UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.
Petitioner

v.

GENENTECH, INC.
Patent Owner

U.S. 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

PETITIONER'S REPLY

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(Filed Pursuant to 37 C.F.R. § 42.6)

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1001	U.S. Patent No. 7,807,799 to Fahrner et al.
1002	Declaration of Todd M. Przybycien, Ph.D.
1003	International Publication No. WO 95/22389 to Shadle et al.
1004	A.P.G. 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)
1005	J.P. Balint, Jr. & F.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)
1006	P. Potier et al., *Temperature-dependent changes in proteolytic activities and protein composition in the psychrotropic bacterium Arthrobacter globiformis S_I55*. 136 J. GEN. MICROBIOL. 283 (1990)
1007	U.S. Patent No. 6,127,526 to G.S. Blank
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1009	European Patent No. EP 1 648 940 B1 to Fahrner et al.
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1017	Guerrier et al. *New method for selective capture of antibodies under physiological conditions*. 9 BIOSEPARATION 211 (2000)
1018	Gagnon, P. Chapter 9, "Protein A Affinity Chromatography," in *Purification Tools for Monoclonal Antibodies*. © Validated Biosystems (1996)
1019	Gagnon, P. *Affinity Chromatography: The Fine Print – Validated Quarterly Resource Guide for Downstream Processing*. pp. 1-5 www.validated.com/revalbio/pdffiles/affinity.pdf (1999)
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I. INTRODUCTION

The Board instituted this *inter partes* review on all eight grounds set forth by Petitioner Hospira, Inc., finding that claims 1 to 3 and 5 to 11 of the '799 Patent (the "Challenged Claims") are likely anticipated and/or obvious in view of the cited prior art. Independent claim 1 of the '799 Patent recites a method of purifying a protein by subjecting a composition to protein A affinity chromatography at a temperature in the range from "about 10º C to about 18º C." In its Response, Patent Owner Genentech argues that this claimed temperature range is critical and nonobvious. However, Patent Owner's arguments read limitations into the claims, and mischaracterize the prior art.

In the '799 Patent, Patent Owner sought and obtained broad claims to conducting protein A chromatography at an intermediate temperature range—above cold room temperatures, and overlapping with low ambient temperatures. Both WO '389 (Ex. 1003) and van Sommeren (Ex. 1004) disclose conducting chromatography at ambient or room temperature, which they identify respectively as being 18-25º C and 20-25º C. Rather than attempting to amend the claims, Patent Owner argues that the prior art fails to teach a method where the composition subjected to protein A chromatography is chilled to "about 10º C to about 18º C." Patent Owner also alleges that WO '389 and van Sommeren do not disclose the temperature of the composition being subjected to chromatography.

This tortured interpretation of the prior art is supported only by Dr. Steven Cramer's speculation, which runs contrary to established practice in the laboratory and in scientific writing.

Patent Owner also attempts to show that the claimed temperature range is critical based on a "reduction in protein A leaching." This argument relies on a series of mischaracterizations. The benefit of the claimed range, according to Patent Owner, is that protein A leaching is "relatively flat" at those temperatures. (Response, Paper 22 at 31.) Patent Owner suggests that protein A leaching sharply increases following the "relatively flat" trend, even though the leaching data follows a smooth exponential curve. Patent Owner and Dr. Cramer fail to acknowledge that "relatively flat" protein A leaching is also achieved at the temperature ranges disclosed in the prior art. Furthermore, in his declaration, Dr. Todd Przybycien explained that protein A leaching is driven by temperature-dependent degradation caused by enzymes known as proteases. Based on this known relationship between proteolysis and protein A leaching, a POSA would have expected leaching to follow an Arrhenius-type exponential curve. Patent Owner and Dr. Cramer never attempt to rebut this analysis.

Similarly, Patent Owner's argument against obviousness rests on Dr. Cramer's erroneous claim that the inventors listed on the '799 Patent were the first in their field to discover the relationship between proteolytic degradation and

protein A leaching. This contrivance was never raised during prosecution of the '799 Patent, likely because it is easily disproved by the teachings of Balint (Ex. 1005) and other available prior art. Now Patent Owner and Dr. Cramer claim that only persons of *extraordinary* skill in the art could have synthesized the teachings of Balint to solve a problem in the field of antibody purification. Scientists specializing in antibody purification have long relied on insights from the biochemistry and immunology fields, and Balint squarely addresses the problem of protein A leaching that the named inventors faced.

