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BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

CHUGAI PHARMACEUTICAL CO., LTD.,
Patent Owner

Inter Partes Review No. IPR2017-01358
Patent No. 7,927,815 B2
Issued: April 19, 2011
Filed: January 23, 2008

Title: PROTEIN PURIFICATION METHOD

PETITION FOR *INTER PARTES* REVIEW

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1019	European Application No. 10011215.0, published as EP 2336149 (“EP ’149”)

I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1–7 and 12–13 of U.S. Patent No. 7,927,815 B2 ("the '815 patent") to Takeda, et al., entitled "Method of Purifying Protein" (Ex. 1001). This Petition, which is supported by the Declaration of Dr. Todd M. Przybycien, Ph.D. (Ex. 1002), explains that every element of the claimed invention was disclosed in a single prior art reference, which anticipates claims 1–7 and 12–13 of the '815 patent. Independently, claims 1–7 and 12–13 would have been obvious to a person of ordinary skill in the art ("POSA") before the effective filing date of the claimed invention.

***Anticipation*.** First, claims 1–7 and 12–13 are anticipated under 35 U.S.C. § 102(b) by International Publication No. WO 95/22389 to Shadle, et al. ("WO '389") (Ex. 1003). While WO '389 was cited during the prosecution of the '815 patent, it was never substantively considered or relied upon by the Examiner before the '815 patent issued in April 2011. WO '389, however, was submitted by a third party and adopted by the European Patent Office ("EPO") as a novelty-destroying reference during the prosecution of foreign counterparts to the '815 patent, European patent application Nos. 02703958.5 (published as EP 1380589) and 10011215.0 (published as EP 2336149).

The claims of the '815 patent are directed to methods of removing DNA contaminants in a sample containing a physiologically active protein, that comprise

the following three purification steps: (1) converting a 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 a pH of 1.5 to 3.9; (2) adjusting the pH to 4 to 8 to form particles, where the molarity of the adjusted sample is 100 mM or less; and (3) removing the particles to thereby remove DNA contaminants. *See* Ex. 1001, 12:38-49. As discussed in detail below and confirmed by Petitioner's declarant and protein-purification expert, Dr. Przybycien, the very first example in WO '389 anticipates the claims of the '815 patent. That example teaches a process of purifying proteins and removing DNA contaminants that either expressly or inherently discloses each of the three recited purification steps. *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2000) ("[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.").

Obviousness. Second, and independently, claims 1–7 and 12–13 would have been obvious in view of WO '389, regardless of whether those claims are invalid as anticipated. Even if WO '389 does not inherently anticipate the challenged claims, it still invalidates the challenged claims as obvious under 35 U.S.C. § 103(a). *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000) ("[A] single prior art reference can render a claim obvious."); *see also, e.g., Kroy IP*

Holdings, LLC v. Safeway, Inc., 107 F. Supp. 3d 656, 672 (E.D. Tex. 2015) (holding single reference did not anticipate the challenged claims but also held that same reference used for the anticipation challenge rendered the claim obvious). Again, WO '389 discloses each of the claimed process steps recited in the '815 patent. Because the claims of the '815 patent do no more than recite conducting a known process at known parameters to achieve a predictable result, the claims would also have been invalid as obvious to a POSA. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

The Board should therefore institute *inter partes* review and cancel claims 1–7 and 12–13 of the '815 patent as unpatentable under 35 U.S.C. §§ 102(b) and/or 103(a).

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** Pfizer, Inc. ("Pfizer" or "Petitioner") is the real party-in-interest. No other parties exercised or could have exercised control over this Petition; no other parties funded or directed this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48,759-60.

2. ***Related matters.*** Petitioner has also filed a petition for *inter partes* review of U.S. Patent Nos. 7,332,289 ("the '289 patent") (IPR2017-01357). The '815 patent issued from U.S. Application No. 12/018,688, a divisional application claiming benefit of U.S. Application No. 10/471,374 ("the '374 Application"), which issued as the '289 Patent.

3. ***Lead and back-up counsel.*** Petition identifies the following:

- *Lead counsel*: Jovial Wong (Reg. No. 60,115)
- *Back-up counsel*: Charles B. Klein*
- *Back-up counsel*: Sharick Naqi*
- *Back-up counsel*: Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. ***Service information.*** Petitioner identifies the following:

- *Email address*: rituximabIPR@winston.com
- *Mailing address*: WINSTON & STRAWN LLP
  1700 K Street NW
  Washington, DC 20006
- *Telephone number*: (202) 282-5000
- *Fax number*: (202) 282-5100

Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

a. ***Grounds for standing*****.** Petitioner certifies that (i) the '815 patent is available for *inter partes* review; and (ii) Petitioner is not barred or estopped from requesting review of any claim of the '815 patent on the grounds identified in this Petition. The required fee is paid through the Patent Review Processing System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

b. Identification of challenge. Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancelation of claims 1–7 and 12–13 of the '815 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1–7 and 12–13	§ 102(b)	WO '389 (Ex. 1003)
II	1–7 and 12–13	§ 103(a)	WO '389 (Ex. 1003)

Pursuant to 37 C.F.R. § 42.104(b)(4), Petitioner identifies the proposed construction of the challenged claims below in Section VII. Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner sets forth a full statement of the reasons for the relief requested below in Section VIII.

IV. LEVEL OF ORDINARY SKILL IN THE ART

A POSA is presumed to be aware of all pertinent art, think along the line of conventional wisdom, and possess ordinary creativity in the pertinent field. A POSA possesses "common sense" and is "not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007).

The '815 patent claims priority to Japanese Application No. 2001-067111, which was filed on March 9, 2001. Without conceding that this priority claim is valid, Petitioner uses March 9, 2001, as the relevant date for analysis of the level of skill and knowledge of a POSA. Ex. 1002 ¶ 27. Petitioner's arguments would not change if the relevant date for analyzing the level of skill and knowledge of a POSA were March 9, 2000. *Id.*

The education level of a POSA would include at least a graduate degree, such as a Ph.D., and several years of postgraduate training or practical experience in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others. *Id.* ¶ 28. Such a person would also understand that protein purification is a multidisciplinary field, and could take advantage of the specialized skills of others using a collaborative approach. *Id.*

V. THE ’815 PATENT

A. The ’815 Patent

The ’815 Patent issued on April 19, 2011, from U.S. Application No. 12/018,688 (“the ’688 Application”), which is a divisional application of U.S. Application No. 10/471,374 (“the ’374 Application”), now U.S. Patent 7,332,289 (“the ’289 patent”), which is the U.S. National Stage Application of International Application No. PCT/JP02/02248 filed on March 11, 2002. The ’688 Application claims priority to a foreign application, Japanese Application No. 2001-067111 (JP ’111 Application), which was filed on March 9, 2001. European Application No. 02703958.5, published as EP 1380589 (“EP ’589,” Ex. 1004), and its continuation European Application No. 10011215.0, published as EP 2336149 (“EP ’149,” Ex. 1019), among other foreign counterparts, also claim priority to the JP ’111 Application.

The inventors listed for each of these applications and patents are Kozo Takeda and Norimichi Ochi. Each of these applications and patents appear to be assigned to Chugai Seiyaku Kabushiki Kaisha, also known as Chugai Pharmaceutical Co., Ltd. (“Chugai” or “Patent Owner”). The assignment of the ’374 Application by the inventors to Chugai is located at reel/frame 015129/0599 of the U.S. Patent & Trademark Office’s patent assignment database.

1. The Claims

The ’815 patent contains 13 claims directed to purification methods for removing contaminant DNA from a sample containing a physiologically active protein. Claim 1 and 13 are independent claims, and claims 2-7 and 12 ultimately depend from claim 1. Claim 1 is reproduced below:

> 1. A method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the followings 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.

Ex. 1001, 12:38-49. Claim 2 further recites that “the acidic aqueous solution of low conductivity has a molarity of 50 mM or less.” *Id.* at 12:50-52. Claim 3 further recites that “the acidic aqueous solution of low conductivity has an ionic strength of 0.2 or less. *Id.* at 12:53-55. Claim 4 further recites that “the acidic aqueous solution is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid and acetic acid.” *Id.* at 12:56-59. Claim 5 further recites that “the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample

containing a physiologically active protein." *Id.* at 12:60-63. Claim 6 further recites that "the physiologically active protein is an antibody." *Id.* at 12:64-65. Claim 7 further recites that "the antibody is a humanized monoclonal antibody." *Id.* at 12:66-67. Claim 12 further recites that "the particles are removed by filtration through a filter." *Id.* at 13:9-10. Claim 13 is another independent claim, which is reproduced below:

> 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.

Id. at 13:12-14:11.

