UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Patent No. 7,807,799
Issue Date: October 5, 2010
Title: REDUCING PROTEIN A LEACHING DURING PROTEIN A AFFINITY CHROMATOGRAPHY

Inter Partes Review No. 2016-01837

PATENT OWNER GENENTECH, INC.'S NOTICE OF APPEAL

Notice is hereby given, pursuant to 37 C.F.R. § 90.2(a), that Patent Owner Genentech, Inc. ("Genentech") hereby appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision entered March 6, 2018 (Paper 40) as it relates to claims 1–3 and 5–11 of U.S. Patent No. 7,807,799 ("the '799 patent"), and any finding or determination supporting or relating to that decision, including the Decision on Institution of Inter Partes Review entered March 15, 2017 (Paper 7). A copy of the Final Written Decision is attached hereto as Exhibit A.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Patent Owner indicates that the issues on appeal include, but are not limited to, the Patent Trial and Appeal Board's determinations that Petitioner demonstrated by a preponderance of the evidence that claims 1 and 5 of the '799 patent are anticipated by WO 95/22389 ("WO '389") and that claims 1, 2, and 5 are anticipated by van Sommeren et al., *Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG_1 Antibodies To Protein A Sepharose 4 Fast Flow*, 22 Preparative Biochemistry 135 (1992) ("van Sommeren"). Patent Owner further appeals the Board's determination that claims 1 and 5 are obvious over WO '389 and that claims 13 and 5 are obvious over a combination of WO '389, Joseph P. Balint, Jr. and Frank R. Jones, *Evidence for Proteolytic Cleavage of Covalently Bound Protein A from a Silica Based Extracorporeal Immunoadsorbent*

and Lack of Relationship to Treatment Effects, 16 Transfus. Sci. 85 (1995) ("Balint"), and P. Potier et al., *Temperature-dependent changes in proteolytic activities and protein composition in the psychrotrophic bacterium Arthrobacter globiformis* S_1*55*, 136 J. Gen. Microbiol. 283 (1990) ("Potier"). Patent owner further appeals the Board's determination that claims 2, 3 and 6–11 are obvious over WO '389 and U.S. Patent No. 6,127,526 ("'526 patent") and that claims 2, 3 and 6–11 are obvious over WO '389, Balint, Potier, and the '526 patent. Patent Owner further appeals the Board's determination that claims 1, 2 and 5 are obvious over van Sommeren and that claims 3 and 6–11 are obvious over van Sommeren and the '526 patent. Patent owner also appeals the Board's claim construction of "about 18° C." Patent Owner appeals any finding or determination supporting or relating to those issues, as well as all other issues decided adversely to Patent Owner in any orders, decisions, rulings, and opinions.

Pursuant to 37 C.F.R. § 90.2(a), with this submission: (1) a copy of this Notice of Appeal is being filed electronically with the Patent Trial and Appeal Board in accordance with 37 C.F.R. § 42.6(b); (2) a paper copy of this Notice of Appeal, an electronic copy of this Notice of Appeal on the CM/ECF Document Filing System, and the docketing fee of $500 are being simultaneously filed with the Clerk's Office for the United States Court of Appeals for the Federal Circuit; (3) the original of this Notice of Appeal is being filed by hand with the United

States Patent and Trademark Office as provided in 37 C.F.R. § 104.2; and (4) a copy of this Notice of Appeal is being served on Petitioner Hospira, Inc.

Dated: May 7, 2018

Respectfully submitted,

/Thomas S. Fletcher/

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CERTIFICATE OF FILING

The undersigned hereby certifies that, in addition to being electronically filed through PTAB E2E, the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal* is being filed by hand with the Director May 7, 2018, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, 10B20
600 Dulany Street
Alexandria, VA 22314

The undersigned also hereby certifies that a true and correct paper copy of the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal*, a true and correct electronic copy of the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal*, and the docketing fee of $500 are being filed by hand, CM/ECF, and Pay.gov, respectively, with the Clerk's Office of the United States Court of Appeals for the Federal Circuit on May 7, 2018.

Dated: May 7, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned *Patent Owner Genentech Inc.'s Notice of Appeal* was served on May 7, 2018 by delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

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Date: May 7, 2018

EXHIBIT A

Trials@uspto.gov
571-272-7822

Paper No. 40
Entered: March 6, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2016-01837
Patent 7,807,799 B2

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Claims 1–3, and 5–11 Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–3, and 5–11 (collectively, "the challenged claims") of U.S. Patent No. 7,807,799 B2 (Ex. 1001, "the '799 patent"). We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving

unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). For the reasons that follow, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–3 and 5–11 of the '799 patent are unpatentable.

A. Procedural History

Hospira, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–3 and 5–11 of the '799 Patent. Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") expressly waived its opportunity to file a Preliminary Response to the Petition. Paper 6.

Petitioner asserted eight grounds of invalidity based on the following references:

WO 95/22389, published Aug. 24, 1995. Ex. 1003. ("WO '389" or "Shadle").

Van Sommeren et al., "*Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG$_1$ Antibodies To Protein A Sepharose 4 Fast Flow*," 22 Preparative Biochemistry 135 (1992). Ex. 1004. ("van Sommeren").

Joseph P. Balint, Jr. and Frank R. Jones, "*Evidence for Proteolytic Cleavage of Covalently Bound Protein A from a Silica Based Extracorporeal Immunoadsorbent and Lack of Relationship to Treatment Effects*," 16 Transfus. Sci. 85 (1995). Ex. 1005. ("Balint").

Potier et al., "*Temperature-dependent changes in proteolytic activities and protein composition in the psychrotrophic bacterium Arthrobacter globiformis S$_1$55*," 136 J. Gen. Microbiol. 283 (1990). Ex. 1006. ("Potier").

US 6,127,526, issued Oct. 3, 2000. Ex. 1007. ("the '526 Patent").

In view of Petitioner's submission, we instituted an *inter partes* review of the challenged claims on the following grounds:

Ground	Reference(s)	Basis	Claims
1	WO '389	§ 102(b)	1 and 5
2	van Sommeren	§ 102(b)	1, 2, and 5
3	WO '389	§ 103(a)	1 and 5
4	WO '389, Balint, and Potier	§ 103(a)	1–3 and 5
5	WO '389 and the '526 Patent	§ 103(a)	2, 3 and 6–11
6	WO '389, Balint, and Potier, and the '526 Patent	§ 103(a)	2, 3 and 6–11
7	van Sommeren	§ 103(a)	1, 2, and 5
8	van Sommeren and the '526 Patent	§ 103(a)	3 and 6–11

Paper 19, 20–21.

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 22, "PO Resp."), to which Petitioner filed a Reply (Paper 28, "Pet. Reply").

In support of its challenges, Petitioner relies on the Declarations of Todd M. Przybycien, Ph.D. Exs. 1002, 1020. Patent Owner relies on the Declarations of Steven M. Cramer, Ph.D. (Ex. 2008) and Christopher J. Dowd, Ph.D. (Ex. 2009).

Patent Owner filed a motion for observations on the second deposition of Petitioner's expert, Dr. Przybycien (Paper 32) and Petitioner filed a response to that motion (Paper 36).

Oral argument was conducted on November 29, 2017. A transcript is entered as Paper 39 ("Tr.").

B. Related Applications and Proceedings

In the Petition, Petitioner stated that "[t]here are no judicial or administrative matters that would affect, or be affected by, a decision in the proceeding." Pet. 4. Patent Owner subsequently identified the following matters: *Genentech, Inc. v. Sandoz, Inc.*, No. 17-13507 (D.N.J.); *Genentech, Inc. v. Celltrion, Inc.*, No. 18-574 (D.N.J.); *Genentech, Inc. v. Pfizer, Inc.*, No. 17-1672 (D. Del.); *Genentech, Inc. v. Celltrion, Inc.*, No. 18-00095 (D. Del.); *Celltrion, Inc. v. Genentech, Inc.*, No. 18-274 (N.D. Cal.); and *Celltrion, Inc. v. Genentech, Inc.*, No. 18-276 (N.D. Cal.). Paper 38, 2.

C. The '799 Patent

The '799 Patent relates to improved methods for purifying antibodies and other proteins containing a C_H2/C_H3 region by protein A affinity chromatography. *See* Ex. 1001, 7:50–53. The methods involve "separation or purification of substances and/or particles using protein A, where the protein A is generally immobilized on a solid phase" glass, silica, polystyrene, or agarose matrix, such as a chromatography column resin. *Id.* at 4:27–47.

Protein A is a cell wall component of *Staphylococcus aureus* that reversibly binds with high affinity to the amino acids of a C_H2/C_H3 region in an antibody Fc domain. *Id*. at 2:6–11, 2:21–27, 4:20–26, 5:17–28. Although "[p]rotein A affinity chromatography is a powerful and widely-used tool for purifying antibodies," elution of antibodies from the solid phase matrix "leache[s] protein A into the product pool." *Id.* at 20:6–13. Because "protein A ligand is immunogenic . . . it must be cleared from the product pool by downstream processing." *Id.* at 20:13–15.

According to the Specification, "'leaching' refers to the detachment or washing of protein A (including fragments thereof) from a solid phase to

which it is bound." *Id*. at 4:48–50. The invention "concerns a method for reducing leaching of protein A during protein A affinity chromatography by reducing temperature or pH of, or by adding one or more protease inhibitors to, a composition that is subjected to protein A affinity chromatography." *Id*. at 1:15–21. "Preferably, the method comprises reducing the temperature of the composition subjected to the protein A affinity chromatography, e.g. where the temperature of the composition is reduced below room temperature, for instance in the range from about 3° C. to about 20° C., e.g. from about 10 °C. to about 18 °C." *Id.* at 18:4–9. "The temperature of the composition may be reduced prior to and/or during protein A affinity chromatography" and, in a preferred embodiment, involves "lowering the temperature of the harvested cell culture fluid (HCCF) which is subjected to chromatography." *Id.* at 18:9–16.

