UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

CHUGAI PHARMACEUTICAL CO., LTD.,
Patent Owner

Inter Partes Review No. IPR2017-01357
Patent No. 7,332,289 B2
Issued: February 19, 2008
Filed: March 11, 2002

Title: METHOD OF PURIFYING PROTEIN

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1–8 and 13 of U.S. Patent No. 7,332,289 B2 ("the '289 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 1–8 and 13 of the '289 patent. Independently, claims 1-8 and 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 1-8 and 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). WO '389 was not before the U.S. Patent and Trademark Office ("USPTO") during the prosecution of the '289 patent and, therefore, this reference was never considered by the Examiner before the '289 patent issued in February 2008. Thereafter, WO '389 was submitted by a third party and adopted by the European Patent Office ("EPO") as a novelty-destroying reference during the prosecution of a foreign counterpart to the '289 patent, European patent application No. 02703958.5 (published as EP 1380589).

The claims of the '289 patent are directed to methods of removing DNA contaminants in an antibody-containing sample that comprise the following four

purification steps: (1) applying affinity chromatography on Protein A or G; (2) eluting the antibody with an acidic aqueous solution of low conductivity that has a molarity of 100 mM or less; (3) neutralizing the eluate to form particles by adding a buffer to raise the pH to 4–8, where the molarity of the neutralized eluate is 100 mM or less; and (4) removing the particles to thereby remove DNA contaminants. *See* Ex. 1001, 12:48-58. 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 '289 patent. That example teaches a process of purifying proteins and removing DNA contaminants that either expressly or inherently discloses each of the four 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 1-8 and 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. *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 ’289 patent. Because the claims of the ’289 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 1–8 and 13 of the ’289 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. 7,927,815 (“the ’815 patent”) (IPR2017-01358). 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 ’289 patent is available for *inter partes* review; and (ii) Petitioner is not barred or estopped from requesting review of any claim of the ’289 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 1–8 and 13 of the ’289 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1–8, and 13	§ 102(b)	WO ’389 (Ex. 1003)
II	1–8, and 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 '289 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.* ¶¶ 28-29. 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 '289 PATENT

A. The '289 Patent

The '289 Patent issued on February 19, 2008, from U.S. Application No. 10/471,374 ("the '374 Application"), which is the U.S. National Stage Application of International Application No. PCT/JP02/02248 filed on March 11, 2002. The

’374 Application’s national stage entry date under 35 U.S.C. § 371 was September 9, 2003. The ’374 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), among other foreign counterparts, also claims 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 ’289 patent contains 13 claims directed to purification methods for removing contaminant DNA from antibody containing samples. Claim 1 is the sole independent claim, and claims 2-8 and 13 ultimately depend from claim 1. Claim 1 is reproduced below:

> 1. 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;
> 2) eluting the antibody with an acidic aqueous solution of low conductivity having a molarity of 100 mM or less;
> 3) neutralizing the eluate from step (2) to form particles by addition of a buffer to raise the pH to 4 to 8, wherein the molarity of the neutralized eluate is 100 mM or less; and
> 4) removing the particles to thereby remove contaminant DNA from the antibody-containing sample.

Ex. 1001, 12:45-58.

Claim 2 further recites that "the acidic aqueous solution of low conductivity has a molarity of 50 mM or less." *Id.* at 12:59-61. Claim 3 further recites that "the acidic solution of low conductivity is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid and acetic acid." *Id.* at 12:63-65. Claim 4 depends on claim 3 and further recites that "the acidic aqueous solution has a pH of 1.5 to 3.9." *Id.* at 12:66-67. 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 an antibody." *Id.* at 13:1-3. Claim 6 further recites that "the buffer is an aqueous solution of Tris." *Id.* at 13:4-5. Claim 7 further recites that "the buffer is added to raise the pH to 4.3 to 7.5." *Id.* at 13:6-7. Claim 8 further recites that "the antibody is a humanized monoclonal antibody." *Id.* at 13:8-9. Claim 13 further recites that "the particles are removed by filtration through a filter." *Id.* at 14:9-10.

