes when they

purport to calculate its *conductivity*. *See, e.g.*, Pet. 37; Ex.1002 ¶ 88. But, without any explanation, Petitioner and its expert simply *omit* those same solutes when purporting to calculate that same solution's *molarity*. This is unsupportable, and underscores that Shadle's solution having 25 mM citrate, pH 3.5 includes contributions to molarity from other solutes—such as, for example, contributions from NaOH or HCl. Pet. 37; Ex.1002 ¶ 88. Petitioner has not established the "molarity" of the ProSep Elution Buffer under the proper construction, including the contributions to molarity from other solutes in the buffer (not just the citrate) (*see* Section IV *supra*).

Petitioner additionally fails to show that the "ProSep Elution Buffer" discussed in Table 1 is actually the solution used in Shadle to elute IgG from the ProSep A affinity column in Example IA. *See* Ex.1003 at 21. Example IA discloses that "IgG was eluted by applying 15 – 20 liters of *ProSep A elution buffer*." *Id.* While Petitioner relies on the molarity of the *ProSep* Elution Buffer in Table 1 for the molarity of the *ProSep A* elution buffer in Example IA, Petitioner never asserts, let alone explains, where, how, or why Shadle teaches that the eluting solution of Example IA (*i.e.*, "*ProSep A* elution buffer") is the same as the buffer listed in Table 1 (*i.e.*, "*ProSep* Elution Buffer"). Thus, for this reason, too, Petitioner has failed to establish the molarity of the "ProSep A Elution Buffer" in Example IA—even under the erroneous construction proposed by Petitioner—and

thus fails to demonstrate that Shadle meets this limitation of all of the Challenged Claims.

(b) Low Conductivity

Claims 1 and 13 of the ’815 require converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less . Ex.1001, claims 1 and 13. As discussed above, Petitioner asserts that Shadle’s elution buffer is the solution whose conductivity is addressed in step 1 of the Challenged Claims (Pet. 36–37), but, among its other failings, Petitioner’s argument that this limitation is disclosed rests entirely on a facially flawed claim of inherency.

The Petition and the Petitioner’s expert’s declaration argue that the conductivity of the elution buffer in the acidic aqueous solution is inherently less than 300 mS/m. Pet. 37–40; Ex.1002 ¶ 89. However, Petitioner’s inherency argument is based on its assertions about the methods a POSA *might* have used to prepare the 25mM citrate, pH 3.5. Pet. 37; Ex.1002 ¶ 88. Indeed, Petitioner argues that a POSA “would have used one of the following four ***most common*** methods for preparing the [citrate].” Pet. 37. But Petitioner fails to prove that any of these methods were actually used in Shadle, and fails to address the other possible, if less common (in Petitioner’s estimation), methods for preparing the citrate buffer. Further, Petitioner fails to explain how Dr. Przybycien’s testing

proves that the conductivity of 25mM citrate, pH 3.5 is necessarily less than 300 mS/m.

Because the Petition fails to demonstrate that the conductivity limitation is disclosed by Shadle, Petitioner has failed to show anticipation of any of the Challenged Claims.

3. The Petition Fails to Establish that Shadle Discloses "Adjusting the pH of the Resulting Sample From Step (1) to pH of 4 to 8 to Form Particles, Wherein the Molarity of the Adjusted Sample is 100 mM or Less," as Claimed in Claim 1; or "Neutralizing the pH of the Resulting Sample from Step (1) by Addition of a Buffer to Raise the pH to a Neutral Level to Form Particles, Wherein the Molarity of the Neutralized Sample is 100 mM or Less," as Claimed in Claim 13

The Petition (at 40–46, 53–55) also fails to demonstrate that Shadle explicitly or inherently discloses adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less, as required by Claim 1 (and thus every dependent claim) or neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles, wherein the molarity of the neutralized sample is 100 mM or less, as claimed in Claim 13.