Example 1 discloses a series of experiments to characterize the temperature dependence of protein A leaching when purifying various proteins from HCCF at different reaction scales. *See id*. at 20:1–24:50. In "small," or "lab scale" experiments, the monoclonal antibody trastuzumab was purified from HCCF protein A affinity columns "at 7 temperature settings (10[], 12, 15, 18, 20, 25, and 30° C.)"; three other antibodies were purified at 10, 20, and 30° C. *Id*. at 20:16–58. In "pilot" scale experiments, trastuzumab HCCF was applied to protein A affinity columns at 10, 12, 15, 18, 20, 25, and 30° C. *Id*. at 20:59–21:3. "The HCCF was stored and chilled in a 400 L-jacketed tank. The temperature of the HCCF was controlled to within 1° C. of the desired temperature," measured prior to application to the protein A column and at the column outlet. *Id*. at 20:60–64. In "full scale" experiments (12,000 liter cell culture), "HCCF was collected and held at 15+/-3° C. for the duration of loading." *Id*. at 21:4–8.

For further context, column diameters ranged from 0.66 cm for small or lab scale columns, to 9 cm for pilot scale columns, and 80 cm for full scale columns. *See, e.g., id.* at 3:15–60, 21:4–8, 23:1–25, 24:1–20.

The Specification concludes that "[t]emperature affects protein A leaching during protein A affinity chromatography of antibodies to varying degrees. Some antibodies are more affected than others; HER2 antibodies Trastuzumab and humanized 2C4 were greatly affected." *Id*. at 24:24–28. "At large scale, Trastuzumab HCCF was chilled to 15+/-3° C. and protein A leaching was controlled to less than or equal to 10 ng/mg." *Id.* at 24:43–45. "At all scales, controlling the temperature of the HCCF during loading could control protein A leaching. Increasing HCCF temperature has an exponentially increasing effect on Protein A leaching." *Id*. at 24:46–50.

Example 2 addresses the use of various protease inhibitors in reducing leaching during protein A affinity chromatography. *Id. at* 24:52–26:66. Of the protease inhibitors tested, EDTA or PEFABLOC were effective in decreasing leaching and increasing concentrations of these compounds resulted in decreasing protein A leaching. *See id*. at 25:56–67.

D. The Challenged Claims of the '799 Patent

Claim 1, the sole independent claim at issue, recites:

> 1. A method of purifying a protein which comprises C_H2/C_H3 region, comprising subjecting a composition comprising said protein to protein A affinity chromatography at a temperature in the range from about 10 ° C. to about 18 ° C.

Id. at 35:44–47.

Dependent claims 2 and 3 further recite "exposing the composition subjected to protein A affinity chromatography to a protease inhibitor" (*id.* at 35:48–50) (claim 2), and in particular, protease inhibitors EDTA or AEBSF (*id.* at 35:51–53) (claim 3). Claims 5–11 define the "protein which

comprises a C_H2/C_H3 region" as either an antibody (claim 5) having a defined identity, substrate specificity, or other property (claims 6–9), or an immunoadhesin (claims 10 and 11). *Id*. at 35:57–36:49.

Because Patent Owner does not specifically address Petitioner's challenge to any dependent claim, we focus our analysis on independent claim 1.

E. Prosecution History Leading to the Issuance of the '799 Patent

The '799 Patent issued from Application No. 12/269,752, filed on November 12, 2008, which is a continuation of application No. 10/877,532, filed on June 24, 2004, now US Patent No. 7,485,704 ("the '704 patent" (Ex. 1008)). The '799 and '704 Patents, as well as related European Patent, EP 1 648 940 B1 ("EP '940" (Ex. 1009)), claim priority benefit of US Provisional Application No. 60/490,500, filed on July 28, 2003. Pet. 7.

A summary of relevant prosecution history is set forth at pages 11–17 of the Petition, which we adopt.

II. ANALYSIS

A. Person of Ordinary Skill in the Art.

Petitioner contends that a person of ordinary skill in the art would have "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." Pet. 22 (citing Ex. 1002 ¶ 32). "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*. Patent Owner does not contest this definition. *See* Ex. 2008 ¶¶ 46–47; Ex. 2009 ¶ 10. Petitioner's proposed

interpretation is consistent with the level of ordinary skill reflected in the prior art of record and we adopt it for the purpose of this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)*; In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). "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). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

i. "Method of Purifying a Protein"

Petitioner proposes, in part, that we construe claim 1 "as a method of purifying a protein, which does not require reduction of protein A leaching." Pet. 17–18 (citing Ex. 1002 ¶ 88). We agree with this portion of Petitioner's construction, as does Patent Owner. *See* PO Resp. 13.

Although the Specification relates to "a method for reducing leaching of protein A during protein A affinity chromatography" (Ex. 1001, 1:15–21), claim 1, on its face, does not require a reduction of protein A leaching. And while "understanding the claim language may be aided by the explanations contained in the written description," our reviewing court cautions that "it is

important not to import into a claim limitations that are not a part of the claim," and we find no reason to do so on the present record. *See SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004); *see also Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) ("Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002)).

Petitioner further proposes, however, that we interpret claim 1 to mean "a method of separating the protein of interest from the other proteins produced by the cell," which could be read to *exclude* a reduction in protein A leaching or the purification of the protein of interest from non-cellular components. Pet. 17–18. For the reasons set forth on pages 11–13 of the Patent Owner Response, we decline to read claim 1 in this manner. *See also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed.Cir.1996) (reasoning that an interpretation that excludes a preferred embodiment is unlikely to be correct).

Further, as noted at page 18 of the Petition, during prosecution leading to the issuance of the '799 Patent, Applicants deleted the phrase "such that protein A leaching is reduced" in order to overcome a rejection under §112, second paragraph. Ex. 1011, 10–11, 15, 18–19. *See Vitronics*, 90 F.3d at 1582 (stating that "the record before the Patent and Trademark Office is often of critical significance in determining the meaning of the claims"). On the present record, we see no reason to interpret the claims to exclude (or require) a limitation expressly deleted during prosecution. Rather, as Patent Owner argues, deleting this requirement broadens the scope such that the

method of claim 1 may, but need not, encompass a reduction in protein A leaching. *See* PO Resp. 12.

Petitioner also appears to argue that claim 1 excludes a reduction in protein A leaching because protein A is not a contaminant of HCCF, but is a by-product of the purification process itself. *See* Pet. Reply 6–7. As an initial matter, we note that claim 1 is directed to "subjecting a composition comprising said protein to protein A affinity chromatography," and is, thus, not limited to purifying proteins from HCCF. Moreover, the '799 Patent is directed to "purifying a C_H2/C_H3region-containing protein from impurities by protein A affinity chromatography" where those impurities are broadly defined as "material[s] different from the desired protein product," and expressly including "leached protein A." Ex. 1001, 4:53–59, 7:50–53; *see also* Ex. 2008 ¶¶ 20, 50–52. Accordingly, we do not find Petitioner's argument persuasive.

Our interpretation with respect to protein A leaching is further supported by the doctrine of claim differentiation. Claim differentiation

> stems from the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope. Although the doctrine is at its strongest where the limitation sought to be read into an independent claim already appears in a dependent claim, there is still a presumption that two independent claims have different scope when different words or phrases are used in those claims.

Seachange Int'l, Inc. v. C-COR, Inc., 413 F.3d 1361, 1368–69 (Fed. Cir. 2005) (internal citations and quotations omitted).

In the present case, claim 12 of the '799 Patent, directed to "[a] method of purifying a protein which comprises a C_H2/C_H3 region," expressly sets forth steps to "reduce leaching of protein A." Ex. 1001, 36:50–65. Similarly, claim 1 of the earlier-issued '704 Patent expressly

recites the limitation "such that protein A leaching is reduced." Ex. 1008, 35:46–59. As claim 12 of the '799 patent and claim 1 of the related '704 patent not only admit, but require, a reduction of protein A leaching, we find no evidence tending to rebut the presumption that a reduction in protein A leaching is encompassed by claim 1 of the '799 patent.

Accordingly, for the reasons set forth above, we interpret a "method of purifying a protein" to mean a method of separating a protein of interest from one or more impurities.

ii. "subjecting a composition comprising said protein to protein A affinity chromatography at a temperature in the range from about 10° C. to about 18° C."

Further with respect to claim 1, Petitioner proposes that we construe "about 18° C" in the upper bound of "a temperature in the range from about 10° C. to about 18° C." as encompassing ±3° C. Pet. 17–20; Pet. Reply 3–5. Patent Owner responds that "about 18 °C" encompasses no more than ±1° C, and "refer[s] to the temperature of the HCCF subjected to purification, not of the room in which the method is performed." PO Resp. 13–21. We address separately, the two parameters raised in Patent Owner Response.

1. "about 18 °C"

In support of its position that "about 18° C" encompasses ±3° C, Petitioner argues that the Specification indicates that this range reflects typical temperature fluctuations during protein A chromatography. Pet. 19. In particular, Petitioner relies on the inventor's representation that in the "full scale" experiments involving 12,000 liter volumes of cell culture, the "HCCF was collected and held at 15+/-3°C. for the duration of loading." *See* Ex. 1001, 21:7–8; *see also id.* 23:61–63, 24:43–45; Ex. 1002 ¶¶ 81–82. Petitioner further relies on Dr. Przybycien's testimony that a person of

ordinary skill in the art would have considered ±3° C to be a normal temperature fluctuation in the context of protein A affinity chromatography. Pet. 19–20 (citing Ex. 1002 ¶ 82).

In response, Patent Owner argues that one of ordinary skill in the art would understand the "about 18° C." limitation as directed to conducting protein A chromatography at "below room temperature." PO Resp. 18. Citing column 18, lines 4–9 of the Specification, Patent Owner reasons that because "the [S]pecification makes it clear that 'about 20° C' means 'below room temperature' . . . [*a*] *fortiori* so does "about 18° C." *Id.*

As an initial matter, we note that the challenged claims do not recite "below room temperature," but a defined range with an upper bound of "about 18 ° C." Moreover, with respect to reducing the temperature of a composition to, for example, "below room temperature," the Specification teaches both the reduction of temperature and "below room temperature" as a merely preferred embodiments. *See* Ex. 1001, 18:4–9 ("*Preferably*, the method comprises reducing the temperature of the composition subjected to protein A affinity chromatography in which the temperature of the composition is reduced *e.g.* . . . below room temperature.") (emphasis added). But "[c]laims are not necessarily and not usually limited in scope simply to the preferred embodiment." *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 805 F.3d 1368, 1375 (Fed. Cir. 2015) (citation omitted). And on the record before us, we decline to rewrite claim 1 to include the term "below room temperature." *See SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004). ("Though understanding the claim language may be aided by the explanations contained in the written description, it is important not to import into a claim limitations that are not a part of the claim.")