2. Specification

The specification of the '815 patent describes a protein purification method where "a sample containing a physiologically active protein is converted into an acidic aqueous solution of low conductivity, preferably by eluting the sample from

Protein A/G affinity chromatography with an acidic aqueous solution of low conductivity." Ex. 1001, 5:23-27. The specification describes an "acidic aqueous solution of low conductivity" as follows:

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

Id. at 5:28-35. The specification further states that "[t]he acidic aqueous solution may be selected from aqueous solutions of hydrochloric acid, citric acid, acetic acid and other acids." *Id.* at 5:35-37. Next, "the resulting sample is neutralized by addition of a buffer to raise the pH to a neutral level." *Id.* at 5:43-46. The '815 patent further explains that a neutral level will vary depending on the type of physiologically active protein or antibody to be purified and it usually ranges from pH 4 to pH 8, preferably pH 4.3 to pH 7.5, and more preferably pH 4.5 to pH 7.5. *Id.* at 5:54-58. According to the specification of the '815 patent, the range of conditions identified above will result in the production of particles. *Id.* at 6:1-4 ("[T]he solution neutralized to a neutral pH level in the above stage, in turn, produces particles (i.e., becomes clouded)."); 2:2-3 (after neutralization, the solution is "then

filtered through a filter to remove the resulting particles."); 4:60 ("removing the resulting particles").

The '815 patent also explains how the particles that will form in the buffer solution contain DNA contaminants:

> Without being bound by any particular theory, the inventors of the present invention estimate that each of these particles is a conjugate formed between physiologically active protein and DNA. Particle removal by filtration results in a small loss of physiologically active protein because it is removed in the form of DNA-physiologically active protein conjugates.

Id. at 6:13-18.

The specification of the '815 patent further describes how the formed particles with DNA contaminants are removed by the use of a filter, resulting in the removal of DNA from the protein sample:

> These particles may be removed by filtration through a filter to ensure efficient removal of contaminant DNA. Examples of a filter available for filtration include, but are not limited to, a 1.0-0.2 μm Cellulose Acetate Filter System (Corning) or TFF.

Id. at 6:3-7.

3. Summary of the Relevant Prosecution Histories

a. The ’815 Patent Prosecution History

i. The ’374 Application Prosecution History

Chugai submitted the ’374 Application to the USPTO on September 9, 2003. In an Office Action dated October 10, 2007, the Examiner rejected the pending claims as invalid under 35 U.S.C. § 102(b) and under 35 U.S.C. § 103(a). *Id.* at 118-124.

In response, Chugai amended the claims to read as follows:

> 3. A method for removing contaminant DNA in an antibody-containing sample, which comprises the followings [*sic*] steps:
>
> 1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity having a molarity of 0 to 100mM;
>
> 2) neutralizing the resulting elate [*sic*] by addition of a buffer to raise the pH to ~~a neutral level~~ 4 to 8, wherein the molarity of the neutralized solution is 0 to 100mM; and
>
> 3) removing the resulting particles.

Id. at 101-102. Chugai concurrently argued:

> [S]ome of the characteristic features of the present invention for removing contaminant DNA from an antibody-containing sample are that an acidic aqueous solution of low conductivity having a molarity of 0 to 100 mM is used, and the resulting eluate is neutralized by addition of a buffer to raise the pH to 4 to 8 and the molarity of the

> neutralized solution is 0 to 100mM. Thus, satisfying each of the limitations, namely the conductivity and the pH range, is critical to the present invention.

Id. at 105 (emphasis in original). Chugai further distinguished the prior art cited and relied on by the Examiner by arguing that none of the references "disclose or make obvious the critical feature of the present invention that the molarity of the neutralized solution must be 0 to 100 mM." *See id.* at 110. More specifically, Chugai argued that "[t]hus, it is recognized that no DNA particle was precipitated in this [prior art Tsuchiya] example because of its higher conductivity, i.e. of a molarity of over 0.1M . . . . Applicants submit that no such particles are formed during the procedure of 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." *See id.* at 107-108.

In a Final Rejection dated May 2, 2007, the Examiner withdrew the prior art-based rejections, but rejected the claims under 35 U.S.C. § 112, first and second paragraphs. *Id.* at 26-30. In response, Chugai amended the claims by changing the molarity limitations to "100 mM or less." *Id.* at 85. In subsequent interviews and communications discussing claim amendments proposed by the Examiner, Chugai stated:

> As we explained in the comments we provided for responding to the previous official actions, an important feature of the present invention

> is to adjust the pH value of the solution, the eluate, to from 4 to 8 while maintaining the molarity of the solution at 100 mM or less, whereby DNA contaminants can be effectively removed as particles.
>
> The purpose of the use of a buffer is to adjust the pH of the solution, and since the amount of the buffer used is very small compared with that of the solution to which the buffer is added, the effect of the molarity of the buffer to the molarity of the whole solution is extremely small. In connection with this point, we would like to point out that use of a small amount of a buffer solution to modulate a pH value of a solution of a relatively large volume is well known in this technical field.
>
> Therefore, the molarity of the buffer solution itself is not critical in the present invention as long as the molarity of the solution is 100mM or less.

Id. at 82-83 (emphasis in original). The Examiner allowed the application on October 5, 2007. *Id.* at 76-78. The '289 patent was issued on February 19, 2008. On July 10, 2008, Chugai submitted a one-page letter informing the USPTO that it had received a communication from the European Patent Office ("EPO") on April 16, 2008 regarding a third party submission in the corresponding European Patent Application No. 02703958.5. *Id.* at 64. Chugai informed the USPTO that the document cited by the third party submission was WO95/22389 and attached a copy of only the first page of WO '389. *Id.* at 64-65.

ii. The ’688 Application Prosecution History

Chugai submitted the ’688 Application to the USPTO on January 23, 2008 as divisional of the ’374 Application, now the ’289 patent. Ex 1005, 66. On June 9, 2008, Chugai submitted an Information Disclosure Statement (“IDS”) listing WO ’389, among other references.

In the first Office Action mailed October 23, 2008, the Examiner rejected the pending claims under 35 U.S.C. § 112, first paragraph, because the specification “does not reasonably provide enablement for alkaline pH less than 8.0.” *Id.* at 62. In the Response dated April 22, 2009, Chugai amended step 1 of the independent claim to remove “alkaline.”

Id. at 53. Chugai also added a new independent claim 15. *Id.* at 55-56.

In a later Office Action mailed August 6, 2009, the Examiner provided new grounds of rejection, a non-statutory obviousness-type rejection (over the claims of co-pending U.S. Application No. 10/527,455, which issued as U.S. Patent No. 8,420,789), an anticipation rejection under 35 U.S.C. § 102(b). *Id.* at 45-51. WO ’389 was also included in the list of references cited by the Examiner but it was not discussed at all in the Office Action. *Id.* at 52.

In response, Chugai filed a terminal disclaimer over U.S. Application No. 10/527, 455 (*id.* at 30) and amended the claims to read as follows:

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.

. . . .

15. 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 adjusted sample is 100 mM or less; and

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

Id. at 20, 22-23. Chugai concurrently argued that the prior art, "fails to disclose the features of the sample solution having 'a molarity of 100 mM or less" and "an acidic aqueous solution of low conductivity of 300 mS/m or less" of main claims 1 and 15. *Id.* at 28.

In a later Office Action dated April 14, 2010, the Examiner withdrew the anticipation and obviousness rejections, but rejected the claims under 35 U.S.C. § 112, first paragraph on written description and enablement grounds. *Id.* at 13. The Examiner explained the written description rejection as follows:

> It is noted that step (2), "wherein the molarity of the adjusted sample is 100mM or less" does not have support from the specification. As has been argued in the Remarks, all the substances in the purification, acidification and neutralization processes should be counted (see Remarks, page 9, last two paragraph where human plasma from fraction II+III, acetic acid and NaOH. In view of the specification, Applicants have not shown sufficient evidence in support of this notion.

Id. at 14-15. The Examiner further explained the enablement rejection as follows,

> [i]t is also not clear in the Examples 1-6 how much total DNA concentration was in the elutes and how much Tris buffer (1000 mM (1M)) was used to adjust the pH. The only information we know is that 2.5 mM HCl and 1 M (1000 mM) aqueous Tris buffer are used to adjust pH (Examples 4-6).

Id. at 18.

In response, Chugai never directly addressed the Examiner's written description and enablement arguments regarding whether the total molarity of the adjusted sample must take all the substances into account. Chugai simply argued that the specification provided sufficient written description and enablement support for the claims. More specifically, Chugai argued the following:

> Further, in the enablement rejection, the examiner states that the second step of elevating the pH level to 4-8 would exceed the maximum level of 100 mM, since the level of molarity in the acidic aqueous has already reached to 100 mM. However, the claim does not say this. The claims do not say that the molarity in the acidic aqueous has already reached to 100 mM already in step 1. *Step 1 only recites that the molarity of the acidic aqueous solution is in a range of 0 to 100 mM. Step 2 also requires for it to stay in this range*.