(a) Molarity

The Petition fails to establish that the molarity of the adjusted or neutralized sample in Example IA is 100 mM or less. Petitioner admits Shadle does not

explicitly disclose the molarity of the adjusted or neutralized sample. Pet. 41, 54. Petitioner instead argues that the molarity limitation is necessarily (or inherently) disclosed, and purports to calculate the molarity by identifying just two of the solutes of the neutralized eluate and then combining them, adding the number of moles of citrate (from the ProSep Elution Buffer) and the number of moles of tris (from the 350 mL tris base used to raise the pH to 5.5), and then dividing by the volume of the eluate (15.35 liters). *Id.* 41–42; Ex.1002 ¶ 96; Ex.1007 at 1. Petitioner argues this calculation would result in a molarity of the neutralized eluate of 47.2 mM. Pet. 41-42.

This analysis is inconsistent with Petitioner's own construction of "molarity," which apparently considers the molarity of just one solute. *See* Pet. 29–32, 41–43; Ex.1002 ¶¶ 95–96. Here, Petitioner adds contributions from *multiple* solutes (citrate and tris), acknowledging that molarity is not limited to the concentration of just one solute. *See, e.g.*, Pet. 41–43; Ex.1002 ¶ 99; Ex.1007 at 1–3; *see also Kingston Tech. Co. v. Imation Corp.*, IPR2015-00066, Paper 19 at 31, 34 (Mar. 24, 2016) (finding improper and prejudicial a "[p]etitioner's approach of altering its theories as to the identity" of a claim term without "proffer[ing] a construction" or "articulating that [petitioner] intended to maintain alternative theories"). Having added two solutes (and thus undermined its claim construction), Petitioner then errs by arbitrarily excluding other solutes—an

unexplained exclusion clearly inconsistent with the proper claim construction. *See* Pet. 41–43.

For example, Petitioner fails to consider the molarity contributions of the *wash buffer* (including PBS and glycine) in the column. Prior to elution with ProSep A elution buffer, the 5-liter column is washed with approximately 15 liters of PBS/gylcine. Ex.1003 at 21. If Petitioner is tacitly assuming that there would be no PBS/glycine in the eluate, it provides no basis for that unstated assumption. *Emerson Elec. Co. v. SIPCO, LLC*, IPR2015-01579, Paper 11 at 5–7 (Mar. 17, 2016) (rejecting a petitioner's argument as "flawed" because it relied on an inaccurate assumption that contradicted the patent specification).

The clear error in Petitioner's omission of the molarity of any wash buffer from the calculations is further underscored by the calculations of the Examining Division in an Office Action in EP Appn. No. 03795400.5, in which claims with similar subject matter were pending. *See, e.g.*, Ex. 2001 (EP '400 File History), 5–6. There, in considering the molarity of the eluate in Shadle, the Examining Division found that "at the start of the elution, the column can be presumed to contain 5 liters of a solution having a molarity of 270 mM [*i.e.*, the PBS/glycine wash buffer]." *Id.* The Examining Division then calculated the molarity of the eluate by including molarity contributions from the PBS/glycine wash buffer. *Id.* This analysis (a matter of public record surely known to Petitioner) confirms that

those skilled in the field would recognize that the claimed adjusted or neutralized sample includes solute(s) from the wash buffer (PBS and glycine), and that contributions from those solutes must be included in any calculation of the molarity of the adjusted or neutralized sample. Nevertheless, Petitioner's analysis ignores that the wash buffer is part of the adjusted or neutralized sample and entirely omits the molarity contributions from the wash buffer from its molarity calculations.

Petitioner also completely fails to consider the molarity contribution from ***the undisclosed solution that raised the pH of the elution buffer in the eluate***. Shadle states that the Protein A eluate was adjusted to pH 3.5 by the addition of 2.5 M hydrochloric acid. Ex.1003 at 21. Thus, the Protein A eluate implicitly had a pH higher than 3.5, which was then lowered by adding an acid. Petitioner fails to explain—and Shadle does not identify—what caused the pH of the eluate to rise above 3.5 during elution. Assuming the addition of a chemical or compound caused the pH increase, Petitioner fails to address its contribution, if any, to the molarity of the eluate.