2. Specification

The specification of the ’289 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 5:27-35. 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 5:45-46. The ’289 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 ’289 patent, the range of

conditions identified above will result in the production of particles. *Id.* at 6:4-7 ("[T]he solution neutralized to a neutral pH level in the above stage, in turn, produces particles (i.e., becomes clouded)."); 1:62-67 (after neutralization, the solution is "then filtered through a filter to remove the resulting particles."); 4:60 ("removing the resulting particles").

The '289 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 6:16-19.

The specification of the '289 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 6:5-11.

3. Summary of the Relevant Prosecution Histories

a. The ’289 Patent 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) (Tsuchiya et al. (EP 1020522), Sun et al. (US Patent No. 5,777,085) or Gourlie et al. (US Patent No. 5,808,033)), and under 35 U.S.C. § 103(a) (Tsuchiya et al. in view of Shibuya et al. (US Patent No. 6,406,909), or Sato et al. (US Patent No. 6,903,194)). Ex. 1005 at 48-54.

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 <u>having a molarity of 0 to 100mM</u>;
>
> 2) neutralizing the resulting elate [*sic*] by addition of a buffer to raise the pH to ~~a neutral level~~ <u>4 to 8, wherein the molarity of the neutralized solution is 0 to 100mM</u>; and
>
> 3) removing the resulting particles.

Id. at 31-32 (alterations in original). 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 35 (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 40. 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 38-39.

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 15. In subsequent interviews and communications discussing claim amendments proposed by the Examiner, Chugai stated:

> In step (3) of the examiner's newly proposed claim, "neutralized solution" is amended to "buffer", and as a result, the limitation of molarity 100mM or less is directed to a buffer used in the step. However, we believe the molarity of the buffer should not be limited to 100mM or less.
>
> 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 12-13 (emphasis in original). The Examiner allowed the application on October 5, 2007. *Id.* at 6-8. The '289 patent was issued on February 19, 2008. On July 10, 2008, several months after the '289 patent issued, 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 1. 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 1-2.

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 '289 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**"); *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.

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, 5. The vector directs the production of the product encoded by the DNA sequence of interest in the host cell. *Id.* at 6. Such recombinant techniques were well known to a POSA decades before March 2001. *Id.* at 5.

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, 13.

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. *Id.* at 30. 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.* 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.*

During protein A affinity chromatography, protein A that has been immobilized on a column is used to capture target proteins that have a C_H2/C_H3 region. *Id.* ¶ 34. The captured proteins are separated from the other cellular proteins, which do not have a C_H2/C_H3 region, and therefore can be washed away. *Id.* The captured proteins are then extracted from the column by elution. Elution is the process of extracting one material from another by washing with a solvent. *Id.* The solvent used to separate materials in elution is known as an eluent. *Id.* The captured protein is collected in the eluate, which is the solution of the absorbed material in the eluent that emerges from the chromatography column during the process of elution.

Other common column chromatography process steps include hydrophobic interaction chromatography (HIC), which separates protein molecules using the properties of hydrophobicity, the physical property of a molecule that is seemingly repelled from a mass of water. Ex. 1003, 5. In this method, proteins containing both hydrophilic and hydrophobic regions are applied under high salt buffer conditions to an HIC column that has hydrophobic ligands attached to a matrix. *Id.* The salt in the buffer (usually ammonium sulfate) reduces the solvation of sample solutes and

exposes the hydrophobic regions along the surface of the protein molecule. *Id.* at 4. This facilitates the adsorption of these hydrophobic regions to the hydrophobic areas on the solid support and precipitates proteins out of the solution. *Id.*

In ion exchange chromatography, charge-charge interactions between proteins and the charges immobilized on resin in a column are exploited. *Id.* at 2. Ion exchange chromatography can be subdivided into cation exchange chromatography, in which positively charged ions bind to a negatively charged resin; and anion exchange chromatography, in which the binding ions are negative, and the immobilized functional group is positive. *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

[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, 1288 (Fed. Cir. 2012) ("[A] prior art printed publication cited by an examiner is

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 (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

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presumptively enabling barring any showing to the contrary by the patent applicant or patentee."); *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003) ("[T]he examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled . . . ."); *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 ¶¶ 55-56.