*See id.*at 9 (emphasis added).

On December 13, 2010, the Examiner allowed the '688 application. *Id.* at 1-6. The '815 patent was issued on April 19, 2011. Notably, WO '389 was never substantively considered or relied upon by the Examiner.

b. The EP '589 prosecution history

Currently pending European Application No. 02703958.5, filed on March 11, 2002 and published as EP '589, is a foreign counterpart of the '815 patent. EP '589 is entitled "Protein Purification Method," and the applicant is also Chugai. On April 4, 2008, during the examination of EP '589, a third party filed Third Party

Observations drawing the attention of the EPO to an additional prior art document, WO ’389, which had not been cited previously. Ex. 1006, 49. The Third Party Observations explained in detail how all pending claims of EP ’589 were not novel or inventive because WO’ 389 anticipated each step of the pending claims, including claim 3, which recited:

> 3. A method for removing contaminant DNA in an antibody-containing sample, which comprises the following steps:
>
> 1) applying the antibody-containing sample to affinity chromatography on Protein A or Protein G to elute the antibody with an acidic aqueous solution of low conductivity having a molarity of 0 to 100 mM;
>
> 2) adjusting the pH of the resulting eluate to pH 4 to 8 by addition of a buffer, wherein the molarity of the adjusted eluate is 0 to 100mM; and
>
> 3) removing the resulting particles.

Id. at 49-56.

In a subsequent communication to Chugai on October 23, 2009, the EPO cited WO ’389 as a prior art reference and adopted the arguments put forth in the Third Party Observations. Specifically, the EPO stated:

> An observation by a third party concerning the present application were filed on 04.04.2008 . . . . For the reasons outlined in said observations, present claims 1-6, 8-10 and 15-17 are not novel over [WO ’389] . . . . For the reasons outlined in the above mentioned observations by a third party, present claims 1-17 are not inventive over [WO ’389].

Id. at 46.

After several further rounds of prosecution between Chugai and the EPO, another Third Party Observations document was submitted on October 2, 2015, detailing again why the pending claims were not novel or inventive over WO ’389. *Id.* at 38-44. Among other things, the additional Third Party Observations demonstrated why the characteristic conditions (molarity, ionic strength, and conductivity) of the claimed acidic aqueous solution were necessarily and inherently present in the process disclosed in WO ’389. *See, e.g.*, *id.* at 39 (“[WO ’389] provides sufficient information to calculate the molarity of the pH adjusted eluate: . . . . In the case of Example IA: . . . [T]he total molarity of the pH adjusted eluate is 25 mM (citrate) + 23 mM (Tris) = **48 mM**”) (emphasis in original); *id.* at 41(“As evidenced below, [WO ’389] describes an acidic aqueous solution with an ionic strength of 0.01959 M (i.e. ‘0.2 or less’) and a conductivity of around 150 mS/m (i.e. ‘300 mS/m or less’).”).

On October 12, 2015, the EPO issued a summons to attend oral proceeding. *See id.* at 32. In a response dated January 21, 2016, Chugai submitted proposed narrowing amendments where “the molarity of the aqueous solution in step 1 and acidic molarity of the adjusted eluate in step 2 [had] been amended to ‘30mM or less.’” *Id.* at 25. Chugai argued that WO ’389 “does not disclose the feature of a molarity of ‘30 mM or less.’” *Id.* at 27. Notably, and in order to support this

argument, Chugai admitted that the molarity of the neutralized eluent in Example IA of WO ’389 was less than 100 mM and could be precisely calculated as follows:

> Example IA in D3 (in particular, page 19, lines 9 to 19) discloses:
>
> - the IgG was eluted by applying 15-20 l of ProSep A elution buffer (25 mM citrate, pH 3.5, see Table 1 on page 18 of D3);
> - immediately after elution, the sample was adjusted to pH 3.5 by the addition of 2.5 M HCl, held for approximately 30 minutes, and adjusted to pH 5.5 by the addition of approximately 350 ml of 1 M Tris base;
> - thereafter, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.
>
> Thus, the eluent before the filtration has:
>
> - 375 mmol (25 mM · 15 l) of citrate
> - “x” mmol (2.5 M · “Y” 1 (unknown)) of HCl
> - 350 mmol (1 M · 0.35 l) of Tris base
> - at least 15.35 l (15 l + “Y” l +0.35 l) in total volume
>
> Based thereon, the molarity of the eluent can be calculated to at least (375 + 350)/15.35 = 47.2 mM.

Id. at 27-28.

After oral proceedings were held on February 23, 2016, the EPO, on March 17, 2016, decided to refuse European Application No. 02703958.5 because no basis could be found in the original application for Chugai’s proposed amendments (i.e., a molarity of “30mM or less”) and the amendments also lacked clarity. *Id.* at 7-12.

Chugai has filed an appeal against the EPO's decision to refuse this application, and the appeal is pending. *Id.* at 1.

c. The EP '149 prosecution history

Currently pending European Application No. 10011215.0, filed as a continuation of European Application No. 02703958.5 and published as EP '149, is another foreign counterpart of the '815 patent. EP '149 is entitled "Protein Purification Method," and the applicant is also Chugai. On July 30, 2013, during the prosecution of EP '149, Chugai filed the following amended independent claim:

> 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 an ionic strength of 0.2 or less or a conductivity of 300 mS/m or less** and having a molarity of ~~0 to 100~~**less than 50** mM and a pH of 1.5 to 3.9;
>
> 2) adjusting the PH of the resulting sample to a pH of 4 to 8; and
>
> 3) removing the resulting particles.

Ex. 1011, 59 (emphasis in original). On October 19, 2015, the EPO issued a summons to attend oral proceeding. *Id.* at 52. The EPO cited WO '389 as a prior art reference and adopted the arguments put forth in the Third Party Observations filed in the proceedings of the parental application. *Id*. at 52-53. Specifically, the EPO stated:

> Third party observations D6 were filed on 02.10.2015 in the proceedings of the parental application. The argumentation in said third party observations as to lack of novelty in view of [WO ’389] also applies *mutatis mutandis* to the present claims.
>
> Example IA of [WO ’389] describes the conversion of a sample containing the humanized monoclonal antibody RSHZ-19 into an acidic aqueous solution of low conductivity, i.e. into an eluate comprising 25 mM citrate and having a pH of 3.5. The eluate is then readjusted to pH 5.5 by addition of TRIS buffer and filter through a prefilter and a 0.2 μm filter ([WO ’389], e.g. page 14, line 10 - page 15, line 2; table 1; page 19, lines 4-20). As calculated in D7, the elution buffer of [WO ’389] exhibits an ionic strength of 0.01959 M and a conductivity at 25°C of around 150 mS/m.
>
> Consequently, [WO ’389] is novelty-destroying for claims 1-7 and 9, even if [WO ’389] does not explicitly refer to a method for removing contaminant DNA in a sample.

Id. The EPO further stated that “it is not clear to which compound(s) the parameter ‘…molarity of less than 50 mM…’ in claim 1.1.) refers to and the nature of the acidic aqueous solution to be used in claim 1.1) is open to interpretation.” *Id*. at 55. In a response dated March 18, 2016, Chugai filed narrowing amendments where the acidic aqueous solution in step 1 of claim 1 was defined as having “a molarity of 50 mM or less and a pH of 2.0 to 3.9” or “a molarity of 30 mM or less.” *Id*. at 28-29. Chugai also stated:

> As evidenced by the third party observations, one of skill in the art would have no problem calculating the molarity in [WO '389]. By the same token, a person of skill in the art would readily understand that a molarity of 50 mM or less relates to the total molarity, inter alia, of all components of the aqueous acidic solution of step 1.

Id. at 32.

On April 12, 2016, Chugai submitted additional experimental data to demonstrate the aggregation of DNA by following the claimed steps, including its own calculations of total molarity after the "Elution and Acid addition" and "pH adjustment" steps. *Id*. at 12-13. After oral proceedings were held on April 19, 2016, the EPO, on April 25, 2016, decided to refuse European Application No. 10011215.0 because no basis could be found in the original application for Chugai's proposed amendments. *Id*. at 7-11. Chugai has filed an appeal against the EPO's decision to refuse this application, and the appeal is pending. *Id.* at 1.

VI. THE SCOPE AND CONTENT OF THE PRIOR ART

A. State of the prior art as of March 2001

Due to advances in gene recombinant technology by 2001, it was possible to prepare and develop specific proteins for use in recombinant antibody drugs. *See* Ex. 1001, 1:13-17. Generally, to produce the recombinant product, genes encoding proteins such as antibodies may be cloned by incorporating DNA sequences coding for the desired regions of the polypeptide into a recombinant DNA vehicle (e.g., vector) and transforming or transfecting suitable prokaryotic or eukaryotic hosts.