As we understand Patent Owner's argument, we should construe "'about' as no[t] more than ±1° C" because the Specification teaches that 20 ℃ is below room temperature, and "every reasonable scientist" would consider 21 ℃ to be room temperature. PO Resp. 18, 21 (citing Ex. 2010, 135:10–14; 2008 ¶¶ 66–67); *see also* Tr. 23:13–14 ("Where 'about' is not defined it should be construed as approximately or alternatively plus or minus 1 degree celsius."), 24:6–22.

Patent Owner's proposed construction is inconsistent with its own logic, however, because if "about" means "no[t] more than ±1 ℃," the upper limit of "about 20 ℃" is 21 ℃—which Patent Owner equates with room temperature. Thus, contrary to its position that claim 1 requires the method to be conducted at below room temperature, Patent Owner's construction would require 21 ℃ to be both room temperature *and* below room temperature.

Patent Owner quotes *Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1555[1] (Fed. Cir. 1996), abrogated on other grounds by *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000), for the proposition: "Although it is rarely feasible to attach a precise limit to 'about,' the usage can usually be understood in light of the technology embodied in the invention." PO Resp. 21. We apply that proposition here. Although the Specification provides no express definition of "about," the scope of "about 18° C." is informed by the variations in temperature noted in the supporting examples. We note, in particular, that

[1] We assume that Patent Owner meant to cite here to page 1555, instead of 155. We regard this as a clerical error, and, in any event, it does not change our analysis.

although the Specification discloses that "pilot scale" experiments were conducted "within 1° C. of the desired temperature" (Ex. 1001, 20:61–64), it repeatedly asserts that HCCF used in the "full scale" experiments was subject to ±3° C. variation around the target temperature, which suggests a broad meaning of the term "about." *See* Ex. 1001, 21:7–8, 23:61–63, 24:43–45; *see also* Ex. 1002 ¶ 82.

Our reading of claim 1 in light of the Specification, thus, supports a construction of "about 18° C." to mean "18 ±3° C.", such that the upper bound of "a temperature in the range from about 10° C to about 18° C" is 21° C.

A broad construction of this term is further supported by the prosecution history of the earlier-issued '704 Patent, which shows that Applicants avoided a rejection over prior art disclosing protein A chromatography at 22° C by amending the upper limit of then-pending claims from "20° C" to "about 20° C" and, subsequently, to "about 18° C," thereby indicating that "about" must mean at least ±2° C., but less than ±4° C. *See* Pet. 12–13, 20; Ex. 1010, 38, 50, 55, 59, 74–75, 79; Ex. 1002 ¶ 82.

Patent Owner attempts to avoid this conclusion by asserting that Applicants did not acquiesce to the rejection in amending the claims. PO Resp. 20. In support, Patent Owner points to Applicants' statements in the prosecution history that:

> Without acquiescing to the rejection, claims 1 and 12 have been amended to recite '20°C' as the upper limit of the temperature range for conducting protein A affinity chromatography, and therefore Horenstein et al. clearly does not anticipate these claims, as currently amended, or the claims dependent therefrom.

and

> All amendments and cancellations were made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any removed subject matter in one or more continuing applications.

Id. (referencing Ex. 1010, 59, 77, respectively). But as Petitioner notes, "Applicant *did* acquiesce by narrowing the claimed range; and it never again pursued a broader temperature range." *See* Pet. Reply 5. Based on the record before us, we accord little weight to the above-cited self-serving statements in the prosecution history.

For the reasons set forth above, we find that during prosecution, Applicants limited the meaning of "about" in the term "about 18 °C" to at least ±2 °C, but less than ±4° C. Consistent with this conclusion, we note that prior to allowing the instant claims to issue, the Examiner pointed out that Stahl[2] and Horenstein[3] taught protein A affinity chromatography at 4°C and 22°C, respectively. Ex. 1011, 11. The Examiner did not base a rejection on Stahl and/or Horenstein, however, because 4°C and 22°C as taught in those references were "not in the temperature range required by claim 20"—now claim 1 of the '799 Patent. *See id*.

Accordingly, in light of the intrinsic record as a whole, we conclude that "about 18° C" means "18 ±3° C," such that the upper bound of "a temperature in the range from about 10° C to about 18° C" is 21° C.

> *2. "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 °C to about 18 °C"*

Patent Owner contends that the temperature range set forth in claim 1 refers to the temperature of the composition being purified. PO Resp. 13–

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[2] Stahl et al., US 6,927,044 B2.
[3] Horenstein et al., 275 J. Immunol. Meth. 99–112 (2003).

17. Patent Owner states, for example, that "the only reasonable construction of the claims is that they refer to the temperature of the HCCF subjected to purification, not of the room in which the method is performed." *Id.* at 14. We agree with Patent Owner's construction with two caveats.

First, the claims do not require the "composition" subjected to protein A affinity chromatography to be HCCF. To the contrary, the Specification indicates that antibodies and other proteins having a C_H2/C_H3 region may be purified from a variety of compositions including whole animal serum, proteolytic digests, and the products of chemical cross-linking reactions. *See* Ex. 1001, 7:50–55, 9:43–10:5, 10:61–67, 12:47–64, 12:65–14:36.

Second, Patent Owner appears to imply that the claims require actively cooling the composition (e.g. HCCF) to a range of about 10° C. to about 18° C. prior to the chromatography step. *See* PO Resp. 14–16 & n.7. But the language of the challenged claims requires neither an express cooling step nor that the target temperature is reached prior to applying the composition to a protein A chromatography matrix. *See, e.g.,* Ex. 1020 ¶¶ 32–36. Moreover, the Specification makes clear that the target temperature may be reached "prior to and/or during protein A affinity chromatography." Ex. 1001, 18:9–11.

With those caveats, we construe "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 °C to about 18 °C" as referring to the temperature of the composition prior to and/or during protein A affinity chromatography.

For purposes of this decision, we determine that no further construction is necessary. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms that are in controversy

need be construed, and only to the extent necessary to resolve the controversy).

C. Anticipation

i. Legal Principles

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002). While the elements must be arranged in the same way as is recited in the claim, "the reference need not satisfy an *ipsissimis verbis* test." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). Moreover, "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." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Accordingly, "a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (alteration in original) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

ii. Anticipation by WO '389 (Ground 1)

Petitioner asserts that claims 1 and 5 are anticipated by WO '389 under 35 U.S.C. § 102(b). Pet. 6, 28–33; Pet. Reply 7–16. Patent Owner opposes. PO Resp. 22–34. Having considered the record as whole, we

determine that Petitioner has shown by a preponderance of evidence that claims 1 and 5 are anticipated by WO ’389. We begin with an overview of the asserted reference.

1. Overview of WO ’389 (Ex. 1003)

WO ’389 states that “[a]lthough Protein A affinity column chromatography is widely used, it is also appreciated that elution of antibody from such columns can result in leaching of residual Protein A from the support.” Ex. 1003 at 4:1–3.[4] The reference teaches that size exclusion chromatography or hydrophobic interaction chromatography (HIC) can be used to remove the residual protein A that leaches from the column during elution. *Id.* at 4:7–9, 13:30–33; *see also* Ex. 1002 ¶¶ 68–69; Ex. 2008 ¶¶ 37, 81.

WO ’389 discloses “the purification of an IgG antibody from conditioned cell culture medium containing same comprising sequentially subjecting the medium to (a) Protein A, (b) ion exchange chromatography, and (c) hydrophobic interaction chromatography.” Ex. 1003 at 4:20–24; *see id*. at 40:23–26 (claim 9), 41:21–34 (claim 20). “The process in its most preferred embodiment consists of three purification steps (Protein A affinity, cation exchange, and hydrophobic interaction chromatography).” *Id*. at 13:9–13. “All steps are carried out at room temperature (18 - 25 °C).” *Id*. at 13:13.

In Example 1, WO ’389 discloses that HCCF harvested by microfiltration or centrifugation is applied to a protein A chromatography

[4] Where possible, we refer to the native pagination of the cited references rather than to that supplied by the parties.

column. *Id.* at 14:10–17. "After loading the column, it is washed with at least 3 column volumes of PBS containing 0.1 M glycine" and eluted with a low pH buffer. *Id.* at 14:20–23; *see also, id.* at 19:1–10 (stating that HCCF was applied to a 5.0 liter affinity column, after which "approximately 15 liters of PBS/glycine was applied to the column at the same flow rate."), 29:1–14 (stating that HCCF was applied to a 5.5 liter affinity column, after which "approximately 17 liters of PBS/glycine was applied to the column at the same flow rate.").

2. Analysis of Ground 1

a) Whether the HCCF in WO '389 is within the claimed range

WO '389 teaches a method for purifying antibodies, including a step wherein HCCF is subject to protein A affinity chromatography. WO '389 teaches that "[a]ll steps are carried out at room temperature (18 - 25 °C)," which overlaps with the temperature range of "about 10 ° C. to about 18 ° C." recited in claim 1.[5] Patent Owner contends, however, that WO '389 "nowhere discloses or suggests chilling the harvested cell culture fluid prior to protein A chromatography" and, thus, fails to disclose "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 ° C. to about 18 ° C." required by independent claim 1. PO Resp. 22.

Patent Owner further contends WO '389's statement that "[a]ll steps are carried out at room temperature (18 - 25 °C)," "refers to the temperature of the laboratory where each 'step' in process was performed," and not to

[5] Because the range set forth in WO '389 overlaps with the "18 ° C." recited in claim 1, our anticipation analysis in view of this reference does not necessarily depend on the construction of "about."

the temperature of the HCCF applied to the protein A column. PO Resp. 23. With respect to the latter, Patent Owner argues that WO '389 is "completely silent" with respect to the temperature of the HCCF. *Id.* at 24.

