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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*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Hospira, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–3 and 5–11 of U.S. Patent No. 7,807,799 B2 (Ex. 1001, "the '799 Patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") expressly waived its opportunity to file a Preliminary Response to the Petition. Paper 6. We have jurisdiction under 35 U.S.C. § 6 and 37 C.F.R. § 42.4(a).

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we institute an *inter partes* review of claims 1–3 and 5–11 of the '799 Patent.

A. Related Applications and Proceedings

Petitioner asserts that "[t]here are no judicial or administrative matters that would affect, or be affected by, a decision in the proceeding." Pet. 4.

B. The '799 Patent

The '799 Patent relates to improved methods for conducting protein A affinity chromatography. *See* Ex. 1001, Abstract. Protein A is a cell wall component of *Staphylococcus aureas* [sic, *aureus*] that binds with high affinity to the Fc region of antibodies, in particular to the amino acids of the C_H2/C_H3 region. *Id*. 2:21–27, 5:17–28. Based on the concept that "a protein comprising a C_H2/C_H3 region may be reversibly bound to, or adsorbed by, the protein A," the Specification defines protein A affinity chromatography as "the separation or purification of substances and/or particles using protein A, where the protein A is generally immobilized on a solid phase," such as a chromatography column resin. *Id*. at 4:27–31, 41–47. The Specification makes clear that such immobilized protein A preparations are commercially available for use in protein A affinity chromatography. *See id*. at 2:31–40.

The Specification provides that, whereas, "[p]rotein A affinity chromatography is a powerful and widely-used tool for purifying antibodies"

(*id*. at 20:6–7), "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). "'[L]eaching' refers to the detachment or washing of protein A (including fragments thereof) from a solid phase to which it is bound." *Id*. at 4:49–50.

Example 1 discloses a series of experiments to characterize the temperature dependence of protein A leaching in purifying various proteins from harvested cell culture fluids (HCCFs). *See id*. at 20:1–24:50. In lab scale experiments, the monoclonal antibody trastuzumab was purified on protein A affinity columns at 10, 12, 15, 18, 20, 25, and 30 °C; three other antibodies were run at 10, 20, and 30 °C. *See id*. at 20:16–58. In pilot scale experiments, trastuzumab HCCF was applied to columns at 10, 12, 15, 18, 20, 25, and 30 °C. *Id*. at 20:59–21:3. "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 20:61–64. In full scale experiments, "HCCF was collected and held at 15+/-3°C for the duration of loading." *Id*. at 21:7–8. The Specification concludes that "[t]emperature affects protein A leaching during protein A affinity chromatography of antibodies to varying degrees." *Id*. at 24:24–25.

> At large scale, Trastuzumab HCCF was chilled to 15+/-30 C. and protein A leaching was controlled to less than or equal to 10 ng/mg. All antibodies are affected by temperature, but to varying degrees. 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 24:43–50.

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.

C. The Challenged Claims

Claim 1, the sole independent claim before us, 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" (claim 2), and in particular, protease inhibitors EDTA or AEBSF (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 characteristics (claims 6–9), or an immunoadhesion (claims 10 and 11). *Id*. at 35:48–36:43–49.

D. The Asserted Prior art and Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 6–7):

Ground	**Reference(s)**	**Basis**	**Claims**
1	WO '389[1]	§ 102(b)	1 and 5
2	van Sommeren[2]	§ 102(b)	1, 2, and 5

[1] WO 95/22389, published Aug. 24, 1995. Ex. 1003.
[2] Van Sommeren et al., "*Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG*$_1$

Ground	Reference(s)	Basis	Claims
3	WO '389	§ 103(a)	1 and 5
4	WO '389, Balint,[3] and Potier[4]	§ 103(a)	1–3 and 5
5	WO '389 and the '526 Patent[5]	§ 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

Petitioner also relies on the Declaration of Todd M. Przybycien, Ph.D. ("Przybycien Declaration"). Ex. 1002. Petitioner further relies on Hjelm[6] as illustrating the use of protein A affinity chromatography to purify IgG as early as 1972. Pet. 23; Ex. 1002 ¶ 33.

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"

Antibodies To Protein A Sepharose 4 Fast Flow," 22 Preparative Biochemistry 135 (1992). Ex. 1004.

[3] 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.

[4] Potier et al., "*Temperature-dependent changes in proteolytic activities and protein composition in the psychotropic bacterium Arthrobacter globiformis $S_1$55*," 136 J. Gen. Microbiol. 283 (1990). Ex. 1006.

[5] US 6,127,526, issued Oct. 3, 2000. Ex. 1007.

[6] Hjelm et al., "*Protein A from Staphylococcus Aureus. Its Isolation by Affinity Chromatography and Its Use As An Immunoadsorbent for Isolation of Immunoglobulins*," 28 FEBS Lett. 73 (1972). Ex. 1013.

(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. We note in particular that prior to allowing the instant claims to issue, the Examiner pointed out that Stahl[7] and Horenstein[8] 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 "[are] not in the temperature range required by claim 20"—now claim 1 of the '799 Patent. *See id*. The Examiner similarly allowed the claims over Balint, noting that "[t]he reference does not teach the temperature range required by claim 20." *Id*. at 11–12.