[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 ¶ 57; Ex. 1003, 16 ("The process description [of

purifying proteins and removing DNA contaminants that either expressly or inherently discloses each of the four purification steps recited in the claims of the ’289 patent. *Id.* at 19-22.

WO ’389 was published on August 24, 1995, more than five years before March 9, 2001, the earliest possible priority date of the ’289 Patent. The identical and critical disclosure from WO ’389 was also published in the ’746 patent on July 4, 1995, more than five years before the earliest possible priority date of the ’289 patent. Therefore, both WO ’389 and the ’746 patent are available as prior art under 35 U.S.C. § 102(b). Despite their prior publication date, neither WO ’389 nor the ’746 patent was before the USPTO during the prosecution of the ’289 patent. Therefore, neither prior art reference was considered by the Examiner before the claims of the ’289 patent were allowed. Ex. 1002 ¶ 58.

Example 1] is normalized for any scale; linear flow rates listed are independent of column diameter, loading ratios are in mass per unit column volume. Examples are provided for the operation and the recovery at 1 gram, 40 gram and 125 gram scales. (Examples IA-ID).”). Therefore, the process description of Example 1 is also part of Example IA. Ex. 1002 ¶ 57; 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 '289 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 term "molarity," a person of ordinary skill in the art would understand, consistent with the plain and ordinary meaning of this term as well as the specification of the '289 patent, that this term describes a characteristic property of a solution and has the following meaning: 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. Ex. 1002 ¶ 61. A person of ordinary skill would further understand that

contributions from the antibody protein and contaminant DNA would not be included when determining this parameter. *Id*. ¶¶ 60-61.

For example, step 2 of independent claim 1 recites, "eluting the antibody with *an acidic aqueous solution of low conductivity having a molarity of 100 mM or less*" Ex. 1001, 12:38-14:5 (emphasis added). The broadest reasonable construction of the term "an acidic aqueous solution of low conductivity having a molarity of 100 mM or less" is that the molarity of the acidic aqueous solution is 100 mM or less, without considering any effects of the contaminant DNA or protein from the sample. Ex. 1002 ¶ 61. The specification of the '289 patent supports and is consistent with this construction because it specifically states, "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 ¶ 61. 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. Ex. 1001, 5:28-37; Ex. 1002 ¶ 61. The specification does not include any written description of molarity that considers the concentrations of protein or contaminant DNA. Ex. 1002 ¶ 61; *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" refers to the properties of the acidic aqueous solution without the protein or contaminant DNA. Ex. 1002 ¶ 61.

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 1–8, and 13 of the '289 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. Claim 1 is anticipated by WO '389

WO '389 expressly or inherently discloses every limitation of claim 1. Ex. 1002 ¶¶ 63-94.

a. Preamble: A method for removing contaminant DNA

The preamble of claim 1 recites "[a] method for removing contaminant DNA in an antibody-containing sample, which comprises the followings [*sic*] steps. . . ."

Ex. 1001, 12:45-47. 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.*, "an antibody-containing sample." Ex. 1002 ¶¶ 66-67. 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 an antibody-containing sample. *Id.* ¶ 67.

b. Step 1: Affinity chromatography on Protein A or G

Step 1 of claim 1 recites "applying the antibody-containing sample to affinity chromatography on Protein A or Protein G." Ex. 1001, 12:48-49. WO '389 also explicitly discloses this limitation. Ex. 1002 ¶¶ 68-70. WO '389 discloses the use of a ProSep A affinity column, which is a commonly used protein A-based affinity chromatography column. *Id.* ¶ 69. Specifically, in Example IA, WO '389 discloses the following:

> [a] 5.0 liter (20 cm diameter by 16 cm length) *ProSep A affinity column* was equilibrated with PBS (see Table 1) at 5.2 liter/min. 100 liters of conditioned *culture medium containing* 0.8 grams per liter of RSHZ-19 *monoclonal antibody was* clarified by microfiltration as described above, and *applied to the column* at a flow rate of 5.2 liter/min.