We do not find this argument persuasive. While we agree with Patent Owner that WO '389 does not expressly call out the temperature of the HCCF, such specificity would be redundant in light of its blanket teaching to carry out "all steps . . . at room temperature (18 - 25 °C)." Consistent with this view, WO '389 *does* specify temperatures that fall outside of this range. *See* Ex. 1003, 14–15 (disclosing that after the viral inactivation step "[t]he resulting solution is . . . held in sterile containers at 4 ℃, or frozen and held at -70 ℃").

Patent Owner relies on the opinions of its expert, Dr. Cramer, which appear predicated on a view that the '799 Patent and relevant art are directed to large-scale, industrial purification. *See, e.g.*, Ex. 2008 ¶¶ 47, 141 (arguing that the '799 Patent is directed to "industrial purification"). According to Dr. Cramer:

> Efficiency is typically a goal of industrial processes, and absent an instruction to wait to allow the harvested cell culture fluid to cool to room temperature, the POSA would have interpreted [WO '389] as allowing the disclosed process to be performed with harvested cell culture fluid that was potentially warmer than room temperature.

Id. ¶ 78; *see id.* ¶ 98 (same argument with respect to van Sommeren). But neither the challenged claims, nor the disclosure of WO '389 are limited to the large scale industrial processes envisioned by Dr. Cramer. *See* Ex. 1003, 14:1–4 (indicating that the process may be "normalized for any scale"); Ex. 1001, 3:15–60, 20:35–58, 23:1–25 (exemplifying "small scale" and "lab scale" processes); Ex. 1020 ¶ 68. We further weigh Dr. Cramer's opinion

against his testimony that even for commercial scale systems he was not aware of any process where HCCF was filtered and applied directly into a protein A column. Ex. 1022, 85:6–15.

We instead credit the testimony of Dr. Przybycien in this matter. *See* Ex. 1020 ¶¶ 25–28. According to Dr. Przybycien,

> absent contrary language, a POSA would understand that experiments are being conducted at ambient temperature with all materials equilibrated, in order to obtain robust scientific data.
>
> * * *
>
> No POSA would understand WO '389 as teaching a practitioner to use HCCF having a temperature above 18º C – 25º C, after being explicitly directed to conduct "all steps" at 18º C – 25º C. In addition, no reasonable POSA would contact 37 º C HCCF to the chromatography column, and report having performed the step at 18º C – 25º C. In this case, the relatively warmer HCCF would raise the temperature of the entire system. A POSA would understand that the disclosure of 18º C – 25º C in WO '389 must refer to the temperature of all of the components involved in the experiment, including the composition being purified.

Id. ¶¶ 27–28; *see also* Ex. 2045, 255:6–19.

For at least the reasons set forth above, we find that WO '389 discloses all elements of claims 1 and 5 of the '799 patent.

b) Whether WO '389 discloses a composition subjected to protein A affinity chromatography within the claimed range

Further, to the extent Patent Owner argues that the HCCF must have been within the range of 18º C – 25º C at the time it was applied to the protein A affinity column in WO '389, we note that this is not a requirement of our claim construction. As set forth in section II(B)(ii)(2), above, we construe "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 ° C. to about 18 ° C." as

referring to the temperature of the composition prior to and/*or during* protein A affinity chromatography.

WO ’389 Example 1 discloses application of HCCF to a protein A affinity column, whereupon the entrained composition is washed with at least three column volumes of buffer before the antibody is eluted. *See* section II(C)(ii)(1), above. Insofar as WO ’389 teaches that “[a]ll steps are carried out at room temperature (18 - 25 °C),” we understand that the apparatus and column buffers are all within that temperature range. Accordingly, we infer that during the washing step, the entrained composition is also at 18–25 °C and, thus, within the temperature range of claim 1 as construed in section II(B)(ii), above. For this additional reason, we find that WO ’389 discloses all elements of claims 1 and 5 of the ’799 patent.

c) Whether the claimed range is critical

As discussed above, WO ’389 discloses a process carried out at temperature range of “18–25 °C,” which overlaps the “temperature in the range from about 10 ° C to about 18 ° C,” recited in independent claim 1, most particularly in light of our construction of that term. Where the patent claims a range, it is anticipated by prior art disclosing a point within the range, *see Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985), *unless* there is evidence establishing that the claimed range is “critical to the operability of the claimed invention.” *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015); *see also ClearValue, Inc. v. Pearl River Polymers, Inc*., 668 F.3d 1340, 1344–45 (Fed. Cir. 2012) (finding the patented range anticipated by a broader range in the prior art because there was no allegation of criticality and no considerable difference between the claimed range and the broader range in the prior art).

Relying on the declarations of Drs. Dowd and Cramer, Patent Owner argues that claims 1 and 5 are not anticipated because the claimed range is critical to the operability of the invention. PO Resp. 22, 30–34 (citing Ex. 2008 ¶¶ 112–21; Ex. 2009 ¶¶ 31–71.[6] In this respect, Patent Owner focuses on the shape of the curve in plots of protein A leaching over a range of temperatures. *Id.* As summarized by Dr. Cramer, "the extent of protein A leaching is relatively flat within the claimed range of about 10℃ to about 18℃, whereas the extent of protein A leaching in the ranges of 18–25℃ and 20–25℃ tends to increase more sharply per degree relative to the claimed range." Ex. 2008 ¶ 115. We do not find Patent Owner's argument persuasive for the reasons set forth on pages 13 through 16 of Petitioner's Reply brief, and further detailed in paragraphs 37–45 of Dr. Przybycien's second declaration (Ex. 1020).

Criticality has been found where only a narrow range of temperature enabled a process to operate as claimed, and problems occurred in practicing the invention below or above the claimed range. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991 (Fed. Cir. 2006). In the present case, however, we credit Dr. Przybycien's testimony that "[t]he claimed range in the '799 Patent is not critical, because protein A chromatography works in the same way at the prior art temperatures of 4° C, 18-25° C and 20-25° C as it does at the claimed range." Ex. 1020 ¶ 38; *see also id.* ¶¶ 37–45, 65; Ex. 1002 ¶¶ 85–89. With respect to the plots referenced by Patent Owner, we agree that protein A leaching shows an exponential or Arrhenius-type dependence

[6] We note that paragraphs 117 and 121 of Exhibit 2008, and paragraphs 51, 69, and 70 of Exhibit 2009 are among the paragraphs at issue in Patent Owner's presumptive motion to seal. *See* section III, below.

with respect to temperature, with a greater increase in leaching for each unit increase in temperature. *See* Ex. 1002 ¶¶ 49, 89, 93; Ex. 1020 ¶¶ 41–42. But, following this logic, one of ordinary skill in the art would expect protein A chromatography to work better—at least with respect to minimizing leaching—at temperatures *outside* the claimed range (e.g., at 4°C).

We also find convincing Petitioner's argument that the observed exponential temperature dependence profiles would have been expected because protein A leaching is driven by proteolysis, which has a well-known exponential temperature dependence. Pet. 33 (citing Ex. 1002, ¶¶ 49, 87, 93, 104); Ex. 1020, ¶¶41–42; *see also* Ex. 1005, 88–89 (concluding that protein A leaching is due to proteolytic activity) (discussed in section II(D)(ii), below). Although Patent Owner characterizes the leaching levels observed in the claimed temperature range of this curve, as "'relatively flat," we credit Dr. Przybycien's testimony that this does not render the relationship "special or optimal, it is simply the middle range of an exponential trend line." Ex. 1020 ¶ 42. As Dr. Przybycien explains, it is well known to conduct protein A chromatography at temperatures below the claimed range, and so doing would reveal "a continuation of the 'relatively flat' leaching trend observed at the claimed and prior art temperature ranges." *Id.* ¶¶ 43–44; *see also* Ex. 2045, 268:5–269:4. Again, because leaching varies inversely with temperature, conducting protein A chromatography at temperatures below the claimed range would be expected to further reduce leaching.

We, therefore, agree with Petitioner that "[t]he claimed range of "'about 10° C to about 18° C' cannot be critical to practicing the alleged invention if the sole alleged benefit is also achieved below the range, at temperatures disclosed in the prior art." Pet. Reply 15 (citing Ex. 1020

¶ 43). For the same reasons, we do not find persuasive Patent Owner's argument that performing protein A chromatography at the claimed temperature range produces unexpected results as compared to performing the process at other temperatures known in the art. *See* PO Resp. 53.

d) Conclusion

Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of evidence that claims 1 and 5 of the '799 patent are anticipated by WO '389.

iii. Anticipation by van Sommeren (Ground 2)

Petitioner asserts that claims 1, 2, and 5 are anticipated by van Sommeren under 35 U.S.C. § 102(b). Pet. 6, 33–37; Pet. Reply 7–16. Patent Owner opposes. PO Resp. 22, 26–34. Having considered the full trial record, we determine that Petitioner has shown by a preponderance of evidence that claims 1, 2, and 5 are anticipated by van Sommeren. We begin with an overview of the asserted reference.

1. Overview of van Sommeren (Ex. 1004)

Van Sommeren explores the effects of temperature, flow rate, and buffer composition on protein A affinity chromatography purification of IgG_1 monoclonal antibodies. Ex. 1004, Abstract, 135. In each of these studies:

> A protein A Sepharose 4 Fast Flow column (⌀10, h 13 mm) was equilibrated with binding buffer. The cell culture supernatant was diluted with an equal volume of binding buffer and filtered through a 0.2 *µm* pore size membrane filter. Subsequently a volume containing a fixed amount of [monoclonal antibody] was loaded onto the column. The non-bound fraction was washed from the column with binding buffer. The fraction bound to the column was desorbed with 0.1 M citric acid (pH 5.0).

Id. at 138.