Although Petitioner admits that WO '389 and van Sommeren were before the Examiner during prosecution (Pet. 15) we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d). *See* Pet. 15; *see also* Ex. 1001, cover page (indicating that WO '389, van Sommeren, the '526 Patent, and Balint were before the Examiner); Ex. 1010 (obviousness rejection involving Balint).

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

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

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*. We adopt Petitioner's proposed interpretation for purpose of this opinion. *See also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the level of ordinary skill in the art may be evident from the prior art).

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 that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("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."). 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).

Petitioner proposes 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 find Petitioner's arguments persuasive. First, 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, includes no such limitation. 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)).

Second, unlike claim 1 of the '799 Patent, claim 1 of the earlier-issued '704 Patent expressly recites the limitation "such that protein A leaching is reduced." Ex. 1008, 35:46–59. Accordingly, we look to the doctrine of claim differentiation, which

> 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). On the present record, we

find no evidence tending to rebut that presumption with respect to a reduction in leaching.

Third, 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 Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (noting 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 include a limitation expressly deleted during prosecution.

Further with respect to claim 1, Petitioner proposes that we construe "about" in the upper bound of "a temperature in the range from about 10° C to about 18° C" to mean ±3° C. Pet. 17–20. Petitioner provides three bases for this construction: First, that the Specification indicates that this range reflects typical temperature fluctuations during protein A chromatography. *Id*. at 19 (citing Ex. 1001 21:6–8, 23:61–63, 24:43–45; Ex. 1002 ¶¶ 81–82). Second, that the testimony of Dr. Przybycien 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). And third, that during prosecution, the Applicant avoided prior art disclosing protein A chromatography at 22° C by amending then-pending claims to recite "about 18° C" instead of "about 20° C," thereby indicating that that "about" must mean at least ±2° C, but less than ±4° C. *Id*. at 20 (citing Ex. 1002 ¶82); *see* Pet. 12–13. Ex. 1010, 38, 50, 55, 59, 74.

In light of the above, and on the present record, we construe "about 18° C" to mean "18 ±3° C".

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. Analysis of Asserted Grounds

i. 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.

1. Overview of WO '389 (Ex. 1003)

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, 4:20–24; *see id*. at 40:23–26 (claim 9), 41:21–34 (claim 20).[9] "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 4:13.

WO '389 further notes that "[a]lthough Protein A affinity column chromatography is widely used, it is also appreciated that elution of antibody

[9] We refer, herein, to the original pagination of the cited references rather than to that supplied by Petitioner.

from such columns can result in leaching of residual Protein A from the support." *Id*. at 4:1–3.

2. Analysis of Ground 1 Under 35 U.S.C. 102(b)

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Petitioner presents a claim chart and argument indicating that this standard is satisfied with respect to claims 1 and 5 of the '799 patent. Pet. 28–33. With respect to the requirement of claim 1 that the purified protein comprise a C_H2/C_H3 region, Petitioner reasonably points to the testimony of Dr. Przybycien that the IgG protein of WO '389 inherently comprises a C_H2/C_H3 region (Pet. 28, citing Ex. 1002 ¶ 90), as well as to the Specification of the '799 Patent, which makes clear that the C_H2/C_H3 motif is found in the IgG heavy chain (*id*. at 28–29 (citing Ex. 1001, 14:66–15:2). *See In re Preda*, 401 F.2d 825, 826 (C.C.P.A 1968) ("[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.").

With respect to the requirement that the process is carried out "at a temperature in the range from about 10° C to about 18° C," WO '389 discloses the overlapping range of "18–25 °C". Ex. 1003 4:4–13. 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). With respect to the present case, however, there is no argument or evidence of record supporting the criticality of the claimed range. *See* Pet. 29 (citing Ex. 1002 ¶¶ 88–89).

Accordingly, we find that Petitioner has established a reasonable likelihood that claims 1 and 5 are anticipated by WO '389.

ii. 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) in view of WO '389. Pet. 6, 37–39; *see also id*. at 28.

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 said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The underlying analysis must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Factual considerations underlying the obviousness inquiry include the scope and content of the prior art, differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations. *KSR*, 550 US at 406. Evidence pertaining to secondary considerations must be taken into account whenever present, but does not necessarily control the

obviousness conclusion. *See, e.g., Pfizer, Inc. v. Apotex, Inc*. 480 F.3d 1348, 1372 (Fed. Cir. 2007).[10]

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*, 20 F.2d 454, 456 (C.C.P.A. 1955)).

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

[10] Petitioner asserts that "there is no evidence of any . . . secondary factors that could outweigh the strong case of prima facie obviousness under Section 103(a) for the Challenged Claims." Pet. 57–58. We discern none upon reading the '799 Patent, and Patent Owner has not pointed to any on the present record.

claimed range in order to observe whether lower temperatures could affect unwanted leaching of protein A").