As discussed below, the prior art teaches conducting protein A chromatography at temperatures that overlap with the claimed temperature range, which is not critical to the patented method. Based on the prior art teachings, and the knowledge that temperature-dependent proteolysis was the primary cause of protein A leaching, it would have been obvious to conduct protein A chromatography at the claimed intermediate temperature range. Therefore, the Challenged Claims are invalid based on the eight asserted grounds, and should be cancelled.

II. PATENT OWNER READS LIMITATIONS INTO THE CLAIMS

A. "Below Room Temperature" Is Not In the Claims

Patent Owner states that the claims must be given their broadest reasonable construction in light of the specification (Response at 11), and that "about" should

be construed to mean "approximately" (*id.* at 17). These positions are consonant with Petitioner's construction of "about 18º C" as encompassing "18±3º C." (Petition at 19; Ex. 1020, Przybycien Decl., ¶13.) However, Patent Owner goes on to say that "approximately 18º C" cannot include 21º C, because 21º C is "room temperature," while the claimed method can only be practiced "below room temperature." (Response at 18.) Both the specification and the prosecution history support Petitioner's claim construction of "about 18º C." (Ex. 1020, ¶¶12-14.)

First, the claimed method is not limited to temperatures "below room temperature." The claims recite subjecting a composition to protein A chromatography at the temperature range of about 10º C to about 18º C, with "about" modifying both endpoints of the claimed range. (Ex. 1020, ¶16.) Similarly, the specification of the '799 Patent discloses performing the method in the temperature range of about 3º C to about 20º C. (Ex. 1001 at 18:8.) Before the priority date of the '799 Patent, POSAs regarded temperatures as low as 18º C and 20º C as being "room temperature." (Ex. 1003 at 15; Ex. 1004 at 16; Ex. 1023 at 2.) Patentee sought and obtained claims encompassing what was considered room temperature. (Ex. 1020, ¶13; *see also* Ex. 1010 at 38; Ex. 1001 at 25; Ex. 1012 at 30.) Patentee never sought or obtained claims reciting "below room temperature."

Patentee never defined "room temperature," yet Patent Owner simply concludes that 21º C means "room temperature" within the '799 Patent. Patent

Owner notes that "the specification makes it clear that 'about 20º C' means 'below room temperature.'" (Response at 18.) Patent Owner also suggests that "the broadest answer consistent with the specification would construe 'about' as no more than ±1° C." (*Id.* at 21.) Even under this narrow interpretation, 20±1º C would be considered "below room temperature" within the context of the '799 Patent. (Ex. 1020, ¶14.) Patent Owner points to no evidence supporting the idea that the methods claimed in the '799 Patent cannot be practiced at 21º C. (*Id*. at ¶¶14-15)

Additionally, Patent Owner cannot avoid the amendments and statements it made during prosecution by claiming that it was expediting prosecution rather than acquiescing to the examiners' rejections. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090 (Fed. Cir. 2013) (adopting a narrow construction of a claim term based on applicants' failure to challenge the examiner's characterization). During prosecution, the Applicant effectively acknowledged that "about" means ±3° C by acquiescing to rejections based on the prior art. (Petition at 20.) Despite Patent Owner's hollow protests, the Applicant *did* acquiesce by narrowing the claimed range; and it never again pursued a broader temperature range. For at least the foregoing reasons, "18±3° C" is the proper construction of "about 18° C." (Ex. 1020, ¶¶15-18.)

B. "Such That Protein A Leaching Is Reduced" Is Not In the Claims

The Board adopted Petitioner's construction of claim 1 as a method that does not require reduction of protein A leaching, and "Genentech agrees with this construction." (Response at 11.) Yet Patent Owner also urges the Board to reject Petitioner's construction because it supposedly excludes the impurity problem that the patent was meant to solve. According to Patent Owner, a POSA would have understood a "method of purifying a protein" to mean a method of separating a protein of interest from impurities, including protein A. However, claim 1 specifically recites a method of purifying a protein by subjecting a composition to protein A affinity chromatography.

Although Patent Owner states that it is "baffling for Hospira to suggest that the claimed invention does not purify the HCCF [(harvested cell culture fluid) of leached protein A]," (Response at 12) additional downstream purification steps are the only way to remove protein A from the composition. (Ex. 1021, Dowd Dep. at 70:6-17.) Dr. Cramer has admitted that protein A chromatography *adds* leached protein A to the composition being purified, and does not remove it. (Ex. 2008, Cramer Decl., ¶¶24, 80.) Dr. Cramer and Genentech's declarant Christopher Dowd, Ph.D., have also acknowledged that claim 1 states the solitary step of conducting protein A chromatography at about 10º C to about 18º C. (Ex. 1021 at 70:3-5; Ex. 1022 at 153:20-25.) Petitioner agrees that protein A is an impurity, but

Petitioner also acknowledges that it is not an impurity that can be removed by the *claimed* method. (Ex. 1020, ¶¶19-21.)