Ex. 1003, 7. The vector directs the production of the product encoded by the DNA sequence of interest in the host cell. *Id.* at 8. Such recombinant techniques were well known to a POSA decades before March 2001. *Id.* at 7.

After the recombinant product is produced, it is desirable to recover the product. *Id.* at 7. The goal of protein purification is to provide a protein product that is essentially free of other proteins, and also to eliminate or reduce to acceptable levels other undesired materials—host cell contaminants, protein aggregates, misfolded species, DNA, RNA, potential pyrogens and the like. *Id*. Specifically for host DNA and contaminant DNA associated with viral contamination, under existing World Health Organization (WHO) criteria, it was understood before March 2001 that the amount of DNA in biological drugs should not exceed 100 pg DNA/dose. Ex. 1001, 1:18-24. Commonly used methods to purify recombinant proteins while removing contaminants included filtration and column chromatography (*e.g.*, affinity chromatography, hydrophobic interaction chromatography, and ion exchange chromatography) process steps. Ex. 1003, 15.

Preliminary separation processes such as depth prefilters, centrifuges, cross-flow microfilters, settling, or even immobilized cell bioreactors, are used to remove cell debris but are typically not capable of producing a sterile or cell- and debris-free effluent in recombinant production processes. Ex. 1010, Martin at 27, 30. Secondary filtration later in the purification process is required to further clarify and

sterilize the collected sample by removing residual cells, cell debris, bacterial contaminants, and particulate impurities. *Id.* at 27. Absolute removal of particulate solids from the process stream, including sterile filtration, also serves as an essential prefiltration/protection step for downstream chromatography and ultrafiltration steps. *Id.* Filtration can extend the service life and protect more costly tangential flow microfiltration (TFF) and ultrafiltration (UF) membrane systems and chromatography columns. Solvents, buffer solutions, and other fluids entering a bioprocess must be sterile filtered to maintain aseptic conditions, and particulate impurities must be removed to prevent premature plugging. *Id.* at 30. In most cases, a 0.2-μm-rated sterilizing-grade membrane filter is employed as the fluid filter. *Id.*

Affinity chromatography is used to purify a protein of interest from other proteins produced in a cell. Ex. 1002 ¶ 33. Affinity chromatography exploits a reversible interaction between the target protein and a specific ligand (i.e., a molecule that is able to bind to a complementary site in the target protein by weak interactions such as ionic bonds, hydrogen bonds, Van der Waals interactions, and hydrophobic effects) that is coupled to a chromatography matrix in a column. *Id.* Protein A is a cell wall protein from the bacterium *Staphylococcus aureus* that binds with high affinity to the Fc (fragment crystallizable) region of antibodies. *Id.* Protein A affinity chromatography was well-established as a standard purification method for antibodies in industry for decades prior to March 2001. *Id.*

B. WO ’389

WO ’389, entitled “Antibody Purification,” is the publication of an international patent application by SmithKline Beecham Corporation on behalf of Shadle et al. (Ex. 1003)[1]. The WO ’389 inventors recognized that while protein A affinity column chromatography is widely used, “elution of antibody from such columns can result in leaching of residual Protein A from the support.” Ex. 1003, 6. The disclosed protein purification processes of WO ’389 involve purifying an IgG

[1] U.S. Patent No. 5,429,746 (“the ’746 patent,” Ex. 1008), also entitled “Antibody Purification,” having the same Shadle et al. inventors, and owned by SmithKline Beecham Corporation, has the identical and critical disclosure as the disclosure from WO ’389 discussed below. As a printed publication and a patent, both WO ’389 and the ’746 patent are presumed to be enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012) (“[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by the patent applicant or patentee.”); *see also Google Inc. & Apple Inc. v. Jongerius Panoramic Techs., LLC*, IPR2013-00191, Paper 70 at 37 (PTAB Aug. 12, 2014) (“Prior art publications and patents are presumed to be enabled.”)). A POSA would also understand that the disclosure of the ’746 patent and WO ’389 is enabling for a POSA to practice the claimed invention without undue experimentation. Ex. 1002 ¶ 69.

(Immunoglobulin) antibody by sequentially subjecting a medium containing the antibody to several purification steps, starting with Protein A affinity chromatography. *Id*. at 15. Indeed, Example IA[2] of WO '389 teaches a process of purifying proteins and removing DNA contaminants that either expressly or inherently discloses each of the three purification steps recited in the claims of the '815 patent. *Id.* at 21-24.

WO '389 was published on August 24, 1995, more than five years before March 9, 2001, the earliest possible priority date of the '815 Patent. The identical and critical disclosure from WO '389 was also published in the '746 patent on July 4, 1995. Therefore, both WO '389 and the '746 patent are available as prior art under 35 U.S.C. § 102(b). Neither WO '389 nor the '746 patent were substantively considered or relied upon by the Examiner before the claims of the '815 patent were allowed. Ex. 1002 ¶ 69.

[2] Example IA 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. *See* Ex. 1002 ¶ 68; Ex. 1003, 16. Therefore, the process description of Example 1 is also part of Example IA. Ex. 1002 ¶ 68; Ex. 1003, 15-16.

VII. CLAIM CONSTRUCTION

"A claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Thus, "[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." *SAS Inst., Inc. v. ComplementSoft, LLC.*, 825 F.3d 1341, 1348 (Fed. Cir. 2016) (citation omitted).

As it relates to this Petition, Petitioner presumes that all claim terms of the '815 patent take on their ordinary and customary meaning based on the broadest reasonable construction of the claim language in view of the specification. With respect to the claim terms "molarity," "conductivity," and "ionic strength," a person of ordinary skill in the art would understand, consistent with the plain and ordinary meaning of these terms as well as the specification of the '815 patent, that these terms describe characteristic properties of a solution and have the following meanings:

- "Molarity" is 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;
- "Conductivity" is the ability of a solution to conduct electricity, and is related to the identities and concentrations of the charged species in the solution as well as to how freely these charged species move in solution; and
- "Ionic strength" is a reckoning of the concentration of the ions present in a solution.

Ex. 1002 ¶ 72. A person of ordinary skill in the art would further understand that contributions from the physiologically active protein and contaminant DNA would not be included when determining molarity, conductivity, and ionic strength. *Id.* ¶¶ 70-73.

For example, step 1 of independent claims 1 and 13 recites, "[c]onverting the sample containing a physiologically active protein into *an acidic aqueous solution of low conductivity of 300 mS/m or less* and *having a molarity of 100 mM* or less at pH of 1.5 to 3.9." Ex. 1001, 12:38-14:5 (emphasis added). The broadest reasonable construction of the terms "an acidic aqueous solution of low conductivity of 300 mS/m or less," and "an acidic aqueous solution of low conductivity . . . having a molarity of 100 mM or less" is that the conductivity and molarity of the acidic

aqueous solution are 300 mS/m or less and 100 mM or less, respectively, without considering any effects of the contaminant DNA or physiologically active protein from the sample. Ex. 1002 ¶ 73. The specification of the '815 patent supports and is consistent with this construction because it specifically states that the preferred way to convert the sample is "by eluting the sample from Protein A/G affinity chromatography *with an acidic aqueous solution of low conductivity*." Ex. 1001, 5:23-27 (emphasis added); Ex. 1002 ¶ 74. The specification then proceeds to define an acidic aqueous solution of low conductivity in terms of conductivity, molarity, ionic strength, or pH ranges, and provides several acids as potential options. *Id.* at 5:28-37; Ex. 1002 ¶ 74. The specification does not include any written description of molarity or conductivity that considers the concentrations of protein or contaminant DNA. Ex. 1002 ¶ 74; *see Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, 824 F.3d 999, 1004 (Fed. Cir. 2016) ("Because the specification makes no mention of wireless communications, construing the instant claims to encompass that subject matter would likely render the claims invalid for lack of written description. The canon favoring constructions that preserve claim validity therefore counsels against construing 'communications path' to include wireless communications.") (citation omitted). Thus, a person of ordinary skill in the art would understand that the claimed "molarity, "conductivity," and "ionic strength"

refer to the properties of the acidic aqueous solution without the protein or contaminant DNA. Ex. 1002 ¶ 74.