With respect to temperature, van Sommeren compares the results of protein A chromatography conducted at "4 °C versus ambient temperature (AT) (20-25 °C)." *Id*. at 145. Van Sommeren notes that other researchers "reported a five times higher binding capacity of protein A Sepharose for mouse monoclonal IgG_1 antibodies at 4 °C in comparison with 20-26 °C, using a 0.1 M sodium phosphate binding buffer (pH 8.2)". *Id*. at 146. In comparison, van Sommeren reports that "[r]esults from the present study show that the temperature effect on the IgG_1 binding capacity becomes of minor importance, if adsorption is performed in a high ionic strength (1.5 M glycine, 3.0 M NaCl) buffer pH 8.9." *Id*. at 147. In particular, Table V of the reference shows that the binding capacity of protein A for various IgG_1 antibodies under these buffer conditions could decrease, stay the same, or increase by as much as 30 or 40% when run at 4°C as compared to ambient temperature (20–25°C). *Id.* at 144, 145.

Van Sommeren also notes that Cathepsin D protease activity in both the starting material and in the purified IgG is undesirable and suggests the addition of the protease inhibitor, pepstatin A to minimize proteolytic degradation of the IgG. *Id*. at 147–48; *see also* Ex. 1022, 127:24–129:18.

2. Analysis of Ground 2

In the Patent Owner Response and Petitioner's Reply brief, the parties largely address WO '389 and van Sommeren together. Accordingly, we refer to our discussion in section II(C)(ii), above, including our discussion regarding the criticality of the claimed range set forth in section II(C)(ii)(2)(c).

Van Sommeron discloses protein A chromatography of HCCF at ambient temperature, defined therein as from 20°C to 25°C, and which overlaps with our construction of "about 18° C." as having an upper bound

of 21 °C. *See* section II(B)(ii), above. Patent Owner contends, however, that the reference "never discloses cooling [the HCCF]" to that temperature. PO Resp. 28. Rather, Patent Owner argues, "van Sommeren discloses the temperature of the *lab space* where the experiments were conducted, not the temperature of the HCCF subjected to purification" and accordingly, "[t]here is no way to know from van Sommeren what temperature the composition was when it was loaded on the column." PO Resp. 27, 28 (citing Ex. 2009 ¶¶ 94–99).

We do not find Patent Owner's argument persuasive for the reasons set forth on pages 10–14 of the Petition.[7] Most particularly, we credit Dr. Przybycien's explanation that because van Sommeren studies binding behavior as a function of temperature, i.e., at 4 °C versus 20–25 °C, all of the starting materials must have been equilibrated to those temperatures in order to obtain valid experimental results. *See* Ex. 1020 ¶¶ 29–30. In contrast, "using HCCF of another temperature would render the experimental results meaningless." *Id.* ¶ 30 (citing Ex. 1022, 126:18–175:5). Thus, one of ordinary skill in the art "would not have interpreted van Sommeren as

[7] We further note that Dr. Cramer states that van Sommeren "does not disclose any intermediate step between the harvest of cell culture fluid from the bioreactor and the harvested cell culture fluid being subjected to protein A affinity chromatography," which, in the context of his report, implies that the HCCF applied to the column would be at 37°C—the temperature at which the antibodies are grown. Ex. 2008 ¶ 97. This is not correct. Van Sommeren discloses intermediate steps between the harvesting of HCCF and application of the composition to protein A affinity chromatography, including the addition of binding buffer, presumably at ambient temperature. *See* Ex. 1004, 138 ("The cell culture supernatant was diluted with an equal volume of binding buffer and filtered through a 0.2 *μm* pore size membrane filter.")

suggesting or allowing the disclosed process to be performed with 'warm' cell culture fluid, given that doing so would guarantee invalid experimental data." *Id.* ¶ 30.

Accordingly, we find that van Sommeren discloses all elements of challenged claims 1, 2, and 5. For the reasons set forth in Section II(C)(ii)(2)(c), above, the overlap between the claimed range and that disclosed in van Sommeren is not critical to the practice of the invention. Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of evidence that claims 1, 2, and 5 of the '799 patent are anticipated by van Sommeren.

D. Obviousness

i. Legal Principles

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

> Rejecting a blinkered focus on individual documents, the [*KSR*] Court required an analysis that reads the prior art in context, taking account of "demands known to the design community," "the background knowledge possessed by a person having ordinary skill in the art," and "the inferences and creative steps that a person of ordinary skill in the art would employ."

Randall Mfg. v. Rea, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (citing *KSR*, 550 U.S. at 418).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill

in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the obviousness conclusion. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 1372 (Fed. Cir. 2007).

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted); *see also Belden Inc. v. Berk–Tek LLC,* 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

ii. Analysis

Petitioner asserts that claims 1 and 5 would have been obvious in view of WO '389 (Ground 3); claims 1–3 and 5 would have been obvious in view of WO '389, Balint, and Potier (Ground 4); claims 2, 3, and 6–11 would have been obvious in view of WO '389 and the '526 Patent (Ground 5); claims 2, 3, and 6–11 would have been obvious in view of WO '389, Balint, Potier, and the '526 Patent (Ground 6); claims 1, 2, and 5 would have been

obvious in view of van Sommeren (Ground 7); and claims 3 and 6–11 would have been obvious in view of van Sommeren and the '526 Patent (Ground 8). Pet. 6–7. Patent Owner generally responds to Grounds 3–8 collectively. *See* PO Resp. 34–55.

With respect the above grounds, we credit Dr. Przybycien's testimony that

> In the early days of protein A chromatography, researchers relied on chromatographic substrates that were unable to support fast flow rates, resulting in long processing times. In order to ensure that the binding, washing and elution of the target protein was not outpaced by proteolytic degradation, chromatography was often run in the cold room. Newer resins with faster flow properties[8]—for example, PROSEP-A® and SEPHAROSE® Fast Flow—became available before July 2003. Using these improved resins allowed researchers to step out of the cold room, and conduct protein A chromatography at ambient temperatures when they preferred to do so. As a result, studies involving protein A chromatography, such as those disclosed in van Sommeren and WO '389, would often use either cold room temperature (~4° C), or ambient temperature.

Ex. 1002 ¶ 34. For the reasons set forth below, and having considered the record as a whole, we agree with Petitioner that because it was well known to conduct protein A chromatography at 4 °C and at ambient temperature, doing so in the claimed intermediate temperature range would have been an obvious design choice that balances the cost and effort of using reduced temperatures against the benefit of reducing proteolysis of the antibody target and/or selection of a protein A column matrix. *See id.* ¶¶ 103–104;

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[8] Although the '799 Specification exemplifies PROSEP-A and SEPHAROSE column matrices, Patent Owner does not argue that the claims are limited to column matrices with such properties. *See* Ex. 1001, 4:28–47 (discussing a range of solid phase supports within the scope of the invention).

Ex. 1020 ¶ 72. Moreover, as summarized by Dr. Przybycien: "There is nothing unexpected or unique about the intermediate level of protein A leaching achieved using an intermediate temperature, because protein A leaching was known to be temperature-dependent." Ex. 1025 ¶ 38.

Because, at a minimum, Balint and Potier provide background with respect to reductions in proteolysis, we begin with a discussion of those references. *See Randall*, 733 F.3d at 1362 ("By narrowly focusing on the four prior-art references cited by the Examiner and ignoring the additional record evidence Randall cited to demonstrate the knowledge and perspective of one of ordinary skill in the art, the Board failed to account for critical background information that could easily explain why an ordinarily skilled artisan would have been motivated to combine or modify the cited references to arrive at the claimed inventions.").

iii. Balint (Ex. 1005) and the role of proteolysis in Protein A Leaching

Balint investigates potential causes of protein A leaching during affinity column chromatography of IgG from blood plasma or serum. Ex. 1005, 85. Balint explores properties relevant to "an extracorporeal immunoadsorbent column (PROSORBA® column) containing purified Staphylococcal protein A (SpA) covalently bound to a silica matrix." *Id*. According to Balint, "[p]rior to the development of this column, there was concern about the potential for [protein A] to 'leach' from the immunoadsorbent matrix into patient plasma." *Id*. at 86. To investigate these concerns, Balint conducted studies using "[p]ooled human plasma, serum, and chicken serum," "to evaluate the potential cause for release of covalently bound Staphylococcal protein A (SpA) from a silica based extracorporeal immunoadsorbent matrix." *Id.* at 85–86; *see id.* at 86 (detailing the protein A–matrix coupling process).

Balint reports that protein A was released from the protein A affinity matrix "in a linear fashion with time . . . indicat[ing] that mere binding of mammalian IgG to the immunoadsorbent is not required for the release of [protein A]." *Id*. at 88. Based on studies involving the addition of either (1) formalin (as a general stabilizer and protease inhibitor) or (2) a cocktail of protease inhibitors to the serum samples, Balint concludes that the protein A leaching was due to inherent endogenous proteolytic activity, which cleaved protein fragments from the chromatography matrix. *Id*. at 88–89.

Patent Owner does not dispute that Balint teaches that protein A leaching is caused by proteolytic cleavage, but argues that Balint is not analogous art and, thus, should not be considered prior art with respect to the claimed invention. PO Resp. 44–49; Ex. 1022 at 147:4–23. "Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (citations omitted).

With respect to the first of these tests, Patent Owner argues that Balint is not within the same field of endeavor because it was published in the journal *Transfusion Science* and concerned therapeutic applications in the "field of apheresis" rather than "protein purification," "bioprocessing" or, as described by Dr. Cramer, "the industrial purification of therapeutic proteins." PO Resp. 45–46; Ex. 2008 ¶¶ 47, 160. With respect to the second test, Patent Owner argues that Balint is not reasonably pertinent to the particular problem with which the inventor is involved insofar as Balint used protein A bound to a silica-based matrix. PO Resp. 47 (citing Ex. 2008

¶ 160; Ex. 2010, 158:9–160:24). According to Patent Owner, such composition "would be unthinkable in the field of bioprocessing because . . . a silica-based matrix would be destroyed by the harsh (very basic) washing conditions used to regenerate protein A columns." *Id*.

For the reasons set forth at pages 21–24 of Petitioner's Reply we do not find Patent Owner's arguments with respect to Balint persuasive. We note, for example, that Balint was repeatedly cited by the Examiner during prosecution. Ex. 1010, 50–52, 70–71 (rejections involving Balint). Applicants did not argue that Balint was nonanalogous, but responded to the rejections with the apparent understanding that Balint was prior art. *See id.* at 54–62 (cancelling claims in view of the Examiner's rejections), 73–81 (arguing rejection on the merits); Pet. Reply 22. Accordingly, we infer that the Examiner—as well as the inventors—considered Balint at least reasonably pertinent to the particular problem addressed in the '799 patent.