Finally, Petitioner's reliance on Chugai's statement during prosecution of a European counterpart to argue that the molarity is below 100mM is misplaced. *See* Pet. 42–43; Ex.1002 ¶ 98. There, Chugai said that the molarity in Example IA of Shadle was "***at least***" 47.2 mM. Ex.1006 at 28. For the purposes of the claims in

that case, Chugai needed to show only that the molarity was greater than 30 mM. *Id.* An assertion that the molarity is at least 47.2 mM does that. It does not, however, imply that the molarity of the neutralized eluate in Example IA was less than 100 mM. Indeed, in Chugai's submission to the European Patent Office, Chugai's calculation did not attempt to determine the precise molarity of the neutralized eluate and, instead, explicitly included a placeholder for an unknown quantity of 2.5 M HCl in the neutralized eluate. *Id.* ("Thus, the eluent before the filtration has: . . . 'x' mmol (2.5 M · 'Y' l (unknown)) of HCL."). Petitioner simply ignores this.

(b) Particle Formation

Petitioner concedes that Shadle is silent about the formation of particles after neutralizing the IgG eluate. Pet. 41, 54; Ex.1002 ¶¶ 93, 126. While Petitioner summarily asserts that formation of particles under the conditions disclosed in Example IA of Shadle is inherent (Pet. 43, 54), Petitioner's inherency assertions are unsupported.

An inherency claim must fail unless the Petitioner presents "persuasive technical reasoning to explain" that a limitation would ***necessarily*** be met. *See, e.g., Albaad Massuot Yitzhak, Ltd. v. Edgewell Pers. Care Brands, LLC,* IPR2017-00693, Paper 11 at 9–10 (July 17, 2017). A conclusory statement of inherency is not entitled to any weight. *Id.* Further, inherency may not 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) (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991)). "The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Id.*

Here, like the patent challengers in *Crown Operations*, Petitioner provides no explanation for its argument of inherency, just a conclusion. Petitioner fails to point to *any* particular pages or portions of Shadle for the alleged disclosure. *See* Pet. 43–46, 54.

Instead, the Petition relies only on conclusory statements from its expert's declaration (¶¶ 100–102), which itself fails to cite to any supporting disclosure in Shadle. Instead of pointing to any disclosure in Shadle, Petitioner and its expert attempt to support their contention that particles were necessarily formed in Example IA with two citations: (1) the Scopes reference (Ex.1009), and (2) the '815, itself, and its prosecution history. *See* Pet. 43–46; Ex.1002 ¶¶ 100–102. Neither supports inherency, and, indeed, the Scopes reference underscores that the formation of particles is *not* inherent.

First, as Petitioner and its expert recognize, Scopes says only that "***some*** proteins form precipitates [*i.e.*, particles]" and that "[i]n ***many*** cases isoelectric precipitates ***can*** be formed in a tissue extract by lowering the pH to between 6.0 and 5.0." Ex.1009 at 28–29; Pet. 45–46; Ex.1002 ¶ 101. Petitioner offers no

explanation of how Scopes's discussion of possibilities ("some" proteins form particles; precipitates "can be formed") could prove inherency. As a matter of law, it cannot. *See Crown Operations*, 289 F.3d at 1377 ("The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient."). Nowhere does Scopes discuss the formation of particles in an IgG solution, and, as described above, even the statements it does contain could not support inherency. Moreover, even if the *possibility* of particle formation were enough for inherency—it is not—Scopes only says that particles ***may*** form "by ***lowering*** the pH to between 6.0 and 5.0." Ex.1009 at 28. In contrast, Example IA of Shadle ***raises***, not lowers, the pH of the IgG eluate from 3.5 to 5.5. Ex.1003 at 21. Thus, even the mere possibilities discussed in Scopes would not be applicable to Shadle, and Scopes certainly does not disclose conditions inherent in Shadle.