Chugai's admissions to the EPO during the prosecution of the '815 patent's European counterpart EP '149 also support this construction. *Id.* ¶ 75. In response to the EPO's argument that molarity was vague, Chugai relied on third party molarity calculations, which notably excluded protein or DNA concentrations, to argue that "[a]s evidenced by the third party observations, one of skill in the art would have no problem calculating the molarity in [WO '389]." Ex. 1011, 32; Ex. 1002 ¶ 75. Chugai further admitted that, "[b]y the same token, a person of skill in the art would readily understand that a molarity of 50 mM or less relates to the *total molarity*, inter alia, *of all components of the aqueous acidic solution of step 1*. Ex. 1011, 32 (emphases added); Ex. 1002 ¶ 75. Chugai further made clear that "total molarity" does not include contributions from protein or DNA concentrations in their submission of additional experimental data to the EPO. Ex. 1011, 12-13 (calculating total molarity without including protein or DNA); Ex. 1002 ¶ 75.

VIII. ANALYSIS OF GROUNDS FOR TRIAL

Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner provides the following detailed statement of reasons for the relief requested in this Petition.

A. Ground I: Anticipation Under 35 U.S.C. § 102(b)

As shown below, claims 1–7, and 12–13 of the ’815 patent are unpatentable under 35 U.S.C. § 102(b) as anticipated by WO ’389 (Ex. 1003). A claim is anticipated in its entirety if a prior art reference “disclose[s] every limitation of the claimed invention, either explicitly or inherently.” *MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

1. Independent claim 1 is anticipated by WO ’389

WO ’389 expressly or inherently discloses every limitation of claim 1. Ex. 1002 ¶ 76.

a. Preamble: A method for removing contaminant DNA

The preamble of claim 1 recites “[a] method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises the following steps . . . .” Ex. 1001, 12:38-40. To the extent that the preamble is a limitation—a matter that the Board need not reach—WO ’389 discloses it.

The term “[c]omprising” is a term of art generally used in claim drafting to indicate “that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.” *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). Thus, because the preamble of claim 1 provides that the “method for removing contaminant DNA . . . comprises the following steps,” claim 1 covers methods with additional process steps beyond those expressly recited.

WO ’389 is entitled “Antibody Purification,” and discloses methods for purifying samples of antibodies. WO ’389 states that the “procedure outlined below was developed for the *isolation and purification of a monoclonal antibody* . . . . The process is designed to prepare RSHZ-19 [*i.e.*, the antibody] of >95% purity while *removing contaminants* derived from the host cell, cell culture medium, or other raw materials.” Ex. 1003, 15 (emphases added). WO ’389 further states that “[t]he *purified antibodies* obtained by practicing the process of this invention have the following properties: . . . *low* (< 1 pg/mg protein) *DNA* . . . .” *Id.* at 14 (emphases added).

WO ’389 discloses a process for purifying antibodies, *i.e.*, “a sample containing a physiologically active protein.” Ex. 1002 ¶¶ 77-81. Specifically, WO ’389 discloses that DNA is among the derived contaminants that are removed because the purified antibody product obtained by practicing the disclosed process has a reduced DNA concentration. *Id.* Thus, WO ’389 explicitly discloses a method for removing contaminant DNA in a sample containing a physiologically active protein. *Id.* ¶ 81.

b. Step 1: Converting the sample to an acidic aqueous solution of low conductivity

i. “converting the sample”

Step 1 of claim 1 recites “converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or

less and having a molarity of 100 mM or less at pH of 1.5 to 3.9." Ex. 1001, 12:41-44. WO '389 explicitly or inherently discloses this limitation. Ex. 1002 ¶ 82. The first step in the WO '389 purification process is to apply the antibody sample (i.e., a sample containing a physiologically active protein) to an affinity chromatography column. *Id.* at ¶ 83. The next step in Example IA of WO '389 is to wash the column, and then the "IgG [antibody is] eluted by applying 15 - 20 liters of ProSep A elution buffer." Ex. 1003, 21. This elution with the elution buffer converts the sample containing a physiologically active protein into an acidic aqueous solution. Ex. 1002 ¶ 84; Ex. 1001, 5:23-27 ("a sample containing a physiologically active protein is converted into an acidic aqueous solution of low conductivity, preferably by eluting the sample from Protein A/G affinity chromatography with an acidic aqueous solution of low conductivity."). Table 1 of WO '389 further discloses that the conditions of the ProSep A elution buffer are "25 mM citrate, pH 3.5." Ex. 1003, 20.

As described above, the elution step in Example IA meets the limitation recited in step 1 of the '815 patent requiring "an acidic aqueous solution of low conductivity." Ex. 1002 ¶ 85. The specification of the '815 patent defines "an acidic aqueous solution of low conductivity" as:

> [G]enerally refer[ing] to an aqueous solution of pH 1.5 to pH 3.9, preferably of pH 2.0 to pH 3.9, more preferably of pH 2.0 to pH 3.0, which has a molarity of 0 to 100 mM, preferably 0 to 50 mM, more

> preferably 0 to 30 mM, or has an ionic strength of 0 to 0.2, preferably 0 to 0.12, or has a conductivity of 0 to 300 mS/m, preferably 0 to 200 mS/m, more preferably 0 to 150 mS/m.

Ex. 1001, 5:28-35. Claim 1 of the '815 patent further limits such eluting solution to the following conditions: having a conductivity of "300 mS/m or less" and having a molarity of "100 mM or less at a pH of 1.5 to 3.9." Each of these recited conditions were either explicitly or inherently disclosed in the Example IA process. Ex. 1002 ¶ 86.

ii. "molarity" and "pH" of the acidic aqueous solution

First, and as described above, the Pro Sep A citrate elution buffer solution used in Example IA of WO '389 has a pH of 3.5, which is a pH between 1.5 and 3.9. Moreover, the ProSep A citrate elution buffer solution has a molarity of 25 mM, which is significantly lower than the required 100 mM. Ex. 1002 ¶ 87.[3] Thus, WO '389 expressly discloses that the antibody sample resulting after purification on the

[3] To the extent Chugai argues that molarity should be determined by considering contributions from the physiologically active protein or contaminant DNA, Dr. Przybycien explains that such added contribution would be negligible (*i.e.* less than 1 mM), and certainly not enough to raise the molarity of the ProSep A citrate elution buffer above the claimed 100 mM limit. Ex. 1002 ¶ 87.

Protein A column is converted into an acidic aqueous solution when eluted with the ProSep A buffer solution, and that this solution has a molarity of 100 mM or less at a pH of 1.5 to 3.9. *Id.*

iii. "conductivity" of the aqueous acidic solution

Second, as Dr. Przybycien explains, the ProSep A buffer solution used and disclosed in Example IA of WO '389 necessarily had a low conductivity of "300 mS/m or less." *Id.* ¶¶ 88-90. Dr. Przybycien demonstrated this by preparing the "25 mM citrate, pH 3.5" ProSep A elution buffer of Example IA and testing its conductivity at room temperature. *Id.* ¶ 88. As Dr. Przybycien explains, a POSA would have used one of the following four most common methods for preparing the "25 mM citrate, pH 3.5" ProSep A elution buffer that is disclosed in WO '389: 1) 25 mM citric acid adjusted to pH 3.5 with NaOH; 2) 25 mM monosodium citrate adjusted to pH 3.5 with HCl; 3) 25 mM citric acid and 25 mM monosodium citrate blended to achieve pH 3.5; 4) 25 mM citric acid and 25 mM trisodium citrate blended to achieve pH 3.5. *Id.* The citrate buffers prepared using preparation methods 1, 3, and 4 are identical in composition because they have the same buffer species and ion concentrations. *Id.* The citrate buffer prepared using preparation method 2 includes different ion species because of the addition of HCl, and therefore has a different composition. *Id.*

In the abundance of caution, Dr. Przybycien prepared and tested two ProSep A elution buffer solutions that covered the two different compositions disclosed in WO '389. Ex. 1016, Protocol at 1-3. His tests show conclusively that the ProSep A elution buffer solution disclosed in WO '389 necessarily had a conductivity of either 194 ± 7 mS/m or 154 ± 7 mS/m (average conductivity +/- 95% confidence limits from samples prepared in triplicate), which are both significantly lower than the claimed conductivity of "300 mS/m" limit.[4] *Id.* ¶¶ 88-89; *see* Ex 1016, Protocol at 1-3. "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citation omitted). Moreover, additional references or evidence can be used to show that a person of ordinary skill in the art would recognize the inherent characteristic of the thing taught by the primary reference. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002)

[4] To the extent Chugai argues that conductivity should be determined by considering contributions from the physiologically active protein or contaminant DNA, Dr. Przybycien explains that this would be improper for calculating conductivity, and in any event would certainly not enough to raise the conductivity of the ProSep A citrate elution buffer above the claimed 300 mS/m limit. Ex 1002 ¶¶ 88-89.