We also agree with Petitioner that protein A chromatography is not limited to protein purification, and the challenged claims are not limited to industrial purification of therapeutic proteins. *See* Pet. 22–23. Nor does our understanding of the challenged claims demand a column matrix be capable of regeneration or prohibit the use of silica-based matrices. To the contrary, the Specification expressly provides that the solid phase matrix "may comprise . . . silica." *See* Ex. 1001, 4:41–47.

Nor, as we have discussed, above, in section II(B)(i), are the challenged claims limited to the use of HCCF. Rather, the Specification provides that antibodies may be separated from the "culture medium, ascites fluid, *or serum* by . . . for example, protein A-Sepharose . . . . Preferably the protein A affinity chromatography procedure described herein is used." *Id.* at 10:61–67 (emphasis added); *see also id*. at 7:50–55, 9:43–10:5, 12:47–64,

12:65–14:36 (indicating that the invention is applicable to purification from a variety of compositions including whole animal serum, proteolytic digests, and chemical cross-linking reactions).

Patent Owner further argues that Balint is not reasonably pertinent because it "report[s] on clinical testing of an immunoadsorbent column marketed as a medical device called 'PROSORBA' . . . . [used for] extracting unwanted antibodies from a patient's blood as it was removed and then returning it to the body by way of intravenous tubing." PO Resp. 45 (citing Ex. 2008 ¶ 150); *see* also, *id.* at 47–48 ("[t]here would have been no reason for the POSA to think that what happened when blood was poured on a silica-based column would have any pertinence to what would happen when HCCF was poured on a protein A column made of different material"); Tr. 29:9–26 (arguing that "the material being purified [in Balint] is human blood").

Patent Owner's attempts to distinguish Balint as limited to the purification of blood are inapposite because Balint described experiments using not blood, but "[p]ooled human plasma, serum, and chicken serum." Ex. 1005, 86. Nor, as Patent Owner appears to suggest, is Balint directed to the analysis of clinical trials, but to the results of *in vitro* testing on the effect of protease inhibitors in reducing the leaching from protein A coupled to a silica matrix.

Thus, based on the record before us, we agree with Petitioner that Balint is within the field of the invention and reasonably pertinent to the particular problem addressed by the inventors. Accordingly, because Balint was published more than one year before the priority date of the '799 patent, Balint qualifies as prior art under 35 U.S.C § 102(b).

Further, although Petitioner relies on Balint as disclosing proteolysis as a cause of protein A leaching in protein A chromatography, we find that this was otherwise known in the prior art. Dr. Cramer, for example, conceded at his deposition that two references, dated prior to the critical date of the '799 patent, suggested proteolysis as the cause of protein A leaching from Protein A affinity columns. *See* Pet. Reply 21; Ex. 1020 ¶¶ 60–61; Ex. 1022, 213:2–8, 220:1–24, 221:7–23, 224:15–23; 225:3–15; Ex. 1017, 212; Ex. 1018, 172. Dr. Cramer's testimony is confirmed by our own reading of those references. Gagnon asserts that protein A chromatography columns are "notorious for leaching" and, in a section titled "leaching by proteolysis," discloses that:

> Leaching occurs by 3 different pathways: breakdown of the support matrix, breakdown of the immobilization linkage, and proteolytic cleavage of the interdomain sequences of protein A. . . . The occurrence of leakage with even commercially purified polyclonal IgG preparations probably reflects their ubiquitous contamination with proteases.
>
> * * *
>
> Other indications that proteolysis is the primary leakage pathway include the fact that leaching is often highly elevated in the first run after storage of used media. . . . Elevated leakage is likewise seen when feedstreams carry high protease loads, such as when there has been a large amount of cell lysis.

Ex. 1018, 172–173.[9]

Guerrier similarly notes the link between proteolysis and protein A leaching. Guerrier discusses hydrophobic charge induction chromatography as an alternative to protein A affinity chromatography. Ex. 1017, Abstract,

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[9] Gagnon, P. Chapter 9, "Protein A Affinity Chromatography," in *Purification Tools for Monoclonal Antibodies*. © Validated Biosystems (1996).

211–212.[10] With respect to the latter, Guerrier notes that "as chromatographers have been called upon to design schemes for process-scale purification of antibodies, various practical complications associated with Protein-A chromatography have come under increasing scrutiny." *Id.* at 211. For example, "Protein A is subject to degradation by proteases present in the feedstocks" and "[l]eaching of Protein A (or fragments) must be addressed in the overall scheme." *Id.* at 212.

For the above reasons, we conclude that one of ordinary skill in the art, as of the filing date of the '799 patent, understood that proteolysis is a known cause of protein A leaching in protein A chromatography.

iv. Potier (Ex. 1006) and the Relationship between Temperature and Proteolytic Cleavage

Potier investigates temperature-dependent changes in proteolytic activities in the bacterium *Arthrobacter globiformis* $S_1$55. Ex. 1006, 283. In one set of experiments, the authors determined that with increasing temperature, insulin– and casein–degrading protease activities showed "similar and expected increases in activity," up to 30° C. *Id*. at 286, Fig. 1a.

According to Patent Owner, "Potier adds nothing" to Petitioner's case. PO Resp. 49–50; *see id.* at 49 ("[Petitioner cites] Potier, for the unremarkable proposition that the POSA would have known that proteolytic activity increases with temperature."). To the contrary, we find that it underscores and exemplifies Dr. Przybycien's opinion that as of the filing date of the '799 patent, "a POSA would have known, based on the general knowledge available to those skilled in the art, that reactions such as

[10] Guerrier et al. *New method for selective capture of antibodies under physiological conditions*. 9 Bioseparation 211 (2000).

proteolysis are temperature dependent, and that decreasing the temperature would decrease proteolysis." *See* Ex. 1002 ¶ 103; *see also id*. ¶ 49; Ex. 1020 ¶ 62; Ex. 2045 at 289:5–20.

Accordingly, we conclude that one of ordinary skill in the art, as of the filing date of the '799 patent, understood that proteolysis was temperature dependent such that decreasing temperature would decrease proteolysis.

v. Obviousness in view of WO '389 (Ground 3)

Petitioner asserts that claims 1 and 5 would have been obvious under 35 U.S.C. § 103(a) over WO '389 in view of the background knowledge of one of ordinary skill in the art. Pet. 6, 37–39; Pet. Reply 17–21. Patent Owner opposes. *See* PO Resp. 34–55.

Petitioner argues that WO '389 teaches that protein A chromatography may be used to purify antibodies at "about 18° C.," which overlaps with the claimed range of "about 10° C. to about 18° C." and, thus, absent evidence that the claimed range is critical (*see* Ex. 1002 ¶¶ 87–89), renders claims 1 and 5 obvious. Pet. 37–38. Petitioner further argues that one of ordinary skill in the art would have understood that protein A chromatography could be carried out at 18° C or lower, and that proteolysis is reduced at lower temperatures. *Id*. at 38–39 (citing Ex. 1002 ¶¶ 102–104). Accordingly, Petitioner contends that it would have been obvious to conduct protein A chromatography at the lower temperatures set forth in claim 1 in order to reduce proteolysis. *See id*; *see also id*. at 39 (arguing that "it would have been obvious to try conducting protein A chromatography at the claimed range in order to observe whether lower temperatures could affect unwanted leaching of protein A").

Patent Owner responds that one of ordinary skill in the art would not have sought to modify WO '389 because the reference already teaches a downstream process to remove leached protein A that avoids the expense and inconvenience of conducting chromatography at reduced temperatures. PO Resp. 35–36, 50–51. Patent Owner makes a similar argument with respect to Balint's suggestion to reduce protein A leaching by adding protease inhibitors. *Id.* at 51. Quoting Dr. Cramer, Patent Owner argues that "it 'would not make sense to the POSA, to consider modifying these processes *further* as part of 'routine optimization.'" *Id.* at 36 (quoting Ex. 2008 ¶ 129). To the contrary, we agree with Petitioner that:

> The fact that means for reducing leached protein A—such as additional purification steps, or employing protease inhibitors—were available, would not prevent a POSA from seeking additional solutions to the problem. (Ex. 1020, ¶¶69–71). Even today, increasing purity is the focus of protein A chromatography optimization. (Ex. 1021 at 48:2–5).

Pet. Reply 19.

Because one of ordinary skill in the art would have recognized that proteolysis resulted in the degradation of matrix-bound protein A (as illustrated in Balint, Gagnon, and Guerrier), and that proteolysis is inherently temperature dependent (as illustrated in Potier), the skilled artisan would have recognized that the temperature for conducting protein A chromatography was a result effective variable. *See* Pet. 39; Pet. Reply 18 (citing Ex. 1002 ¶¶ 83–84; Ex. 1020 ¶ 67); *see also*, Ex. 2006, 310 (binding capacity of protein A affinity columns are "affected by many variables, including . . . column temperature"); Ex. 1004, 146–147 (temperature a result effective variable with respect to binding capacity for some antibodies, and under some buffer conditions). That WO '389 suggests removing

leached protein A by subjecting the eluate of a protein A column to hydrophobic interaction chromatography does not negate the motivation to develop other, possibly faster, simpler, or less expensive solutions to the problem.

In light of the above, and "[g]iven the ease with which temperature can be varied, it would have been obvious to try conducting protein A chromatography at the claimed range in order to observe whether lower temperatures could affect unwanted leaching of protein A" or the degradation of the desired antibody product. *See id*. (citing Ex. 1002 ¶ 103). In this respect, we do not find persuasive Patent Owner's argument that the inventors developed a system of temperature adjustment in order to precisely control the temperature of their chromatography experiments. *See* PO Resp. 40–41; Ex. 2009 ¶ 71 (estimating that it took four weeks and 150 man hours to set up and conduct lab-scale experiment similar to those disclosed in the '799 patent). Considering the record as a whole, we conclude that exploring the temperature dependence of protein A leaching is not more than routine experimentation. *See, e.g.*, Ex. 1002 ¶ 35; Ex. 1020 ¶ 68 (well known to regulate chromatography column temperature by using refrigerated HCCF and chromatography buffers, and/or conducting the procedure in jacket-cooled chromatography columns, refrigerated spaces, or temperature-controlled water baths).