Ex. 1003, 21 (emphases added). WO '389 further discloses that the aforementioned step is describing Protein A affinity chromatography on the ProSep A column. *See id.* at 15 ("The first step in the process (Protein A affinity chromatography on ProSep A) can be rapidly cycled to accommodate varying amounts of cell-free culture fluid (CCF) . . . .").

As described above, the first step in the WO ’389 purification process is exactly the same as what is required in step 1 of claim 1: the antibody-containing sample (*i.e.* the medium containing the monoclonal antibody) is applied to a ProSep A Protein A affinity chromatography column. Ex. 1002 ¶ 70. The purpose of this first step of using a Protein A column is to “remove[] a large proportion of cell and media derived impurities (particularly protein and DNA in the flow-through and wash fractions), and concentrate[] RSHZ-19 [the antibody] in the elution buffer for further processing.” Ex. 1003, 16; *see also* Ex. 1002 ¶ 70. Thus, WO ’389 explicitly discloses step 1 of the claimed purification process of applying the antibody-containing sample to affinity chromatography on Protein A. Ex. 1002 ¶ 70.

c. Step 2: Elution with acidic aqueous solution of low conductivity

Step 2 of claim 1 recites “eluting the antibody with an acidic aqueous solution of low conductivity having a molarity of 100 mM or less.” Ex. 1001, 12:50-51. WO ’389 also explicitly discloses this limitation. Ex. 1002 ¶ 71.

After purifying the antibody sample using the ProSep A column, the next step in Example IA of WO ’389 is to wash the column, and then the “IgG [antibody] was eluted by applying 15 - 20 liters of ProSep A elution buffer.” Ex. 1003, 21. Table 1 of WO ’389 further discloses that the conditions of the ProSep A Elution Buffer are “25 mM citrate, pH 3.5.” *Id.* at 20.

As described above, the elution step in Example IA meets the limitation recited in step 2 of the '289 patent. Ex. 1002 ¶¶ 71-73. The specification of the '289 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, 5:29-35.

More particularly, step 2 further limits such eluting solution to "having a molarity of 100 mM or less." *Id.* at 12:50-51. By comparison, the citrate elution buffer solution used in Example IA of WO '389 has a pH of 3.5, which is an acidic pH, and has a molarity of 25 mM, which is significantly lower than the required 100 mM. Ex. 1002 ¶ 73.[3]

[3] To the extent Chugai argues that molarity should be determined by considering contributions from the 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 ¶ 73.

Thus, WO ’389 explicitly discloses step 2 of the claimed purification process. That is, WO ’389 uses the ProSep A Elution Buffer for eluting the antibody, and this ProSep A Elution Buffer is an acidic aqueous solution of low conductivity having a molarity of 100 mM or less. *Id.*

d. Step 3: Neutralizing the eluate

Step 3 of claim 1 recites “neutralizing the eluate from step (2) to form particles by addition of a buffer to raise the pH to 4 to 8, wherein the molarity of the neutralized eluate is 100 mM or less.” Ex. 1001, 12:52-56. WO ’389 explicitly or inherently discloses this limitation. Ex. 1002 ¶¶ 74-85.

The next step in the purification process disclosed in Example IA of WO ’389 is to neutralize and filter the eluate before further chromatography. Ex. 1002 ¶ 75. 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 (emphasis added). As described above, 350 milliliters of 1M Tris base is added to the eluate to neutralize it to pH 5.5. Ex. 1002 ¶ 75. 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 neutralizing the eluate from step (2) of Example IA by addition of a Tris buffer to raise the pH to 5.5, which is within the pH range of 4 to 8 that is required by this claim element. Ex. 1002 ¶ 75.

Example IA of WO '389 does not explicitly describe the particular molarity of the neutralized 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 ¶¶ 76-85. "[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) (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 explained by Dr. Przybycien, the particular molarity of the neutralized eluate of Example IA, although not expressly disclosed in WO '389, can nevertheless be calculated based on other disclosures in WO '389. Ex. 1002 ¶ 77. 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 25mM 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 ¶¶ 78-82; Ex. 1007, 1-3. In fact, WO '389 explicitly states that the HCl addition step can be omitted. Ex. 1003, 17 ("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 neutralization to pH 5.5 requires the addition of 350 ml of 1M Tris which contains 350 mmol Tris. Ex. 1002 ¶ 79; 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 ¶¶ 79-82; Ex. 1007, 1. Thus, the molarity of the large volume of eluate neutralized 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 ¶¶ 79-82; Ex. 1007, 1-3.[4]

This conclusion is supported by Patent Owner's own statements during prosecution of the '289 patent and its European counterpart, EP '589. 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, 13 (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 solution on the molarity of the neutralized eluate

[4] To the extent Chugai argues that molarity should be determined by considering contributions from the 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 ¶ 79.