(recognizing that courts permit "the use of additional references to confirm the contents of the allegedly anticipating reference"); *see also* MPEP § 2124; *In re Wilson*, 311 F.2d 266, 269 (C.C.P.A. 1962) (finding that the use of a later-issued publication was proper where used to show that the characteristics of prior art polyurethane foam products—"a state of fact"— were known). As confirmed by Dr. Przybycien's testing, the elution solution used in Example IA of WO '389 must necessarily—and, thus, inherently—satisfy the limitation that requires a conductivity of 300 mS/m or less. Ex. 1002 ¶¶ 88-90.

The results of Dr. Przybycien's testing are also consistent with the assertions of the third party during the prosecution of EP '149 that, "when measured at 25°C, 25 mM citrate, pH 3.5 displayed a conductivity of around 150 mS/m." Ex. 1011, 39. In both instances, the conductivity of the elution buffer in Example IA of WO '389, as measured by the third party and Dr. Przybycien, was significantly lower than the claimed conductivity of "300 mS/m" limit. Ex. 1002 ¶89.

Thus, WO '389 explicitly or inherently discloses step 1 of the claimed purification process. Ex. 1002 ¶ 90. That is, WO '389 discloses converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity by using the ProSep A Elution Buffer for eluting the antibody, and this ProSep A Elution Buffer is an acidic aqueous solution of low conductivity

of "300 mS/m or less" and having a molarity of "100 mM or less at a pH of 1.5 to 3.9." *Id.*

c. Step 2: Adjusting the pH to form particles

i. "adjusting the pH"

Step 2 recites "adjusting the pH of the resulting sample from step (1) to pH of 4 to 8 to form particles, wherein the molarity of the adjusted sample is 100 mM or less." Ex. 1001, 12:45-47. WO '389 explicitly or inherently discloses this limitation. Ex. 1002 ¶ 91.

The next step in the purification process disclosed in Example IA of WO '389 is to adjust the pH and filter the eluate before further chromatography. *Id.* ¶ 92. WO '389 describes this step as follows:

> The eluate was approximately 15 liters in volume, and contained approximately 5 milligrams protein per milliliter. Immediately *after elution, the sample was* adjusted to pH 3.5 by the addition of 2.5 M hydrochloric acid, held for approximately 30 minutes, and *adjusted to pH 5.5 by the addition of approximately 350 milliliters of l M Tris base*. After *neutralizing to pH 5.5*, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.

Ex. 1003, 21 (emphases added). As described above, 350 milliliters of 1M Tris base is added to the eluate to adjust it to pH 5.5. Ex. 1002 ¶ 92. WO '389 further discloses that the 1M Tris base is a buffer. *See* Ex. 1003, 16 ("[eluate is] readjusted to pH 5.5

by the addition of Tris buffer."). Thus, WO '389 explicitly discloses adjusting the pH of the resulting sample from step (1) to pH of 4 to 8. *Id.*

ii. "molarity" of the adjusted sample

Example IA of WO '389 does not explicitly describe the particular molarity of the adjusted eluate solution, or the formation of particles. Both claim elements, however, are conditions that are necessarily present and inherent in the neutralized elution solution disclosed in the Example IA process. Ex. 1002 ¶ 93; *see also Schering Corp.*, 339 F.3d at 1377; *Teleflex, Inc.*, 299 F.3d at 1335.

As explained by Dr. Przybycien, the particular molarity of the adjusted eluate solution of Example IA, although not expressly disclosed in WO '389, can nevertheless be calculated based on other disclosures in WO '389. Ex. 1002 ¶ 94. As such, the molarity is necessarily present and inherently disclosed. *Id.* Example IA discloses that eluate of 15 L in volume is produced using 15-20 liters of the 25 mM Citrate elution buffer with a pH of 3.5. Ex. 1003, 21. As such, the volume of 2.5 M HCl needed to adjust the pH of the eluate to 3.5 is minimal. Ex. 1002 ¶¶ 95-99; Ex. 1007, 1-3. In fact, WO '389 explicitly states that the HCl addition step can be omitted. Ex. 1003, 15 ("The pH 3.5 treatment can be omitted if desired."). As Dr. Przybycien explains, 25 mM Citrate in 15 liters contains 375 mmol Citrate, and subsequent adjustment to pH 5.5 requires the addition of 350 ml of 1M Tris, which contains 350 mmol Tris. Ex. 1002 ¶ 96; Ex. 1007, 1. Adding the 350 mmol Tris

and 375 mmol Citrate in a total volume of 15.35 liters gives a total molarity of **47.2 mM** (Citrate and Tris), which is less than 100mM. Ex. 1002 ¶¶ 94-98; Ex. 1007, 1.[5] Thus, the molarity of the large volume of eluate neutralized and adjusted by adding 350 ml of 1M Tris base to raise the pH to 5.5 in Example IA of WO '389 must necessarily—and, thus, inherently—be less than 100 mM. Ex. 1002 ¶¶ 95-99; Ex. 1007, 1-3.

This conclusion is supported by Patent Owner's own statements during prosecution of the '289 patent and its European counterparts, EP '589 and EP '149. The '815 patent derives from the same initial application as the '289 patent and both patents contain the same claim limitation that the neutralized sample has a molarity of 100 mM or less. Thus, Patent Owner's statements during the prosecution of the '289 patent apply with equal force to the subsequently issued '815 patent. *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999).

[5] To the extent Chugai argues that molarity should be determined by considering contributions from the physiologically active protein or contaminant DNA, Dr. Przybycien explains that such added contribution would be negligible (*i.e.* less than 1 mM), and certainly not enough to raise the molarity of the adjusted ProSep A citrate elution buffer above the claimed 100 mM limit. Ex. 1002 ¶¶ 96-98.

To secure allowance of the ’289 patent, Patent Owner argued that because the amount of buffer used to adjust the pH of the solution “is very small compared with that of the solution to which the buffer is added, *the effect of the molarity of the buffer to the molarity of the whole solution is extremely small*.” Ex. 1005, 83 (emphasis added). Patent Owner further argued that “use of a small amount of a buffer solution to modulate a pH value of a solution of a relatively large volume is well known in this technical field.” *Id.* More specifically, with regards to Example IA of WO ’389, Patent Owner admitted to the EPO that “the molarity of the eluent can be calculated to at least (375 + 350)/15.35 = 47.2 mM.” Ex. 1006, 27-28. Dr. Przybycien also confirms that, even if the minimal effect of the HCl on the molarity of the neutralized eluate were included, the overall effect would be insignificant and the molarity of the neutralized eluate in Example IA would still be well below the required 100 mM. Ex. 1002 ¶ 99; Ex. 1007, 1-3.

iii. “to form particles”

As to the formation of particles, neutralizing and adjusting the pH of 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 form particles, and is thus also inherently disclosed in the Example IA process of WO ’389. Ex. 1002 ¶ 100. This is confirmed by the ’815 patent itself. *See In re Preda*, 401 F.2d 825, 826 (C.C.P.A 1968) (“[I]n considering the disclosure of a reference, it is proper to take into account not only

specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom."); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) ("Even if no prior art of record explicitly discusses the [limitation], the [patent applicant's] application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in the [claimed invention]."") (brackets in original) (citation omitted); *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, No. 2016-1184, 2017 WL 744055, at *4 (Fed. Cir. Feb. 27, 2017) (holding challenged patent's specification disclosed that prior art taught the same claimed method because the challenged specification identified the same steps and results as the prior art); *see also In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011). The conditions from Example IA fall within the same range of conditions (pH of 4-8 and molarity less than 100 mM) recited in step 2 of the claimed process that the '815 patent claims is sufficient to form particles. Ex. 1002 ¶¶ 100-102.

As the Patent Owner conceded in the '815 patent specification, these claimed conditions of the neutralized eluate "produce[] particles." *See* Ex. 1001, 6:4-7 ("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).") (emphasis added); *see also id.* at 2:2-3 (after neutralization, the solution is "then filtered through

a filter to remove *the resulting particles*.") (emphasis added); Ex. 1002 ¶ 100. The '815 patent specification further describes that the formed particles will contain contaminant DNA. *See* Ex. 1001, 6:12-19 ("Without being bound by any particular theory, the inventors of the present invention estimate that *each of these particles is a conjugate formed between physiologically active protein and DNA.* Particle removal by filtration results in a small loss of physiologically active protein because it is removed in the form of *DNA-physiologically active protein conjugates*.") (emphases added); Ex. 1002 ¶ 100.

Patent Owner also made the same concessions in arguments presented to the USPTO during the prosecution of the related '289 patent. *See* Ex. 1005, 107-108 ("Thus, it is recognized that no DNA particle was precipitated in this [prior art Tsuchiya] example because of its higher conductivity, i.e. of a molarity of over 0.1M. . . . Applicants submit that no such particles are formed during the procedure of 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. 1002 ¶ 100; *see also Elkay Co.*, 192 F.3d at 980.