Patent Owner also argues the secondary considerations of unexpected results and recognition by others in the field. PO Resp. 53–55. We do not find these arguments persuasive. With respect to the temperature range set forth in WO '389, even a slight overlap in range may establish obviousness unless there is evidence of unexpected results to show criticality in the claimed range. *See In re Peterson*, 315 F.3d 1325, 1329, 1330 (Fed. Cir.

2003). But where the general conditions of a claim are disclosed in the art, "it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (citing *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)). As discussed in section II(C)(ii)(2)(c), above, we do not find the evidence to support that the claimed temperature range achieves unexpected results or is critical to the claimed purification method.

We also find unpersuasive Patent Owner's remaining evidence of secondary considerations. In this respect, Patent Owner relies on the selection of a presentation relating to the claimed method for oral presentation at the 2005 National Meeting of the Division of Biochemical Technology of the American Chemical Society. PO Resp. 53–55; Ex. 2012. According to Patent Owner, this reflects "[i]ndustry praise" and "[r]recognition by one's peers." *Id.* at 54–55. But Patent Owner does not establish *why* the presentation was selected; why the meeting was particularly prestigious, how the presentation was received by the attendees, or whether the disclosure has been relied on by others in the field, or been the subject of recognition or praise since the 2005 presentation. *See* Pet. Reply 24–25. For these reasons we accord little weight to Patent Owner's evidence of secondary considerations.

Considering the record as a whole, we conclude that Petitioner has demonstrated by a preponderance of evidence that claims 1 and 5 of the '799 patent would have been obvious in view of WO '389.

vi. Obviousness in view of WO '389, Balint, and Potier (Ground 4)

Petitioner asserts that claims 1–3 and 5 would have been obvious under 35 U.S.C. § 103(a) in view of WO '389, Balint, and Potier (Ground

4). Pet. 7, 40–44; Pet. Reply 17–21. Patent Owner opposes. PO Resp. 34–55.

Petitioner's arguments with respect to Ground 4 are largely the same as for Ground 3, except that Petitioner relies expressly on Balint and Potier. In this respect, Petitioner contends that "Balint teaches that protein A leaching following affinity chromatography 'is due to inherent endogenous proteolytic activity which cleaves protein fragments from the matrix'" (Pet. 41–42 (citing Ex. 1005, 4)); it was known in the art that lower temperatures tend to reduce protease activity (*id*. at 42 (citing Ex. 1002 ¶¶ 87, 105)); and Potier expressly demonstrates increasing proteolytic activity with increasing temperature (*id*. (citing Ex. 1006, 7, 9; Ex. 1002 ¶ 105)). One of ordinary skill in the art would, therefore, have understood that lowering temperature reduces the activity of proteases and consequently reduces "protein A leaching." *Id*. (citing Ex. 1002 ¶ 105). As with Ground 3, the skilled artisan

> would have been motivated to practice the protein A chromatography at intermediate temperatures such as the claimed range, rather than the coldest available range. The predictable temperature dependence of protein A leaching follows an exponential Arrhenius curve, which means that relatively small changes in protein A reduction are observed at lower temperatures. In view of these diminishing returns, and the higher cost and effort required to maintain very cold temperatures, finding an optimal middle range would have been nothing more than routine experimentation.

Id. at 42–43 (internal citations to Ex. 1002 ¶ 104 omitted).

With respect to claims 2 and 3, Petitioner argues that one of ordinary skill in the art would have been motivated to include the protease inhibitor EDTA as taught by Balint "to further reduce the leakage of protein A—thereby preserving costly column materials while obtaining effective purification of the target antibody." *Id*. at 43 (citing Ex. 1002 ¶ 108).

Patent Owner's arguments with respect to Ground 3 apply equally with respect to Ground 4, as does our analysis. *See*, *e.g.*, PO Resp. 55. For the reasons set forth in section II(D)(v), above, we conclude that Petitioner has demonstrated by a preponderance of evidence that claims 1, 2, and 5 of the '799 patent are obvious in view of WO '389, Balint, and Potier.

vii. Obviousness in view of WO '389 and the '526 Patent (Ground 5)

Petitioner asserts that claims 2, 3, and 6–11 would have been obvious under 35 U.S.C. § 103(a) in view of WO '389 and the '526 Patent. Pet. 7, 44–49; Pet. Reply 17–21. Patent Owner opposes. PO Resp. 34–55. As the teachings of WO '389 and the knowledge of those of ordinary skill in the art regarding the links between protein A leaching, proteolysis, and temperature have been discussed above, we begin with an overview of the '526 Patent.

1. Overview of the '526 Patent

The '526 Patent discloses "a method for purifying C_H2/C_H3 region-containing proteins, such as antibodies and immunoadhesins, by Protein A affinity chromatography." Ex. 1007, 1:9–14. The invention comprises the steps of (a) adsorbing the protein to protein A immobilized on a solid phase comprising silica or glass; (b) removing contaminants bound to the solid phase by washing the solid phase with a hydrophobic electrolyte solvent; and (c) recovering the protein from the solid phase. *Id*. at 2:28–37. Buffers used in the practice of the method may include the protease inhibitor EDTA. *See id*. at 3:33–39, 14:27–30.

"In preferred embodiments, the protein is an antibody (e.g. an anti-HER2, anti-IgE or anti-CD20 antibody) or an immunoadhesin (e.g. a TNF receptor immunoadhesin)." *Id*. at 2:38–40; *see* 13:67–14:6.

> Preferred molecular targets for antibodies encompassed by the present invention include . . . members of the ErbB receptor

> family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mac1, p150,95, VLA-4, ICAM-1, VCAM and αv/β3 integrin including either α or β subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; IgE . . . .

Id. at 6:13–20. Example 1 of the '526 Patent involves protein A chromatography of the C_H2/C_H3 region containing protein; humanized anti-HER2 antibody (humAb4D5-8). *Id*. at 15:22–24.

2. Analysis of Ground 5 Under 35 U.S.C. 103(a)

Petitioner's arguments with respect to Ground 5 are largely the same as for Ground 3, except regarding dependent claims 2, 3, and 6–11. With respect to dependent claims 2 and 3, Petitioner argues that:

> The '526 Patent additionally discloses including EDTA in the buffer used to equilibrate the solid phase for the protein A chromatography. ([Ex. 1007] at 3:34–35; 14:27–30.) A POSA, knowing EDTA to be a commonly used chelator and protease inhibitor, would immediately have appreciated the benefits of including EDTA in the buffer for the purpose of reducing impurities. (Ex. 1002, Przybycien Decl. at ¶ 110.) Therefore, it would have been obvious to combine the teachings of WO '389 and the '526 Patent as discussed here, in order to optimize the chromatography process while using only common excipients widely known in the prior art. (*Id*.)

Pet. 45. With respect to dependent claims 6–11, Petitioner further points to the '526 Patent's disclosure of specific C_H2/C_H3 region-containing antibodies and immunoadhesins that may be purified using protein A affinity chromatography. *See* Pet. 45–49.

Patent Owner does not address the '526 Patent with any degree of specificity, and its arguments with respect to Grounds 3 and 4 apply equally with respect to Ground 5, as does our analysis. *See, e.g.*, PO Resp. 56. Considering the record as a whole, and for the reasons set forth with

particularity in section II(D)(v), above, we conclude that Petitioner has demonstrated by a preponderance of evidence claims 2, 3, and 6–11 would have been obvious under 35 U.S.C. § 103(a) in view of WO ’389 and the ’526 Patent.

viii. Obviousness in view of WO ’389, Balint, Potier, and the ’526 Patent (Ground 6)

Petitioner asserts that claims 2, 3, and 6–11 are obvious under 35 U.S.C. § 103(a) in view of WO ’389, Balint, Potier, and the ’526 Patent. Pet. 7, 49–51; Pet. Reply 17–21. Patent Owner opposes. PO Resp. 34–55.

Patent Owner does not address Ground 6 separately from Grounds 3–5, and its arguments with respect to those grounds apply equally with respect to Ground 6, as does our analysis. *See, e.g.*, PO Resp. 56. Considering the record as a whole, and for the reasons set forth with particularity in section II(D)(v), above, we conclude that Petitioner has demonstrated by a preponderance of evidence claims 2, 3, and 6–11 would have been obvious under 35 U.S.C. § 103(a) in view of WO ’389, Balint, Potier, and the ’526 Patent.

ix. Obviousness in view of van Sommeren (Ground 7)

Petitioner asserts that claims 1, 2, and 5 would have been obvious under 35 U.S.C. § 103(a) in view of van Sommeren. Pet. 7, 51–53; Pet. Reply 17–21. Patent Owner opposes. *See* PO Resp. 34–55.

Petitioner’s arguments with respect to Ground 7 (based on van Sommeren) are essentially the same as those with respect to Ground 3 (based on WO ’589) but add an additional reason that one of ordinary skill in the art would be motivated to practice protein A chromatography at the claimed range, which Patent Owner addresses on pages 37–38 of its Response.

Our analysis of van Sommeren is set forth in section II(C)(iii), above, in the context of anticipation. Because the bulk of Patent Owner's arguments regarding obviousness address van Sommeren and WO '589 together, we further rely on the analysis set forth in section II(C)(ii), above, and address Petitioner's additional argument below.