Patent Owner argues that claim 12 serves to illustrate the proper scope of claim 1, because claim 12 recites a method of purifying a protein in which multiple steps are performed to "reduce levels of leached protein A." (Response at 13.) This reasoning runs counter to the doctrine of claim differentiation, which the Board referenced when it accepted Petitioner's claim construction. The Patentee chose to claim a method "such that protein A leaching is reduced" in claim 1 of the '704 Patent and claim 12 of the '799 Patent. For claim 1 of the '799 Patent, the Patentee chose to eliminate this term,[1] and so claim 1 of the '799 Patent has a different scope. (Ex. 1020, ¶¶21-22.) Ultimately, the prior art relied upon by Petitioner need not show any particular level of protein A leaching in order to invalidate the claims. (*Id.*, ¶23.)

III. WO '389 AND VAN SOMMEREN ANTICIPATE

A. WO '389 Discloses Practicing Protein A Chromatography at the Claimed Temperature Range

WO '389 discloses practicing protein A chromatography, such that all steps are carried out at room temperature, 18º C – 25 º C. (Ex. 1003 at 15.) In spite of

[1] Dr. Cramer also suggests that the Applicant deleted "such that protein A leaching is reduced," merely to "avoid confusion." (Ex. 2008, ¶56.) However, any amendment that removes an impediment to allowance is relevant to claim construction. *Glaxo Group Ltd. v. Ranbaxy Pharm., Inc.*, 262 F.3d 1333, 1339 (Fed. Cir. 2001).

this clear teaching, Patent Owner argues that its disclosure does not refer to the temperature of the composition.[2] It is not uncommon for an article addressing chromatography to omit descriptions of temperature, as seen from papers co-authored by Dr. Cramer (Exs. 1015, 1016) and the Fahrner Review (Ex. 2006). (Ex. 1020, ¶26.) In these cases, a reasonable POSA would understand that the chromatography was carried out at ambient temperature. (*Id.*, ¶¶25-26; *see* Ex. 1022 at 86:8-18.) A POSA would understand that WO '389's disclosure of 18º-25º C refers to the temperature of the lab where the experiment was conducted, including the temperature of the components involved in the experiment. (*Id.*, ¶¶24-28.)

Dr. Cramer argues that WO '389's disclosure of conducting chromatography at 18º C – 25º C refers *only* to the lab, and that the HCCF being purified could have been at any temperature. However, using HCCF that was warmer than the chromatography column and its containment would raise the temperature of the whole system, making it impossible to conduct all steps at room temperature. (Ex. 1020, ¶¶26-27.) Purifying above room temperature HCCF using protein A chromatography, and yet reporting that the experiment was conducted at room

[2] During the European prosecution, the Applicant narrowed the claims "to refer to an upper temperature limit of 15ºC" in an effort to overcome the teachings of WO '389. (Ex. 1012 at 37.)

temperature, would have been a drastic departure from accepted laboratory practices. (*Id*., ¶27.)

Dr. Cramer did not cite to any literature supporting his speculation that, absent instruction to wait, a POSA would have immediately subjected 37º C HCCF to protein A chromatography. During his deposition, Dr. Cramer admitted that he was not aware of any procedures in practice by 2003 where HCCF was taken directly from the bioreactor to the chromatography column. (Ex. 1022 at 85:6-15.) He also admitted that WO '389 says nothing to contradict the presumption that the HCCF in question was at 18º-25º C, when all steps were conducted at 18º-25º C. (*Id.* at 113:13-16.)

The possibility that the inventors of the WO '389 methods could have allowed the disclosed process to be performed with HCCF that was "potentially" above room temperature is merely speculation, and is contradicted Dr. by Przybycien's observations. (Ex. 1020, ¶27.) The published disclosure of WO '389 teaches carrying out all steps at 18-25º C. Therefore, WO '389 teaches every limitation of claims 1 and 5, including conducting "protein A affinity chromatography at a temperature in the range of "about 10º C. to about 18º C." (*Id.*, ¶28.)