Second, the disclosures in the '815 and its prosecution history do not support Petitioner's contention that particles *necessarily* formed *in Example IA of Shadle*. Petitioner says the conditions in Example IA "fall within the same range of conditions" recited in step 3 of claim 1 of '815, and thus the eluate in Example IA necessarily produced particles. Pet. 44. But as an initial matter, as discussed above, Petitioner's argument fails because it has failed to show its underlying premise that the conditions in Example IA "fall within the same range of conditions." Moreover, even if this premise had been proven to be true (it hasn't),

the ’815 explains that 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***.” Ex.1001 5:37–40. And, although the specification states, as Petitioner and its expert point out, that the disclosed solution “neutralized to a neutral pH level in the above stage, in turn, produces particles,” Ex.1001 at 6:1–3, immediately before that statement the specification also says that a “neutral [pH] level ***will vary depending on the type of physiologically active protein or antibody to be purified***.” *Id*. at 5:53–59. Petitioner and its expert simply ignore the specification’s earlier disclosure while improperly trying to use the ’815 itself to provide the hindsight disclosure that Petitioner has clearly been unable to find in the prior art. *See* Pet. 44–45; Ex.1002 ¶ 100; *see also Zoltek Corp. v. United States*, 815 F.3d 1302, 1312–13 (Fed. Cir. 2016) (reversing lower court’s decision on invalidity because it fell victim to the “insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher”); *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”). Simply put, the ’815 cannot provide the missing support for Petitioner’s contention that particles will ***necessarily*** form in the IgG eluate in Example IA of Shadle. And, unlike the ’815, the goal of Shadle is not to form particles comprising contaminant DNA.

Moreover, contrary to Petitioner's arguments that Chugai's statements during prosecution support Petitioner's inherency theory (Pet. 45), Chugai never told the Patent Office that particles would necessarily form under the conditions of Example IA of Shadle. During prosecution, to overcome a *different* reference, Tsuchiya, Chugai argued that 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." Ex.1005 at 108. Chugai argued that 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 the molarity of the neutralized eluate in Tsuchiya was high, *i.e.*, over 100 mM. *Id.* at 107. Nowhere did Chugai suggest the inverse—that the eluate in Tsuchiya would *necessarily* form particles if its molarity was 100 mM or less. And Chugai certainly never suggested that *any* protein eluate having its pH raised to *any* level between 4 and 8 would *necessarily* form particles.

4. The Petition Fails to Establish that Shadle Discloses "Removing the Particles Thereby To Remove Contaminant DNA," as Claimed in Claim 1 or "Filtering the Resulting Sample From Step (2) to Remove Particles Containing Contaminant DNA," as Claimed in Claim 13

Even if Example IA of Shadle inherently disclosed the formation of particles—and it does not—Petitioner fails to explain how Shadle discloses, explicitly or inherently, that (1) those particles were removed; and (2) removing those particles removed contaminant DNA.

First, Petitioner has failed to establish that the filters used in Example IA of Shadle explicitly or inherently remove any contaminant DNA from the Example IA eluate. When arguing that Shadle explicitly discloses removing particles, neither Petitioner nor its expert cites to a single page of Shadle. *See* Pet. 47, 55; Ex.1002 ¶¶ 105, 127. Moreover, although examples in '815's specification disclose using a 0.2 μm or a 0.22 μm cellulose acetate filter to remove contaminant DNA from the neutralized solutions of hPM-1 antibody, anti-PTHrP antibody, anti-HM1.24 antibody, erythropoietin, and G-CSF *involved in those examples* (*see* Ex.1001 8:10–12, 9:27–31, 10:47–49, 11:53–56, 11:62–12:12), Petitioner provides no explanation why a "0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200" filter would necessarily, and thus inherently, remove any particles comprising DNA from the IgG eluate *under the conditions of Example IA of Shadle* while still allowing the purified protein or antibody to pass through. *See*,

e.g., Ex.1003 at 21. Petitioner's expert's assertion that a 0.1 μm filter would "inevitably and necessarily" remove the DNA in Example IA (Ex.1002 ¶ 106; Pet. 46–47) is conclusory, unexplained, and unsupported. *See, e.g.*, *Smith & Nephew*, IPR2017-00487, Paper 7 at 13–14 (denying institution and noting that "the Petition and the Declaration do not offer more than conclusory assertions . . . beyond mere possibilities or probabilities . . ."); *C.R. Bard*, IPR2015-00511, Paper 9 at 11 (denying institution where petition and expert declaration both lacked "any explanation," "beyond conclusory statement[s]," about how a claim element was disclosed in the prior art). Neither Petitioner nor its expert provides any information about the size of the particles allegedly formed in Shadle or whether and why they would comprise contaminant DNA, and 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 '815. Thus, Petitioner has failed to prove that the filters used in Example IA would remove any particles if they were to form as claimed (*see supra*), let alone particles comprising contaminant DNA.