The inherent formation of particles under the recited eluate solution conditions and those particles containing contaminant DNA is also consistent with the teachings in the prior art. Ex. 1002 ¶ 101; Ex. 1009, Scopes at 28 ("In the ionic

strength range from zero to physiological, some proteins form precipitates because the repulsive forces are insufficient . . . . In many cases isoelectric precipitates can be formed by lowering the pH to between 6.0 and 5.0.) and 29 ("[m]ost isoelectric precipitates are aggregates of many different proteins and may include particulate fragments and protein-nucleic acid complexes."). For all these reasons, the formation of particles in step 2 is inherently disclosed by the Example IA process of WO '389. Ex. 1002 ¶¶ 100-102.

In sum, all limitations of step 2 are expressly or inherently disclosed in the Example IA process of WO '389. *Id.* ¶ 102.

d. Step 3: Removing particles

Step 3 is the final step of the claimed purification process and recites "removing the particles thereby to remove contaminant DNA in the sample." Ex. 1001, 12:48-49. WO '389 either expressly or at least inherently discloses this limitation.

After neutralizing the eluate to pH 5.5, the next step of Example IA discloses that "the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container." Ex. 1003, 21.

As Dr. Przybycien explains, the particles that formed according to the steps of Example IA, including those containing contaminant DNA, would inevitably and necessarily be removed by the disclosed filters, because the purpose of such filters

is to remove all particles above a certain size through filtration. Ex. 1002 ¶¶ 104-106; *see also* Ex. 1010, Martin at 27, 30. As such, WO '389 expressly disclosed using its two filters to remove particles, including those formed in step 2 and containing contaminant DNA. Ex. 1002 ¶¶ 104-107. The specification of the '815 patent confirms:

> According to the present invention . . . *particles may be removed by filtration through a filter* to ensure efficient removal of contaminant DNA. Examples of a filter available for filtration include, but are not limited to, a 1.0-0.2 μm Cellulose Acetate Filter System (Corning) or TFF.
>
> . . . .
>
> *[E]ach of these particles is a conjugate formed between physiologically active protein and DNA.* Particle removal by filtration results in a small loss of physiologically active protein because it is removed in the form of DNA-physiologically active protein conjugates.

Ex. 1001, 6:1-18 (emphases added); *see* MPEP § 2112.02 ("When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process.") *citing In re King*, 801 F.2d 1324, (Fed. Cir. 1986); *see also In re Preda*, 401 F.2d at 826; *Alcon Research, Ltd.*, 687 F.3d at 1369; *Knauf Insulation, Inc.*, 2017 WL 744055, at *4; *In re Huai-Hung Kao*, 639 F.3d at 1070.

In both WO ’389 and the ’815 patent, the neutralized eluates are filtered by a 0.2 µm filter. Ex. 1002 ¶ 108. WO ’389 also discloses the use of a smaller 0.1 micron filter, which will remove even more particles than the 0.2 µm filter. *Id.* Therefore these filters will inherently perform the claimed process of removing particles, including those containing DNA, just as the ’815 patent claims and describes. *Id.* Indeed, it is legally irrelevant whether it was known, expressly described, or intended in the Example IA process of WO ’389 that the filtration step would remove particles. *See Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) (“[A] reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.”). Thus, WO ’389 either expressly or at least inherently discloses the final step 3 of the claimed purification process of removing particles to thereby remove contaminant DNA. Ex. 1002 ¶ 108. Therefore, all limitations of step 3 are either expressly or at least inherently disclosed by the Example IA process of WO ’389. *Id.*

In sum, the Example IA purification process in WO ’389 discloses, either expressly or inherently, each of the process steps of claim 1, and thus anticipates claim 1. *Id.* ¶ 108-109.

2. Claims 2–7 and 12 are Anticipated by WO ’389

The limitations in each of dependent claims 2–7 and 12 of the ’815 patent are also anticipated by WO ’389.

a. Claim 2 is anticipated

Claim 2 depends from claim 1 and requires that "the acidic aqueous solution of low conductivity has a molarity of 50 mM or less." Ex. 1001, 12:50-52. The composition of the ProSep A Elution Buffer used in Example IA of WO '389 is "25 mM citrate, pH 3.5." Ex. 1003, 20. As described above for claim 1, a pH of 3.5 is an acidic pH and 25 mM is a molarity significantly lower than 50 mM. Ex. 1002 ¶ 111. As such, the ProSep A Elution Buffer used in Example IA meets the limitation of an acidic aqueous solution of low conductivity that has a molarity of 50mM or less. *Id.*

b. Claim 3 is anticipated

Claim 3 depends from claim 1 and requires that "the acidic aqueous solution of low conductivity has an ionic strength of 0.2 or less." Ex. 1001, 12:53-55. WO '389 does not explicitly describe the ionic strength of the ProSep A elution buffer solution. But as Dr. Przybycien explains, this value can be calculated as 0.02059 M or 0.02653 M for the two compositions of the ProSep A buffer solution, such that it necessarily had an ionic strength of "0.2 or less."[6] Ex. 1002 ¶ 112; Ex. 1007, 3-8;

[6] To the extent Chugai argues that ionic strength should be determined by considering contributions from the physiologically active protein or contaminant

see also Ex. 1011, 52 ("As calculated in [Third Party Observation], the elution buffer of [WO '389] exhibits an ionic strength of 0.01959 M . . . ." assuming ideal conditions). Thus, the elution solution used in Example IA of WO '389 must necessarily—and, thus, inherently—have an ionic strength of 0.2 or less. Ex. 1002 ¶ 112; *see also Schering Corp.*, 339 F.3d at 1377; *Teleflex, Inc.*, 299 F.3d at 1335.

c. Claim 4 is anticipated

Claim 4 depends from claim 1 and requires that "the acidic aqueous solution is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid and acetic acid." Ex. 1001, 12:56-59. As discussed above, the composition of the ProSep A Elution Buffer used in Example IA of WO '389 is "25 mM *citrate*, pH 3.5." Ex. 1003, 20 (emphasis added). As a POSA would readily appreciate, the 25mM Citrate buffer solution contains citric acid. Ex. 1002 ¶ 113. As such, the composition of the Prosep A elution buffer used in example IA of WO '389 is a citric acid solution of low conductivity. *Id.*

d. Claim 5 is anticipated

Claim 5 depends from claim 1 and further requires that "the contaminant DNA is present at a DNA concentration of 22.5 pg/ml or less in the treated sample

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DNA, Dr. Przybycien explains that this would be improper for calculating ionic strength. Ex. 1002 ¶ 112.

containing a physiologically active protein." Ex. 1001, 12:60-63. WO '389 discloses that "[t]he purified antibodies obtained by practicing the process of this invention have the following properties: . . . low (< 1 pg/mg protein) DNA . . . ." Ex. 1003, 14. Example IA of WO '389 results in a purified antibody sample containing "approximately 2.4 milligrams protein per milliliter." *Id.* at 14. Multiplying <1 pg/mg protein DNA by 2.4 mg/ml protein results in the contaminant DNA in Example IA of WO '389 being <2.4 pg/ml—within the claimed range of "22.5 pg/ml or less." Ex. 1002 ¶ 114.

e. Claim 6 is anticipated

Claim 6 depends from claim 1 and further requires that "the physiologically active protein is an antibody." Ex. 1001, 12:64-65. As discussed above for claim 1, the sample that is purified in Example IA is an antibody sample. Ex. 1002 ¶ 115.

f. Claim 7 is anticipated

Claim 7 depends from claim 6 and further requires that "the antibody is a humanized monoclonal antibody." Ex. 1001, 12:66-67. In Example IA of WO '389, "[t]he procedure . . . was developed for the isolation and purification of a monoclonal antibody against Respiratory Syncytial Virus (RSV)." Ex. 1003, 15. WO '389 specifies that "[t]his antibody is a 'humanized' IgG . . . ." *Id.* IgG is Immunoglobulin G, a type of antibody. Ex. 1002 ¶ 116.

g. Claim 12 is anticipated

Claim 12 depends from claim 1 and further requires that "the particles are removed by filtration through a filter." Ex. 1001, 13:9-10. Example IA of WO '389 discloses that "[a]fter neutralizing to pH 5.5, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container." Ex. 1003, 21. As discussed above for claim 1, the particles that are necessarily present and inherently formed in Example IA of WO '389 are also necessarily removed by filtration through a filter. Ex. 1002 ¶ 117. Thus, WO '389 either expressly or at least inherently discloses that the particles are removed by filtration through a filter, and anticipates claim 13. *Id.*

In sum, WO '389 discloses, either expressly or inherently, every limitation of each of claims 2–7 and 12, and, therefore, anticipates each of these claims. *Id.* ¶ 118.