B. Van Sommeren Discloses Practicing Protein A Chromatography at the Claimed Temperature Range

In van Sommeren, "[t]he effect of temperature, 4 ºC versus ambient temperature (AT) (20-25 ºC), was studied" on binding capacity of certain antibodies during protein A chromatography. (Ex. 1004 at 16.) During prosecution of the European counterpart, the Applicant acknowledged that van Sommeren was concerned with the effect of temperature on binding "between protein A columns and *the antibody in preparations for purification*." (Ex. 1012 at 40, emphasis added.) Patent Owner now argues that the disclosures in van Sommeren regarding temperature are inapplicable because they do not refer to the HCCF subjected to purification.

Dr. Cramer concludes that because there is no discussion of a specific step between culturing the cells and performing protein A chromatography, that the HCCF could have been above room temperature. (Ex. 2008, ¶98.) Dr. Cramer cited no literature for this proposition, and could not name one real world situation where this had taken place. (*Id.*; *see* Ex. 1022 at 84:19-85:15.) As explained below, van Sommeren could not have studied the effects of temperature at 4º C and 20-25º C by conducting protein A chromatography on a composition that had a different temperature. (Ex. 1020, ¶¶29-31.)

Dr. Cramer agreed that van Sommeren is a peer-reviewed publication. (Ex. 1022 at 124:23-25.) A POSA would understand a peer-reviewed publication as

disclosing accurate and reproducible conditions, which would be impossible if the temperatures reported applied to the room, but not to the "preparations for purification" used in the experiments. (Ex. 1020, ¶¶29-30.) Indeed, Dr. Cramer agreed that the validity of temperature-controlled experiments would be destroyed if the composition being studied was not at the reported temperatures. (Ex. 1022 at 126:18-127:5.) Dr. Cramer's attempts to dismiss the clear disclosure of van Sommeren that chromatography was conducted at 4º C and 20-25º C are not supported by any evidence.

C. WO '389 and Van Sommeren Need Not Disclose Actively Chilling the HCCF

Patent Owner asserts that "[n]either of Hospira's two anticipation references, WO '389 and van Sommeren, disclose the Fahrner Patent's method of chilling HCCF to the claimed temperature range." (Response at 2.) Dr. Cramer concludes that "[n]either reference suggests, let alone discloses, chilling the cell culture fluid." (Ex. 2008, ¶72; *see also* ¶¶87-93.) However, the claims do not recite whether, when or how the composition is reduced to the range of about 10º C to about 18º C. (Ex. 1020, ¶¶32-33.) What Patent Owner proposes is a textbook case of improperly reading limitations from the specification into the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005).

The Patentee had ample opportunity to amend the claims to recite an active chilling step, or to argue that the prior art failed to disclose chilling during

prosecution, but it never did so. The specification provides examples "by way of illustration and not by way of limitation," (*id.* at 19:64-65) that describe methods where HCCF temperature was actively controlled. (*Id.* at 20:1-26:65.) Despite describing these embodiments in the specification, the Patentee omitted details such as "reducing temperature" and "chilling" from the claims in order to obtain broad coverage. (Ex. 1020, ¶34.) Under the broadest reasonable interpretation, the claimed method can be practiced by conducting chromatography at an ambient temperature within the range of about 10º C to about 18º C. (*Id.*, ¶35.)

Patent Owner states that Dr. Przybycien conceded that the only reasonable construction of the claims is that they do not refer to the temperature of the room in which the methods is performed. This mischaracterizes Dr. Przybycien's testimony that the claims set a temperature, and do not invoke any special cooling method or technique. (*Id.* at 116:14-25; Ex. 1020, ¶¶35-36.) In fact, Dr. Przybycien repeatedly explained that, while the named inventors mentioned the possibility of active cooling, the claims also encompassed practicing the claimed methods at ambient temperature. (Ex. 2010 at 117:24-118:16.) The claims do not mention controlling or changing the temperature, and the specification does not preclude the embodiment in which the temperature of the HCCF is at the temperature of the laboratory. Because the Patentee chose to claim a static

temperature range, the disclosures of WO '389 and van Sommeren anticipate the claims. (Ex. 1020, ¶36.)

D. The Claimed Temperature Range Is Not Critical to the Claimed Methods

Criticality has been found where only a narrow range of temperatures enabled the 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). Criticality of a claimed range may also be established by evidence of unexpected results that are commensurate in scope with the claims. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Patent Owner's evidence illustrates that there is not a considerable difference in protein A leaching between the claimed range versus the ranges in the prior art. This evidence also shows that protein A leaching follows an expected exponential trend at the claimed range—intermediate temperature invariably leads to an intermediate level of leaching. (Ex. 1002, ¶¶37-38, 45.) As Dr. Przybycien explains in this declaration, the claimed range is not critical, because protein A chromatography works in the same way at the prior art temperatures of 4º C, 18-25º C and 20-25º C as it works within the claimed range. (*Id.*, ¶38.)