In short, Petitioner argues that "van Sommeren anticipates claims 1 and 5 because it discloses purifying an antibody using protein A chromatography at temperatures that overlap with the claimed range of about 10° C to about 18° C." Pet. 51. Petitioner argues that there is nothing critical about the claimed temperature range. *Id.* at 51–52, (citing Ex. 1002 ¶¶ 34–35, 121) (indicating that the 4°C and 20–25° C disclosed in van Sommeren are merely convenient temperatures found in laboratory settings, and there is no evidence that researchers actively sought to avoid intermediate temperatures). Petitioner argues that, to the extent temperature ranges disclosed in van Sommeren "were not deemed anticipatory, other disclosures in van Sommeren render the claimed range of about 10° C to about 18° C obvious." *Id.*

Similar to its argument in Ground 3 with respect to WO '589, Petitioner argues that because van Sommeren's disclosure that contamination due to proteolysis was a known problem (*see* Ex. 1004, 147–148), it would have been obvious "to try temperatures within the claimed range, since temperature is an easily varied condition, in order to see if lower temperature could affect contamination caused by proteolysis." Pet. 52 (citing Ex. 1002 ¶ 120); *see also* sections II(D)(iii) and (iv), above (finding that one of ordinary skill in the art would have understood that proteolysis is temperature dependent and a well-known cause of protein A leaching). For the reasons discussed in section II(D)(v), above, we find Petitioner's

argument sufficient to establish a reason to practice protein A chromatography in the claimed range.

Petitioner also argues that in light of van Sommeren's teaching that conducting protein A chromatography at 4° C improves the binding of certain antibodies as compared to room temperature, one of ordinary skill in the art "would have appreciated that lowering the temperature of the process below ambient temperature could enhance its performance, and would have been motivated to determine a more optimal range using routine experimentation." Pet. 51–52 (citing Ex. 1002, ¶ 119); *see* Ex. 1004, 145–147.

Responding to the latter argument, Patent Owner states that "[w]hile binding capacity may well have been a reasonable target for optimization efforts," one of ordinary skill in the art "'would have understood . . . that temperature had an unpredictable, typically relatively minor effect on dynamic binding capacity' and that it 'was not an important or reasonable parameter to investigate if the POSA were trying to improve dynamic binding capacity.'" PO Resp. 37–38 (quoting Ex. 2008 ¶¶ 101–02).

We do not find Patent Owner's arguments persuasive in light of van Sommeren's teaching that for IgG_1–class antibodies, binding may be as much as 5 fold higher at 4°C as compared to 20–26°C under some buffer conditions. *See* Ex. 1004, 146–147; *see also*, Ex. 2006, 310 (indicating that temperature is a result effective variable with respect to protein A capacity). In particular, referencing other prior art, van Sommeren states: "When adso[r]ption buffers of relatively low ionic strength are used, improvement of the binding of IgG_1 antibodies to protein A can also be obtained by lowering the temperature." Ex. 1004, 136; *see id.* at 146 ("For the IgG_1 mabs however, [a prior art reference] reported a five times higher binding

capacity of protein A Sepharose for mouse monoclonal lgG1 antibodies at 4 ℃ in comparison with 20-26 ℃, using a 0.1 M sodium phosphate binding buffer (pH 8.2).").

In contrast to the five-fold increase in binding in low ionic strength buffers shown by others, van Sommeren reports that where absorption is performed in a high ionic strength buffer (1.5 M glycine, 3.0 M NaCl at pH 8.9), "the temperature effect on the IgG_1 binding capacity becomes of minor importance." *Id.* at 147; *see id.* at 144, Table V (up to 30 or 40% increase in binding capacity at 4 ℃ for some IgG1 antibodies; no change, or decrease for others). Patent Owner does not, however, explain why one of ordinary skill in the art would choose to employ the buffer conditions used in van Sommeren, rather than, for example, the "0.1 M sodium phosphate binding buffer (pH 8.2)" reportedly associated with a five-fold increase in protein A binding capacity at lower temperatures. *See id.* at 146. Nor are we persuaded that one of ordinary skill in the art would not have been motivated by the more modest temperature-dependent increases reported by van Sommeren in a high ionic strength buffer. *See* Ex. 2008 ¶ 102, 141–43 (referencing development of "industrial purification process[es]").

Considering the record as a whole, and for the reasons set forth with particularity in section II(D)(v), above, with respect to WO '389, we conclude that Petitioner has demonstrated by a preponderance of evidence claims 1, 2, and 5 would have been obvious under 35 U.S.C. § 103(a) in view of van Sommeren.

x. Obviousness in view of van Sommeren and the '526 Patent (Ground 8)

Petitioner asserts that claims 3 and 6–11 would have been obvious under 35 U.S.C. § 103(a) in view of van Sommeren and the '526 Patent.

Pet. 7, 53–57. Patent Owner opposes. *See* PO Resp. 56. Petitioner asserts that "[i]t would have been obvious to use the protein A chromatography method of van Sommeren to purify the claimed C_H2/C_H3 region-containing antibodies and immunoadhesins as disclosed in the '526 Patent for the same reasons discussed above with regard to WO '389." Pet. 57 (citing Ex. 1002, ¶¶ 115, 126). We agree with Petitioner.

Considering the record as a whole, and for the reasons set forth with particularity in sections II(D)(v) and (ix), above, we conclude that Petitioner has demonstrated by a preponderance of evidence claims 3 and 6–11 would have been obvious under 35 U.S.C. § 103(a) in view of van Sommeren and the '526 Patent.

III. (PRESUMPTIVE) MOTIONS TO SEAL

The parties have filed Paper 22 (Patent Owner's Response), Paper 28 (Petitioner's Reply), and Exhibits 1020, 2008, 2009, 2011, 2016–2018, and 2029 under seal, along with redacted versions of Papers 22 and 28, and Exhibits 2008 and 2009. The Office Patent Trial Practice Guide states:

> 3. A party intending a document or thing to be sealed may file a motion to seal concurrent with the filing of the document or thing. § 42.14. The document or thing will be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on motion.
>
> 4. *Protective Orders:* A party may file a motion to seal where the motion contains a proposed protective order, such as the default protective order in Appendix B. § 42.54. Specifically, protective orders may be issued for good cause by the Board to protect a party from disclosing confidential information. § 42.54. Guidelines on proposing a protective order in a motion to seal, including a Standing Protective Order, are provided in Appendix B. The document or thing will be protected on receipt of the motion and remain so, pending the outcome of the decision on motion.

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). Although the redacted material in Papers 22 and 28, and Exhibits 1020, 2008, 2009, 2011, 2016–2018, and 2029, appears to relate to Patent Owner's confidential information, none of these submissions are accompanied by a corresponding motion to seal, statement of good cause, or reference to any protective order. We, nonetheless, interpret the parties' sealed and redacted filings as presumptive motions to seal under our default Standing Protective Order.

"There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an inter partes review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs.*, LLC, IPR2012–00001, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). For this reason, except as otherwise ordered, the record of an *inter partes* review trial shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Motions to seal may be granted for good cause; until the motion is decided, documents filed with the motion shall be sealed provisionally. *See* 37 C.F.R. §§ 42.14, 42.54(a). The moving party bears the burden of showing that there is good cause to seal the record. *See* 37 C.F.R. § 42.20(c).

As set forth in the Board's Trial Practice Guide, confidential information that is sealed subject to a protective order ordinarily will become public 45 days after final judgment in a trial. Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). A party seeking to maintain confidentiality of information may file a motion to expunge the information before it becomes public; however, if the existence of the information is identified in a final written decision following trial,

there is an expectation that the information will be made public. *Id.* This rule "balances the needs of the parties to submit confidential information with the public interest in maintaining a complete and understandable file history for public notice purposes." *Id.*

Under the Board's procedures, there is an expectation that all exhibits, including those filed under seal here, will be made part of the public record. Furthermore, the public's interest in understanding the basis for our decision on patentability means that any good cause alleged in a motion to seal must overcome this heightened public interest. As neither party has formally filed a motion, no argument of record suggests good cause for sealing any document filed in this case. Because the Patent Owner Response and Petitioner's Reply are critical to our analysis, and to the public's understanding of the instant Opinion, the presumptive motions to seal are denied with respect to Papers 22 and 28.

We also deny the presumptive motions to seal with respect to Exhibits 1020, 2008, 2009, 2011, 2016–2018, and 2029. The normal consequence of a denial of a motion to seal would be to immediately unseal these documents. However, because the public release of documents would be irreversible, either party may file, within ten business days of this Decision, a motion to seal, addressing its justification for sealing one or more of these documents. Any such motion may be accompanied by narrowly redacted public versions of the exhibits sought to be sealed, which may be substituted for the redacted exhibits of record.

In the absence of any action on the part of a party, at the expiration of ten days from the date of this Decision, Exhibits 1020, 2008, 2009, 2011, 2016–2018, and 2029 will be made available to the public.

IV. CONCLUSION

Having weighed Petitioner's claim charts, arguments, and evidence as to those claims against Patent Owner's countervailing arguments and evidence, we determine that Petitioner has established by a preponderance of the evidence the unpatentability of claims 1–3 and 5–11 of the '799 Patent.

V. ORDER

For the above reasons, it is

ORDERED that claims 1 and 5 of the '799 Patent are unpatentable under 35 U.S.C. § 102(b) by WO '389;

FURTHER ORDERED that claims 1, 2, and 5 of the '799 Patent are unpatentable under 35 U.S.C. § 102(b) by van Sommeren;

FURTHER ORDERED that claims 1 and 5 of the '799 Patent are unpatentable under 35 U.S.C. § 103(a) in view of WO '389;

FURTHER ORDERED that claims 1–3, and 5 of the '799 Patent are unpatentable under 35 U.S.C. § 103(a) in view of WO '389, Balint, and Potier;

FURTHER ORDERED that claims 2, 3, and 6–11 of the '799 Patent are unpatentable under 35 U.S.C. § 103(a) in view of WO '389 and the '526 Patent;

FURTHER ORDERED that claims 2, 3, and 6–11 of the '799 Patent as unpatentable under 35 U.S.C. § 103(a) in view of WO '389, Balint, Potier, and the '526 Patent;

FURTHER ORDERED that claims 1, 2 and 5 of the '799 Patent are unpatentable under 35 U.S.C. § 103(a) in view of van Sommeren;

FURTHER ORDERED that claims 3 and 6–11 of the '799 Patent are unpatentable under 35 U.S.C. § 103(a) in view of van Sommeren and the

’526 Patent.

FURTHER ORDERED that, within ten business days of this Order, either party may file a renewed motion to seal Exhibits 1020, 2008, 2009, 2011, 2016–2018, and 2029.

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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