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 ¶ 82; Ex. 1007, 1-3.

As to the formation of particles, 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 form particles, and is thus also inherently disclosed in the Example IA process of WO '389. Ex. 1002 ¶¶ 83-85. This is confirmed by the '289 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)

(holding that there was substantial evidence located in challenged patent's specification to support Board's finding that the prior art reference inherently disclosed the claimed limitation). 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 3 of the claimed process that the '289 patent claims is sufficient to form particles. Ex. 1002 ¶¶ 83-85.

As the Patent Owner conceded in the '289 patent specification, these claimed conditions of the neutralized eluate "produce[] particles." *See* Ex. 1001, 6:4-6 ("According to the present invention, the solution neutralized to a neutral pH level in the above stage, *in turn, produces particles* (i.e., becomes clouded)."") (emphasis added); *see also* at 1:62-67 (after neutralization, the solution is "then filtered through a filter to remove *the resulting particles*."") (emphasis added); Ex. 1002 ¶ 83. The '289 patent specification further describes that the formed particles will contain contaminant DNA. *See* Ex. 1001, 6:16-19 ("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 ¶ 83.

Patent Owner also made the same concessions in arguments presented to the USPTO during the prosecution of the ’289 patent. *See* Ex. 1005, 38-39 (“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 ¶ 83.

The inherent formation of particles under the recited eluate solution conditions and containing contaminant DNA is also consistent with the teachings in the prior art. Ex. 1002 ¶ 84; 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 3 is inherently disclosed by the Example IA process of WO ’389. Ex. 1002 ¶ 85.

In sum, all limitations of step 3 are expressly or inherently disclosed in the Example IA process of WO ’389. *Id.*

e. Step 4: Removing particles

Step 4 of claim 1 is the final step of the claimed purification process and recites "removing the particles to thereby remove contaminant DNA from the antibody-containing sample." Ex. 1001, 12:56-57. WO '389 either expressly or at least inherently discloses this limitation. Ex. 1002 ¶¶ 86-91.

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 ¶¶ 86-88; *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 3 and containing contaminant DNA. Ex. 1002 ¶ 88. The specification of the '289 patent confirms this:

> 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, 6:5-22 (emphasis 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 '289 patent, the neutralized eluates are filtered by a 0.2 µm filter. Ex. 1002 ¶ 91. Indeed 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 '289 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 4 of the claimed purification process of removing particles to thereby remove contaminant DNA. Ex. 1002 ¶ 91. Therefore, all limitations of step 4 are either expressly or at least inherently disclosed by the Example IA process of WO '389. *Id.* ¶¶ 86-91.

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.* ¶ 92.

2. Claims 2–8 and 13 are Anticipated by WO '389

The limitations in each of dependent claims 2–8 and 13 of the '289 patent are also anticipated by WO '389. Ex. 1002 ¶ 93.

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, 12:59-61. 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 ¶ 94. 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.* WO '389 thus also anticipates claim 2. *Id.*

b. Claim 3 is anticipated

Claim 3 depends from claim 1 and requires that "the acidic solution of low conductivity is selected from the group consisting of aqueous solutions of hydrochloric acid, citric acid and acetic acid." Ex. 1001, 12:62-65. 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 ¶ 95. 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.* WO '389 thus also anticipates claim 3. *Id.*

c. Claim 4 is anticipated

Claim 4 depends from claim 3 and further requires that "the acidic aqueous solution has a pH of 1.5 to 3.9." Ex. 1001, 12:66-67. 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. A pH of 3.5 is within the claimed range of "1.5 to 3.9." Ex. 1002 ¶ 96. Thus, WO '389 anticipates claim 4. *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 containing an antibody." Ex. 1001, 13:1-3. 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 ¶ 97. Thus, WO '389 also anticipates claim 5. *Id.*