According to Patent Owner, conducting protein A chromatography at the claimed range of about 10º C to about 18º C leads to a "relatively flat" level of protein A leaching. (Response at 31.) Patent Owner also states that protein A

leaching in the 18-25º C and 20-25º C ranges "tends to increase more sharply per degree relative to the claimed range." (*Id*.) Being "relatively flat" as opposed to increasing sharply is the only alleged difference between the claimed temperature range and the prior art ranges that Patent Owner and Dr. Cramer have identified. Nevertheless, in multiple instances, the data shows "relatively flat" protein A leaching above "about 18º C." (Ex. 1020, ¶39.) Notably, Patent Owner does not, and cannot contend that protein A chromatography cannot be practiced outside of the claimed range.

As shown in Fig. 1 of the '799 Patent, protein A leaching is consistently low between 10º and 25º C degrees for multiple antibodies.

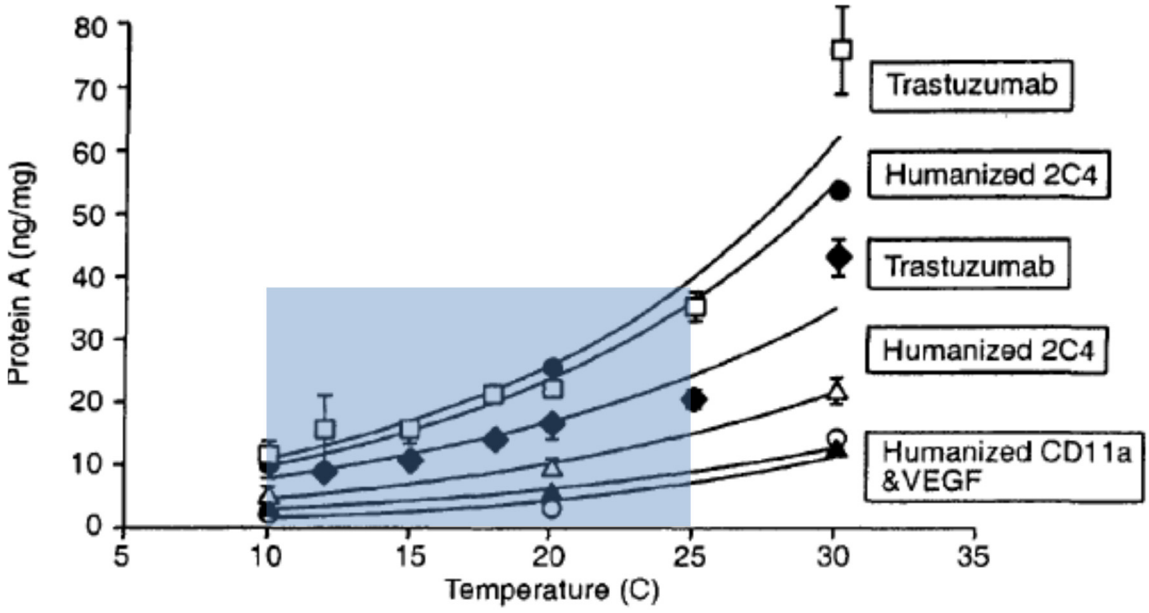

FIG._1

(Ex. 1001 at 2; [redacted].)[3] In fact, the levels of protein A leaching that Patent Owner measured for several antibodies at the claimed temperature range and at room temperature would all have been considered typical in the bioprocessing field, and were removable by subsequent processing. (Ex. 1020, ¶¶39-40.) Therefore, the alleged "considerable difference" Patent Owner identified is simply not present for most antibodies, and Patent Owner's evidence of criticality is not commensurate with the claims. (*Id.*, ¶38)

"Relatively flat" protein A leaching would also be observed at temperatures below the claimed temperature range. (*Id.*, ¶43; Ex. 1021 at 83:23-84:18.) As Dr. Przybycien stated at his deposition, "the lower you went with temperature, the less leaching you would observe." (Ex. 2010 at 123:17-19.) While the '799 Patent discloses conducting protein A chromatography at temperatures as low as 3º C, and the Patentee claimed ranges extending to 3º C, the Response is completely silent on the behavior of protein A leaching at temperatures below 10º C. The claimed range of "about 10º C to about 18º 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. (Ex. 1020, ¶43.)