Petitioner also fails to address Shadle's describing the use of the filters at issue as part of providing "viral inactivation" and "prepar[ing] the solution for cation exchange chromatography" (Ex.1003 at 17), while the later *HIC step*, in contrast, is described as being used for DNA removal (*id.* at 16). Further,

Petitioner and its expert fail to explain how their citations to the Martin reference and the ’815 specification show that particles asserted to be inherently *formed* in Shadle are also inherently *removed*. *See* Ex.1002 ¶¶ 105–107. Even setting aside these various other problems, the language to which Petitioner points in Martin and the ’815 discusses possibilities that simply cannot support an argument of inherency: Martin does not address the removal of particles comprising contaminant DNA, but rather using a membrane filter before other filtration steps such as column chromatography in order to “prevent premature plugging.” Ex.1010 at 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 ’815 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* Ex.1002 ¶¶ 106–107 (quoting Ex.1010 at 30 and Ex.1001 6:3–7). In sum, the Petition fails to support that the filters used in Example IA of Shadle would necessarily remove the particles purportedly formed in the IgG eluate, let alone particles comprising contaminant DNA, while still allowing the purified protein or antibody to pass through.

Second, even if particles were formed and removed in Example IA (they are not), Petitioner fails to establish that the particles they argue were formed and

removed comprise "contaminant DNA." Petitioner does not explain why any formed particles in Example IA would necessarily comprise contaminant DNA. For its inherency argument, Petitioner again relies on Scopes. *See* Pet. 45–46; Ex.1002 ¶ 101. But Scopes merely says that "***[m]ost*** isoelectric precipitates are aggregates of many different proteins and ***may*** include particulate fragments and protein-nucleic acid complexes." Ex.1009 at 29. Petitioner fails to explain how this equivocal language in Scopes means that any particles formed in Shadle *necessarily* comprise DNA. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In Re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)) ("Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."). Petitioner's reliance on the '815 is equally insufficient to show inherency, as Petitioner fails to explain how particle formation in the '815 means that particles of contaminant DNA are necessarily formed in Example IA of Shadle. *See* Pet. 44–45; Ex.1002 ¶ 100.

Moreover, Petitioner's expert opines that there are two types of DNA that need to be removed: "*host DNA* and *contaminant DNA* associated with viral contamination." Ex.1002 ¶ 31 (citing Ex.1001 1:27–33). Notwithstanding this opinion, neither Petitioner nor its expert explains where Example IA of Shadle discloses (1) the formation of particles comprising the claimed "contaminant

DNA" and (2) the removal of "contaminant DNA," as required by the Challenged Claims. Indeed, Petitioner makes no showing that the IgG solution of Example IA—a mere "trial run"—ever comprised "contaminant DNA" to begin with. *See* Pet. 28 n.2. Moreover, even if Petitioner's conclusory allegations that particles comprising DNA were formed and removed in Example IA were accepted as true, Petitioner's expert only alleges (without support) that particles *comprising "DNA contaminants"* are formed, without discussing whether or why those "DNA contaminants" are "contaminant DNA." Ex.1002 ¶ 102 ("For the reasons discussed above, it is my opinion that neutralizing the eluate solution by the addition of a Tris buffer to raise the pH to 5.5 at a molarity of 47.2 mM would inevitably and necessarily result in the formation of particles that contain ***DNA contaminants***.").