3. Independent Claim 13 is Anticipated by WO '389

WO '389 expressly or inherently discloses every limitation of claim 13. Ex. 1002 ¶ 119. Independent Claim 13 is substantially identical to independent claim 1 and is anticipated for substantially the same reasons discussed above for claim 1.

a. Preamble: A method for removing contaminant DNA

The preamble of claim 13 recites "[a] method for removing contaminant DNA in a sample containing a physiologically active protein, which comprises . . . ." Ex. 1001, 13:11-12. To the extent that the preamble is a limitation—a matter that the Board need not reach—WO '389 discloses it.

For the same reasons discussed above for the substantially identical preamble of claim 1, WO ’389 explicitly discloses a method for removing contaminant DNA in an antibody-containing sample. Ex. 1002 ¶¶ 120-122.

b. Step 1: Converting the sample to an acidic aqueous solution of low conductivity

Step 1 of claim 13 recites “converting the sample containing a physiologically active protein into an acidic aqueous solution of low conductivity of 300 mS/m or less and having a molarity of 100 mM or less at pH of 1.5 to 3.9.” Ex. 1001, 14:1-4. This limitation is identical to step 1 of claim 1. Thus, for the same reasons discussed above for step 1 of claim 1, WO ’389 also explicitly or inherently discloses step 1 of claim 13. Ex. 1002 ¶ 123.

c. Step 2: Neutralizing the pH to form particles

Step 2 recites “neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level to form particles, wherein the molarity of the neutralized sample is 100 mM or less.” Ex. 1001, 14:5-9. WO ’389 explicitly or inherently discloses this limitation. Ex. 1002 ¶ 124.

The next step in the purification process disclosed in Example IA of WO ’389 is to adjust the pH and filter the eluate before further chromatography. *Id.* ¶ 125. WO ’389 describes this step as follows:

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

> *elution, the sample was* adjusted to pH 3.5 by the addition of 2.5 M hydrochloric acid, held for approximately 30 minutes, and *adjusted to pH 5.5 by the addition of approximately 350 milliliters of l M Tris base*. After *neutralizing to pH 5.5*, the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.

Ex. 1003, 21 (emphases added). As described above, 350 milliliters of 1M Tris base is added to the eluate to neutralize it by raising the pH to 5.5. Ex. 1002 ¶ 125. WO '389 further discloses that the 1M Tris base is a buffer. *See* Ex. 1003, 16 ("[eluate is] readjusted to pH 5.5 by the addition of Tris buffer."). A pH of 5.5 is a neutral level as defined by the '815 patent. *See* Ex. 1001, 5:53-56. ("A neutral level will vary depending on the type of physiologically active protein or antibody to be purified. It usually ranges from pH 4 to pH 8, preferably pH 4.3 to pH 7.5, and more preferably pH 4.5 to pH 7.5."). Thus, WO '389 explicitly discloses neutralizing the pH of the resulting sample from step (1) by addition of a buffer to raise the pH to a neutral level. Ex. 1002 ¶ 125.

The identical limitations "to form particles, wherein the molarity of the neutralized sample is 100 mM or less" are present in both claims 1 and 13. Example IA of WO '389 does not explicitly describe the particular molarity of the adjusted eluate solution, or the formation of particles. As discussed above for step 2 of claim 1, both claim elements, however, are conditions that are necessarily present and inherent in the neutralized elution solution disclosed in the Example IA process. In

sum, all limitations of step 2 of claim 13 are expressly or inherently disclosed in the Example IA process of WO ’389. *Id.* ¶ 126.

d. Step 3: Filtering to removing particles

Step 3 is the final step of the claimed purification process and recites “filtering the resulting sample from step (2) to remove particles containing contaminant DNA.” Ex. 1001, 14:9-10. This limitation is the same as claim 12. WO ’389 expressly discloses filtering.

After neutralizing the eluate to pH 5.5, the next step of Example IA discloses that “the sample was filtered through a 0.1 micron Polygard CR filter in tandem with a sterile 0.2 micron Millipak 200, into a sterile container.” Ex. 1003, 21. For the same reasons discussed above for claim 12, WO ’389 either expressly or at least inherently discloses all elements of step 3 of claim 13.

In sum, the Example IA purification process in WO ’389 discloses, either expressly or inherently, each of the process steps of claim 13, and thus anticipates claim 13. Ex. 1002 ¶¶ 127-129.

B. Ground II: Obviousness Under 35 U.S.C. § 103(a)

Claims 1–7 and 12–13 of the ’815 patent are also unpatentable under 35 U.S.C. § 103(a) as obvious over WO ’389. A patent claim is invalid under 35 U.S.C. § 103(a) if the subject matter as whole would have been obvious to a POSA at the

time the claimed invention was made. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

While anticipation and obviousness are separate doctrines with separate proofs of elements, "[t]here is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. § 103 and for anticipation under 35 U.S.C. § 102."); *In re Best*, 562 F.2d 1252, 1255 n.4 (C.C.P.A. 1974); *see also* MPEP § 2112. Thus, a patent challenger can use a single reference to argue that the claim is both anticipated and obvious. *In re Application of Meyer*, 599 F.2d 1026 (C.C.P.A. 1979). Indeed, "[i]n appropriate circumstances, a single prior art reference can render a claim obvious." *SIBIA Neurosciences*, 225 F.3d at 1356 . This showing can easily be made because the same principles of inherency found within the doctrine of anticipation apply to obviousness. *See In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995). ("The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.").

Therefore, should a cited reference not be found to anticipate the challenged claim, that same single reference can render the claim obvious. *See e.g.*, *Kroy*, 107 F. Supp. 3d at 672 (holding single reference did not anticipate the challenged claims but also held that same reference used for the anticipation challenge rendered the claim obvious); *In re Application of Skoner*, 517 F.2d 947, 950 (C.C.P.A. 1975) (holding single reference rendered claim obvious and noted that had the board

determined it was anticipated it would have upheld anticipation finding). As explained above, the challenged claims are anticipated by WO ’389. But just as in *Kroy*, the Board should also institute on the grounds that the challenged claims are obvious, if not anticipated, over the same single WO ’389 prior art reference.

1. Claims 1–7 and 12–13 are obvious over WO ’389

In view of the disclosures of WO ’389 as discussed above for Ground I, all limitations of claims 1–7 and 12–13 were expressly or inherently disclosed. Thus, for the reasons explained above, it would also have been at least obvious for a POSA, based on the purification process disclosed in WO ’389, to arrive at and perform the method steps of claims 1–7 and 12–13—with a reasonable expectation of success. Ex. 1002 ¶¶ 130-133.

As discussed above for anticipation, WO ’389 discloses an antibody purification process that falls within the scope of claims 1–7 and 12–13 in the ’815 patent. *Id.* ¶ 131. There is no patentable difference between the prior art antibody purification process of Example IA in and the claimed invention. *Id*. In light of these circumstances, the single prior art reference WO ’389 renders the claims obvious. In particular, a POSA would understand from the teachings of WO ’389 that DNA contaminants would be removed from an antibody sample by 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, and then adjusting or neutralizing the pH of the resulting sample from 4 to 8 or a neutral level, wherein the molarity of the adjusted sample is 100 mM or less. *Id.* The resulting neutralized and adjusted pH buffer solution is then filtered using a 0.1 micron and a 0.2 micron filter. *Id.*

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. *Id.* ¶ 132. Indeed, a POSA would understand that the purpose of the 0.1 micron and 0.2 micron filters in the Example IA process is to filter and remove particulates at this particular stage of the process to protect the subsequent chromatography columns. *Id.*; *see also* Ex. 1010, Martin at 27 ("Absolute removal of particulate solids from the process stream, including sterile filtration, serves as an essential prefiltration/protection step for downstream chromatography . . . ."). 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. Ex. 1002 ¶ 132; *See KSR*, 550 U.S. at 416 ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Accordingly, all of claims 1–7 and 12–13 of the ’815 patent would have been at least obvious to a POSA in view of the disclosures in WO ’389. Ex. 1002 ¶ 133.

2. There is no evidence of secondary considerations

Patent Owner did not rely on any evidence of secondary considerations of non-obviousness to support its application before the USPTO, and Petitioner is not aware of any. Regardless, any alleged secondary considerations could not render the claimed inventions here nonobvious in view of the WO ’389 disclosures discussed above. *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) (even “substantial evidence” of secondary considerations is insufficient to “overcome the clear and convincing evidence that the subject matter sought to be patented is obvious”). Furthermore, Petitioner has no burden to anticipate and rebut potential secondary considerations. It is the patentee who must first present a *prima facie* case for such considerations, which Petitioner may then rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2014-01453, Paper 11 at 20 (PTAB Mar. 10, 2015).

IX. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1–7 and 12–13 of the '815 patent as unpatentable.

Dated: May 19, 2017

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,788 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: May 19, 2017

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on May 19, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 7,927,815 B2.

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