[3] Patent Owner has also not provided any evidence or argument showing that protein A leaching differs outside of the claimed range when a protease inhibitor is used, as recited in claims 2 and 3. (Ex. 1020, ¶43.)

Further, the temperature dependence of protein A leaching would have been expected. Dr. Przybycien explained that because protein A leaching is driven by proteolysis, a POSA would expect an exponential dependence on temperature. (Ex. 1002, ¶¶49, 87, 93, 104; Ex. 1020, ¶¶41-42.) He reiterated this during his deposition, stating that protein A leaching decreases monotonically with decreasing temperature. (Ex. 2010, 123:16-17.) Dr. Cramer avoids discussing the exponential fit that was consistently used by the named inventors in plotting their empirical protein A leaching data (Ex. 2008, ¶113; [redacted]). He makes no attempt to rebut Dr. Przybycien's discussion of protein A leaching predictability. (Ex. 1002, ¶¶43-44; Ex. 1020, ¶¶65-66.) Instead, Dr. Cramer conclusorily states that "the relative efficiency and consistency of this temperature range would not have been predictable to the POSA." (Ex. 2008, ¶122.) This claim is based on Dr. Cramer's mistaken belief that the relationship between protein A leaching and proteolysis was unknown. Any suggestion that criticality of the claimed range is supported by unexpected results or unpredictability is likewise based on this factual error.

Because Patent Owner has failed to show criticality of the claimed range, claims 1, 2 and 5 are anticipated under Grounds 1 and 2.

IV. THE CLAIMED METHODS ARE ALSO OBVIOUS

Patent Owner mischaracterizes the law regarding routine optimization, and ignores the motivations to modify the methods of WO '389 and van Sommeren that Petitioner identified in the prior art. As noted above, Patent Owner never argues that the limitations of any dependent claims are novel. In fact, Patent Owner admits that the prior art teaches using protease inhibitors (claims 2 and 3) to prevent protein A leaching. (Response at 39, 56.) Dr. Cramer likewise admits that it was known to purify antibodies and immunoadhesins with protein A chromatography (claims 5-11). (Ex. 1022 at 130:12-131:12.) Patent Owner's argument against obviousness is based on the mistaken assumptions that a POSA would not have tried to vary the temperature of protein A chromatography, and that the relationship between protein A leaching and proteolytic activity was unknown. (Ex. 1020, ¶¶46-47.)

A. It Would Have Been Obvious to Vary the Temperature for Conducting Protein A Chromatography

Claims 1 and 5 are obvious over WO '389 alone, and claims 1, 2 and 5 are obvious over van Sommeren alone, because temperature is a result-effective variable, which a POSA would have been able to modulate using widely available implements. (*Id.* at ¶¶64-66.) As discussed in Section III above, WO '389 and van Sommeren teach the general conditions of claim 1, because they both teach conducting protein A chromatography at temperature ranges that overlap with the

claimed range. "Such overlap itself provides sufficient motivation to optimize the ranges." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). 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." *Id.*

Dr. Cramer argues that temperature is not a result-effective variable because it is not on a list of variables provided in the Fahrner Review. (Ex. 2008, ¶139.) Contrary to Dr. Cramer's statement, temperature ***is*** on the Fahrner Review's list of variables relevant to the capacity of chromatography columns. (Ex. 1020, ¶67.) Moreover, temperature is a result-effective variable based on the teachings in van Sommeren and WO '389, as well as the knowledge generally available to those in the relevant art. (*Id.*; *see also* Ex. 1002, ¶¶83-84.) It was within the purview of a POSA before July 2003 to develop her own system of temperature adjustment using commercially available tools such as water baths or jacketed columns. (*Id.*, ¶68.) Knowing that temperature would affect the reactions involved in antibody purification, a POSA would have been motivated to "discover the optimum or workable ranges by routine experimentation." *See In re Applied Materials*, 692 F.3d at 1295 (affirming the Board's conclusion that a variable was result-effective because a POSA would have recognized it to affect a particular result).

Claims 1 to 3 and 5 are also obvious over the combination of WO '389, Balint and Potier. Patent Owner argues that the chromatography method taught by

WO ’389 did not present a problem with protein A leaching. (Response at 35-37.) Patent Owner suggests that the motivation to modify WO ’389 must be taught by the reference itself. (*Id.*) However, obviousness may be based on any motivation or suggestion found in the prior art. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). In this case, the teachings of Balint and Potier would have motivated a POSA to reduce temperature to avoid protein A leaching in the method taught by WO ’389.