Finally, Petitioner and its expert never explain why—if, as they argue, contaminant DNA is inherently removed in Shadle's Example IA by filtering particles they say are inherently formed to begin with—Shadle discloses the use of a HIC column in the steps *after* the steps that Petitioner argues satisfy claim 1. Ex.1003 at 19–21. While Shadle explains that the later use of the HIC column (separate and distinct from the .1 micron Polygard and .2 micron Millipak 200 filtering step of Shadle that Petitioner argues satisfies the Challenged Claims) is to "remove[ ] additional protein and non-protein ***impurities***, most notably residual

Protein A, IgG aggregates, and host ***DNA***" (Ex.1003 at 18), Petitioner and its expert never say a word about the purpose of Shadle's HIC column. Moreover, Petitioner and its expert fail to explain why the HIC column is 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. Pet. 46–48. Far from disclosing the invention claimed in Claims 1, 13, and the other Challenged Claims of the '815, Shadle describes a method that omits key aspects of that invention, and adds precisely the extra chromatographic processes that the '815 criticizes and renders unnecessary. As the '815 explains, the practice of the method of the '815 allows efficient removal of contaminant DNA "***without*** using complicated chromatographic processes." Ex.1001 1:61–2:4.

VI. The Petition's Obviousness Grounds Are Unclear, Confusing, and Legally Insufficient

In violation of 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); *Magnum Oil Tools*, 829 F.3d at 1380), the Petition fails to articulate and explain any of its arguments for obviousness, improperly leaving it to the Board and Patent Owner to guess what Petitioner might be suggesting. *John Crane*, IPR2016-01827, Paper 6 at 11 (describing 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"); *Infobionic, Inc. v. Braemer Mfg., LLC*, IPR2016-01236, Paper 8 at 13 (Dec. 23, 2016) (denying institution where petitioner "does not persuasively articulate an adequate reason why and how the teachings of the three relied-upon references would have rendered obvious the claimed subject matter"); *Free-Flow Packaging Int'l, Inc. v. Automated Packaging Systems, Inc.*, IPR2016-00351, Paper 7 at 14 (June 27, 2016) (denying institution where petitioner failed to show that "a person of ordinary skill in the art would have had a reason to combine" the prior art references).

Petitioner provides ***no*** explanation as to what the differences are between the claims and Example IA of Shadle, or how it argues such differences are to be addressed. *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). Indeed, Petitioner and its expert do not cite to even a single page of Shadle in their obviousness arguments. *See* Pet. 55–59; Ex.1002 ¶¶ 130–133; *John Crane*, IPR2016-01827, Paper 6 at 11 (denying institution because Petition failed "to identify sufficiently or precisely the differences between the prior art and claims, and fail[ed] even to identify the specific prior art teachings upon which Petitioner relies, preventing proper evaluation of this asserted ground of unpatentability"). In fact, Petitioner insists that there "is no patentable difference between the prior art antibody purification

process of Example IA in [sic, Shadle] and the claimed invention." Pet. 57. Petitioner further never explains how or why Shadle would be modified to achieve the claimed invention. Thus, Petitioner fails to explain why a person of ordinary skill would have been motivated to make whatever modification(s) Petitioner might imagine, and also improperly conflates inherency with obviousness.

For these reasons, Petitioner has failed in multiple ways to meet its burden and the Board should deny institution on Petitioner's obviousness ground. *See, e.g.*, *Axon Enter., Inc.*, IPR2017-00515, Paper 10 at 18–19 (denying institution because Petitioner and its expert did not explain what specific modification to the prior art would have been necessary or how a person of ordinary skill would have been motivated to make the necessary modification based on the structure and operation of the prior art); *Vizio, Inc. v. Nichia Corp*., IPR2017-00551, Paper 9 at 12 (July 7, 2017) (denying institution because Petitioner did not explain what it believed to be missing from prior art and why one of ordinary skill would have found it obvious to modify the prior art to achieve the recited limitation); *Apple Inc. v. SmartFlash LLC*, CBM2015-00029, Paper 11 at 16–18 (May 28, 2015) (denying institution of an asserted obviousness ground based on Petitioner's failure to explain adequately any differences between the asserted prior art and the claimed invention); *Dep't of Justice v. Envisionit, LLC.*, IPR2017-00186, Paper 8 (May 3, 2017) (denying institution, noting that the Board is "not inclined to play

archaeologist with the record in an attempt to fill the gaps in Petitioner's argument").