We find that Petitioner's unopposed arguments and evidence establish a reasonable likelihood that claims 1 and 5 would have been obvious in view of WO '389.

iii. 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. Pet. 7, 40–44.

1. Overview of Balint

Balint investigates potential causes of protein A leaching during affinity column chromatography of IgG from plasma and serum samples. Balint, 85; *see id*. at 86 ("there was concern about the potential for [protein A] to 'leach' from the immunoadsorbent matrix into patient plasma"). Balint discloses that protein A was released from the 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 general protease inhibitors to the serum samples, Balint concluded that this leaching of protein A was due to inherent endogenous proteolytic activity, which cleaved protein fragments from the chromatography matrix. *Id*. at 88–89.

2. Overview of Potier

Potier investigates temperature-dependent changes in proteolytic activities in the bacterium *Arthrobacter globiformis S*$_{I}$*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.

3. Analysis of Ground 4 Under 35 U.S.C. 103(a)

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)). Thus, one of ordinary skill in the art "would have understood that lowering temperature reduces the activity of proteases and consequently reduces protein A leaching." *Id*. (citing Ex. 1002 ¶ 105). According to Petitioner, a person of ordinary skill in the art

> 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. Therefore, claim 1 is obvious over WO '389, and further in view of Balint and Potier.

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). With respect to antibody recited in claim 5, Petitioner points to the use of protein A chromatography to purify IgG set forth in WO '389, discussed above in section II(C)(i)(1). *Id*. at 43–44 (citing Ex. 1002 ¶ 105).

On the present record, Petitioner's unopposed arguments and evidence establish a reasonable likelihood that claims 1–3 and 5 would have been obvious in view of WO '389, Balint, and Potier.

iv. 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.

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 CH2/CH3 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)

In section II(C)(ii), above, we discussed obviousness of claim 1 in light of WO '389. With respect to dependent claims 2 and 3, Petitioner further argues that:

> The '526 Patent additionally discloses including EDTA in the buffer used to equilibrate the solid phase for the protein A chromatography. (*Id*. 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.

On the present record, Petitioner's unopposed arguments and evidence establish a reasonable likelihood 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.

v. 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. Each of these references and their applicability to the challenged claims are discussed above. On the present record, Petitioner's unopposed arguments and evidence establish a reasonable likelihood that 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.

vi. 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.

1. Overview of Van Sommeren

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. With respect to temperature, van Sommeren compared 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 studies "showed that the temperature had a negligible effect on the binding capacity for monoclonal antibodies of the subtypes IgG_{2a}, IgG_{2b} and IgG_3," but IgG_1 binding was five times higher at 4°C as compared to 20–26°C under certain buffer conditions. *Id*. at 146. "Results from the present study[, however,] show that the temperature effect on the IgG_1 binding capacity becomes of minor importance, if adsorption is performed at high ionic strength." *Id*. at 147.

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.

2. Analysis of Ground 2 Under 35 U.S.C. 102(b)

Petitioner presents a claim chart and argument indicating that van Sommeren expressly or inherently discloses all limitations of claims 1, 2, and 5 of the '799 patent. Pet. 33–37. For the reasons set forth therein, we find that Petitioner has established, on the current record, a reasonable likelihood that claims 1, 2, and 5 are anticipated by van Sommeren.

vii. 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.

Petitioner 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. Petitioner further argues that given 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). As discussed above in section II(C)(ii), Petitioner contends that there is nothing critical about the claimed temperature range. *See id*., (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).

On the present record, Petitioner's unopposed arguments and evidence establish a reasonable likelihood that claims 1, 2, and 5 would have been obvious under 35 U.S.C. § 103(a) in view of van Sommeren.

viii. 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. Obviousness of claims 1, 2, and 5 in view of van Sommeren is discussed, above, in Section II(C)(vii). With respect to claims 3 and 6–11, Petitioner further relies on the '526 Patent for essentially the same reasons as discussed in Section II(C)(iv), above. On the present record, Petitioner's unopposed arguments and evidence establish a reasonable likelihood 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.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has shown there is a reasonable likelihood that it would prevail in proving the unpatentability of claims 1–3 and 5–11 of the '799 Patent.

IV. ORDER

ORDERED that *inter partes* review is instituted with regard to the following asserted grounds:

Claims 1 and 5 of the '799 Patent as anticipated under 35 U.S.C. § 102(b) by WO '389;

Claims 1, 2, and 5 of the ’799 Patent as anticipated under 35 U.S.C. § 102(b) by van Sommeren;

Claims 1 and 5 of the ’799 Patent as unpatentable under 35 U.S.C. § 103(a) in view of WO ’389;

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, and Potier;

Claims 2, 3, and 6–11 of the ’799 Patent as unpatentable under 35 U.S.C. § 103(a) in view of WO ’389 and the ’526 Patent;

Claims 1, 2 and 5 of the ’799 Patent as unpatentable under 35 U.S.C. § 103(a) in view of van Sommeren;

Claims 3 and 6–11 of the ’799 Patent as unpatentable under 35 U.S.C. § 103(a) in view of van Sommeren and the ’526 Patent.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’843 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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