It is undisputed that undesirable protein A leaching occurs during protein A chromatography. (Ex. 1022 at 60:17-22; Ex. 1020, ¶¶59, 71.) 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.)

Patent Owner does not deny the “unremarkable” fact that enzymes are activated at increased temperature, which is also disclosed by Potier. (Ex. 1020, ¶62.) Balint’s teaching that enzyme degradation causes protein A leaching would have motivated POSAs to reduce the temperature at which protein A chromatography was conducted. (*Id.*, ¶63.) And, because lower temperatures result in lower leaching, a POSA would have expected an intermediate level of

protein A leaching at the intermediate temperatures within the claimed range. (*Id.*, ¶¶71-72.)

None of the evidence presented by Patent Owner weighs against the concrete teachings, suggestions and motivations pointed out by Petitioner, which render claims 1 to 3 and 5 obvious under Grounds 3, 4 and 7. (*Id.*, ¶¶69-72.) In addition, Patent Owner has not contested the teachings of the '526 Patent as applied in Grounds 5, 6 and 8. (*Id.*, ¶46.) Therefore, claims 1 to 3 and 5 to 11 are invalid under obviousness Grounds 3 through 8.

B. The Relationship Between Protein A Leaching, Temperature and Proteolytic Activity Was Known

It is surprising that Patent Owner would attempt to claim that proteolytic activity was not known as a cause of protein A leaching (*see* Ex. 2008, ¶¶171-181)—contradicting, but not rebutting Dr. Przybycien's first declaration. (Ex. 1020, ¶58.) The Patentee never raised this argument during prosecution of the '799 Patent family. Additionally, Patent Owner admits that if a POSA were concerned about protein A leaching, "Balint already provides the answer—add a cocktail of protease inhibitors." (Response at 51.) Dr. Cramer acknowledged that Balint's disclosure regarding protease inhibitors would teach a POSA that proteolysis causes leaching. (Ex. 1022, 147:4-23.) Contrary to Dr. Cramer's arguments, van Sommeren, WO '389 and Blank all disclose the use of protease inhibitors in connection with protein A chromatography. (Ex. 1020, ¶46; *see* Ex.

1022, 127:24-128:20.) In addition, Dr. Cramer admitted that two prior art references—Guerrier 2000 (Ex. 1016) and Gagnon 1996 (Ex. 1017)[4]—would also have apprised a POSA of the link between protein A leaching and enzyme-derived degradation.[5] (Ex. 1022 at 213:2-8, 221:7-13; Ex. 1020, ¶60.)

Finally, neither Patent Owner nor Dr. Cramer contest the teachings of Potier. (Ex. 1020, ¶¶62-63.) Petitioner relied on Potier only to teach the widely known fact that proteolytic activity increases with temperature. Patent Owner agrees, stating that this proposition is "unremarkable." (Response at 49.) Dr. Cramer admitted during his deposition that enzymes can be activated by higher temperatures, and that he had not opined on the conclusions set forth in Potier. (Ex. 1022 at 133:12-16.) Dr. Przybycien's testimony that proteolytic activity was known to exponentially increase with temperature following an Arrhenius curve stands unchallenged.

1. Balint Is Analogous Art

Patent Owner does not deny that Balint teaches that proteolysis causes protein A leaching. Patent Owner and Dr. Cramer only contend that a POSA in the

[4] Dr. Cramer himself authored and relied on articles that have cited to Gagnon 1996. (Ex. 1020, ¶61.)

[5] On May 14, 2012, the European Examiner cited "Affinity Chromatography: the Fine Print" by Pete Gagnon (Ex. 1019, "Gagnon 1999"). (Ex. 1012 at 34.) This reference also disclosed that protein A leaching is caused by proteolysis. (Ex. 1019 at 3.)

field of antibody purification would not have looked to Balint because it is nonanalogous art. This is a startling new argument, given that Balint was cited by the Examiner during prosecution,[6] and the Applicant never previously claimed that Balint was nonanalogous. Balint is from "the same field of endeavor" because it relates to purification using protein A affinity chromatography. (Ex. 1020 at ¶¶48-53.) Balint is also reasonably pertinent to the particular problem with which the inventor was involved, because it directly addresses protein A leaching. (*Id.*, ¶¶48, 54-57.)