e. Claim 6 is anticipated

Claim 6 depends from claim 1 and further requires that "the buffer is an aqueous solution of Tris." Ex. 1001, 13:4-5. As discussed above for claim 1, the buffer used in example IA of WO '389 is 1M Tris base—an aqueous solution of Tris. Ex. 1003, 21 ("Immediately after elution, the sample was . . . adjusted to pH 5.5 by the addition of approximately 350 milliliters of *l M Tris base*.") (emphasis added). Thus, WO '389 also anticipates claim 6. Ex. 1002 ¶ 98.

f. Claim 7 is anticipated

Claim 7 depends from claim 1 and further requires that "the buffer is added to raise the pH to 4.3 to 7.5." Ex. 1001, 13:6-7. As discussed above for claim 1, in example IA of WO '389, the buffer in that example is added to raise the pH to 5.5—within the claimed range of "4.3 to 7.5." Ex. 1003, 21. Thus, WO '389 also anticipates claim 7. Ex. 1002 ¶ 99.

g. Claim 8 is anticipated

Claim 8 depends from claim 1 and further requires that "the antibody is a humanized monoclonal antibody." Ex. 1001, 13:8-9. In Example I 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 ¶ 100. Thus, WO '389 also anticipates claim 8. *Id.*

h. Claim 13 is anticipated

Claim 13 depends from claim 1 and further requires that "the particles are removed by filtration through a filter." Ex. 1001, 14:9-10. 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 ¶ 101. 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 2–8 and 13, and, therefore, anticipates each of these claims. *Id.* ¶ 102.

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

Claims 1–8 and 13 of the '289 patent are also unpatentable under 35 U.S.C. § 103(a) as obvious over WO '389. Ex. 1002 ¶ 103. 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). Anticipation is the "epitome of obviousness," and while it is the "epitome of obviousness" they are separate and distinct doctrines. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1363 (Fed. Cir. 2008). "While it is commonly understood that prior art references that anticipate a claim will usually render that claim obvious, it is not necessarily true that a verdict of nonobviousness forecloses anticipation." *Id.* at 1364. Likewise, the converse is true. *See, e.g.*, *Kroy*, 107 F. Supp. 3d at 672.

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). Just as in *Kroy*, the Board should institute the challenged claims on the grounds that they are obvious, if not anticipated, over the same single WO '389 prior art reference.

1. Claims 1–8 and 13 are obvious over WO '389

In view of the disclosures of WO '389 as discussed above for Ground I, all limitations of claims 1–8 and 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 1–8 and 13—with a reasonable expectation of success. Ex. 1002 ¶¶ 103-106.

As discussed above for anticipation, WO ’389 discloses an antibody purification process that falls within the scope of claims 1-8 and 13 in the ’289 patent. *Id.* 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 applying the sample to Protein A affinity chromatography column, eluting the antibody sample with an acidic citrate solution of 25 mM and pH of 3.5, and then neutralizing the solution by raising the pH to 5.5 using a Tris buffer while the molarity of the solution remains below 100 mM. *Id.* The neutralized 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 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 buffer solution of Example IA as part of the purification process. *Id.* 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. Ex. 1002 ¶ 105; *see also* Ex. 1010, Martin at 37

("Absolute removal of particulate solids from the process stream, including sterile filtration, serves as an essential pre-filtration/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 ¶ 105; *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 1–8 and 13 of the '289 patent would have been at least obvious to a POSA in view of the disclosures in WO '389. *Id.* ¶ 106.

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). Thus, panels routinely reject arguments against institution based on secondary considerations. *See, e.g.*, *Mylan Pharm. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8 at 18 n.4 (PTAB Dec. 8, 2016); *Petroleum Geo-Services, Inc. v. WesternGeco LLC*, IPR2014-01478 Paper 18 at 36 (PTAB Mar. 17, 2015).

IX. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1–8 and 13 of the '289 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 11,127 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. 7,332,289 B2.

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