Petitioner similarly fails to explain what in Shadle would be modified or why, particularly because *Shadle already purports to accomplish DNA purification* (without need for any modification) using the very prior-art chromatography techniques that the '815 sought to *avoid*. *See* Ex.1001 1:61–2:4; Ex.1003 at 16, 18; *see, e.g.*, *Arris Int'l Plc. v. Sony Corp.*, IPR2016-00828, Paper 10 at 13–18 (Oct. 7, 2016) (denying institution because prior art already addressed the alleged problem/need that Petitioner asserted would provide a motivating reason to seek a solution).

A. Petition Fails To Address Known Secondary Indicia of Nonobviousness

Additionally, although it is a mandatory part of any obviousness analysis, Petitioner fails to address known secondary indicia of nonobviousness that are expressly set forth in the very first column of the '815:

> However, 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.

* * *

> As a result of extensive and intensive efforts made to overcome these problems, the inventors of the present invention have made the surprising finding that contaminant DNA can be efficiently removed from a sample containing a physiologically active protein without using complicated chromatographic processes in a case where the sample is converted into an acidic aqueous solution of low conductivity, neutralized by addition of a buffer to raise the pH to a neutral level, and then filtered through a filter to remove the resulting particles. This finding led to the completion of the present invention.

Ex.1001 1:49–2:4. The inventors of the '815 explained that their discovery solved a problem in the prior art and that the results of their efforts were "surprising." *Id.* Petitioner was aware of this disclosure, having described and cited disclosures in this very same column in its Petition. Pet. 25.

Secondary indicia, such as unexpected results, must be considered in any obviousness analysis. *See, e.g.*, *Graham*, 383 U.S. at 17–18 ("[S]econdary 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 of nonobviousness play a critical role in the obviousness analysis."); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed.Cir.1983)) ("[E]vidence rising out of the so-called 'secondary considerations' must always

when present be considered en route to a determination of obviousness."). Indeed, the Board has determined that the failure to address evidence of such indicia at the pre-trial stage is a reason to deny institution. *See Lupin Ltd. v. Vertex Pharmaceuticals Inc.*, IPR2015-00405, Paper 13 at 21–22, 26–27 (July 9, 2015). This is particularly true where, as here, the petitioner was aware of but chose not to address known evidence of nonobviousness. *See Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13 at 26–27 (Jan. 22, 2015) (denying institution for, *inter alia*, failure to address known evidence of unexpected results). As the Board has warned, it is "unfair to impose on [Patent Owner] in the first instance the burden of establishing unexpected results in a trial" when a petitioner knew of those unexpected results. *Id.* at 26–27. Here, as in *Lupin* and *Merial*, significant objective evidence squarely before the Petitioner in the intrinsic record (indeed, in the very words) of the '815 affirmatively supports nonobviousness of the Challenged Claims. Among other things, as the '815 explicitly explains, the ability to precipitate and thereby remove DNA under the conditions described in the claim, as discovered by the inventors of the '815, was unexpected, and allowed practitioners to remove contaminant DNA while avoiding the costly, labor-intensive, time-consuming, complicated and unstable additional steps of chromatography required by prior art methods—including Petitioner's cited Shadle reference. *See, e.g.*, Ex.1001 1:61–2:4. Nevertheless, like the petitioner in *Merial*, Petitioner here was acutely aware of but

ignored such evidence when filing its petition. *Cf. Transocean*, 699 F.3d at 1349 (such evidence "*must* [] be considered"). This failure to perform a required step of any obviousness analysis is yet another basis on which the Board should deny institution on the obviousness ground set forth in the Petition.

VII. Conclusion

Even from this preliminary record, Petitioner has failed to show that Shadle anticipates or renders obvious any of the Challenged Claims of the '815. Because the Petition fails to show that there is a reasonable likelihood that the Petitioner will prevail in proving any Challenged Claim is unpatentable, the Petition should be denied in its entirety, and, pursuant to 35 U.S.C. § 314, no *inter partes* review should be instituted.

Respectfully submitted by: Dated: September 5, 2017

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 complies with the type-volume limitation in 37 C.F.R. § 42.24(c)(1). According to the word-processing system's word count, the brief contains 9,513 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 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:

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