Although the claims are not limited to "industrial purification," Dr. Cramer asserts that the '799 Patent is narrowly directed to the field of "industrial purification of therapeutic proteins that comprise a CH2/CH3 region." (Ex. 2008, ¶47; Ex. 1020, ¶48.) Dr. Cramer was forced to admit at his deposition that practitioners in the field of industrial protein purification have relied on insights from the closely related fields of immunology and biochemistry. (Ex. 1022 at 38:19-39:3.) He also stated that protein A chromatography was first developed by practitioners of immunology and biochemistry, and that today, protein A immunoadsorbents are used for two main purposes: immunology diagnostics and protein purification. (Ex. 1022 at 40:16-41:3; Ex. 1020, ¶¶50-52.)

[6] Note that Balint was cited during prosecution of the '704 Patent. (Ex. 1010 at 50-52.)

While the '799 Patent does not include the word "industrial," it does mention "blood," "ascites fluid" and "serum" (Ex. 1001, 9:27, 10:62-63), which all relate to immunological applications. In addition, the '799 Patent was classified in U.S. Classes 530/413, 530/412 and 530/387.1, which relate to immunological separation and purification of proteins, for example by affinity chromatography or immunoadsorbents. (Ex. 1001 at 1; Ex. 1024 at 4, 6.) The '799 Patent's specification states that "[t]he present invention concerns protein purification." (Ex. 1001 at 1:16.) TRANSFUSION SCIENCE, in which Balint was published, addresses topics relating to protein separation and purification, such as immunoglobulins and immunohematology. (Ex. 1020, ¶49.) Balint and the '799 Patent relate to the same field of endeavor: protein chromatography.

Dr. Cramer collapsed his analysis of the "particular problem" into the "field of endeavor" question, and he has never articulated why Balint does not relate to protein A leaching. (Ex. 1020, ¶54.) Balint's use of blood and silica do not diminish its references to "protein A," "monoclonal antibody," "leach," "protease inhibitor," etc. (*Id.*, ¶57.) In fact, the '799 Patent encompasses the purification of blood, and explicitly contemplates using a silica chromatography matrix (Ex. 1001, 4:27-44). (*Id.*, ¶¶55-56.) Balint would have logically commended itself to the POSA's attention in attempting to solve the problem of protein A leaching. *See In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992). As Dr. Przybycien explains, "[n]one

of the differences between the Patentee's research and Balint would have dissuaded a POSA from finding, reading, and learning from the teachings in Balint."[7] (Ex. 1020, ¶57.)

V. SECONDARY CONSIDERATIONS DO NOT OVERCOME OBVIOUSNESS

As discussed above, Patent Owner's claim to unexpected results rests on the mistaken belief that proteolysis was not known to cause protein A leaching. Laboring under this misapprehension, Patent Owner failed to address Petitioner's evidence that a POSA would expect protein A leaching to follow an exponential curve with changes in temperature. (*Id.*, ¶¶73-75.) Accordingly, Patent Owner has not established that there are any unexpected results that have a nexus with the claimed methods.

Patent Owner's allegation of industry praise is also unavailing. (*Id.*, ¶¶73, 76-77.) Patent Owner has identified a single meeting at which Genentech's researchers presented their work. Dr. Cramer praises this meeting as "prestigious," but did not testify that it was particularly selective. Patent Owner did not provide evidence showing how the inventor's research was received by the attendees, or how it has been relied upon and praised since [redacted]. (*Id.*, ¶77.) Patent Owner also failed to prove that there was any nexus between the

[redacted]

presentation and the *claimed* invention. Indeed, the presentation may have been selected because it was by a major manufacturer, or because of the drug at issue, and not due to the data regarding the claimed temperature range of "about 10º C to about 18º C." (*Id*.)

The objective indicia alleged by Patent Owner are insufficient to disprove the strong case of *prima facie* obviousness discussed at Section IV above. (*Id.*, ¶78.) Accordingly, claims 1 to 3 and 5 to 11 of the '799 Patent are obvious under Grounds 3 through 8 as set forth in the Petition.

VI. CONCLUSION

For all of the reasons set forth above, as well as in the Petition and the Declarations of Dr. Przybycien (Exs. 1002 and 1020), claims 1 to 3 and 5 to 11 of the '799 Patent are invalid.

Dated: September 11, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of this Petitioner's Reply and all Exhibits filed together with this Reply were served electronically via electronic mail on September 11, 2017 upon the following attorneys of record for the Patent Owner:

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CERTIFICATE OF COMPLIANCE PURSUANT TO 37 C.F.R. § 42.24

I hereby certify that this Petition complies with the word count limitation of 37 C.F.R. § 42.24(c)(1) because the Reply contains 5,563 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(c).

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