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. Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,807,799 UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42

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List of Exhibits

(Filed Pursuant to 37 C.F.R. § 42.6)

Hospira Exhibit Number	Description
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
1008	U.S. Patent No. 7,485,704 to Fahrner et al.
1009	European Patent No. EP 1 648 940 B1 to Fahrner et al.
1010	Excerpts from the Prosecution File History of U.S. Patent No. 7,485,704
1011	Excerpts from the Prosecution File History of U.S. Patent No. 7,807,799
1012	Excerpts from the Prosecution File History of European Patent No. EP 1 648 940 B1

1013	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)

Hospira, Inc. requests *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 et seq. of claims 1 to 3 and 5 to 11 of U.S. Patent No. 7,807,799 (the "'799 Patent") to Fahrner et al., titled "Reducing Protein A Leaching During Protein A Affinity Chromatography" (Exhibit 1001).[1]

Pursuant to 37 C.F.R. § 42.15, the Petition Fee of $23,000 is being paid concurrently with the filing of this Petition. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to deposit account 232405.

I. OVERVIEW

Claims 1 to 3 and 5 to 11 of the '799 Patent (the "Challenged Claims") are invalid over the prior art cited in this Petition and should not have been issued. The Challenged Claims merely recite a well-known method of purifying proteins using protein A chromatography. Because Petitioner is, at a minimum, reasonably likely to prevail in demonstrating invalidity, this Petition should be granted and trial instituted on all of the Challenged Claims.

This Petition and the Declaration of Dr. Przybycien (Ex. 1002, the "Przybycien Decl.") explain that every element of the Challenged Claims was disclosed in the prior art, and also that the claimed subject matter would have been obvious to those of ordinary skill in the art. The '799 Patent as a whole is directed

[1] "Exhibit" shall hereinafter be referenced as "Ex."

to methods for reducing leaching of protein A during protein A affinity chromatography by reducing temperature or pH, or by adding protease inhibitors. Well before the earliest priority date of the '799 Patent, protein A affinity chromatography was widely used to purify proteins having a C_H2/C_H3 region. The Challenged Claims require the step of conducting protein A chromatography "at a temperature in the range from about 10° C to about 18° C." The Challenged Claims are anticipated and/or or rendered obvious by the prior art under Grounds 1 through 8 as set forth below.

It was known in the prior art to conduct protein A chromatography at ambient temperature, as well as at temperatures below ambient temperature. International Publication No. WO 95/22389 to Shadle et al. ("WO '389," Ex. 1003) as well as 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) ("van Sommeren," Ex. 1004) each disclose purifying an antibody using protein A affinity chromatography at temperature ranges overlapping with the claimed range of "about 10° C to about 18° C." As set forth in detail below, the temperature range of "about 10° C to about 18° C" is not critical to the operability of the claimed invention. In other words, performing protein A chromatography at the claimed range does not produce unexpected results when compared to the

temperature ranges disclosed in the prior art. Accordingly, the claims are anticipated and/or rendered obvious by WO '389 and van Sommeren.

Protein A chromatography is used to purify a protein of interest from other proteins produced in a cell. During protein A affinity chromatography, protein A that has been immobilized on a column is used to capture proteins that have a C_H2/C_H3 region. The captured proteins are separated from the other cellular proteins, which do not have a C_H2/C_H3 region, and therefore can be washed away. However, purifying proteins using this type of column chromatography can also cause some of the immobilized protein A to leach from the column. The alleged invention of the '799 Patent is based on the idea that protein A leaching is caused by protease activity. Protease activity can be reduced by lowering the temperature of the composition comprising the proteins, or by adding protease inhibitors to this composition. By extension, reducing temperature and adding protease inhibitors also must reduce protein A leaching.

However, the inventors of the '799 Patent did not invent the idea of reducing protein A leaching by reducing protease activity. As explained in this Petition, it was well-known in the art that protease activity could cause protein A leaching. It was also known that protease inhibitors and lower temperatures could inhibit protease activity during protein A chromatography. The temperature activation of proteolysis is not fundamentally different in the range of "about 10° C to about 18°

C" versus other temperature ranges. That is, a relative temperature reduction at any temperature at which chromatography is practicable, such as 3° C or 30° C, will lead to a reduction in protein A leaching. Protein A chromatography need not be practiced at the *claimed* range in order to achieve reductions in protein A leaching. Because the Challenged Claims recite conducting a known process at known parameters using known components, they are invalid under §§ 102 and 103 as set forth in detail below, and should be cancelled.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Hospira, Inc. ("Hospira" or "Petitioner") is the real party-in-interest for Petitioner. Out of an abundance of caution, and as a result of ongoing integration and reorganization activities, Petitioner identifies Pfizer Inc. as a real party-in-interest who, going forward, may have control or an interest in the outcome of this proceeding. No other parties exercised or could have exercised control over this Petition; no other parties funded or directed this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759-60.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

There are no judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

There are no child applications claiming benefit of U.S. Application No. 12/269,752 (the "'752 Application"), which issued as the '799 Patent, listed in the Patent Application Information Retrieval System.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Pursuant to 37 C.F.R. §§ 42.8(b)(3) and 42.10(a), Petitioner designates the following counsel:

Lead Counsel	Back-Up Counsel
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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to lead counsel at the contact information above. Hospira consents to service by electronic mail at tmeloro@willkie.com and mjohnson1@willkie.com. A Power of Attorney is being filed concurrently herewith under 37 C.F.R. § 41.10(b).

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the '799 Patent is available for IPR, and that Petitioner is not barred or estopped from requesting IPR of any claim of the '799 Patent on the grounds set forth herein.

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22)

Petitioner requests *inter partes* review and cancellation of claims 1 to 3 and 5 to 11 of the '799 Patent under 35 U.S.C. § 102 and/or § 103, as set forth herein. Petitioner's detailed statement of the reasons for the relief requested is provided in Section VIII below.

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Inter partes review of claims 1 to 3 and 5 to 11 of the '799 Patent is requested. Per 37 C.F.R. § 42.6(c), copies of the references are filed herewith. In support of the proposed grounds for invalidity, this Petition is accompanied by the Declaration of Todd M. Przybycien, Ph.D. (Ex. 1002), which explains the '799 Patent, its prosecution history and the teachings of the cited prior art.

A. The Challenged Claims and Grounds (37 C.F.R. §§ 42.104(b)(1) and (2))

Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), the following grounds are offered as reasons for cancelling the Challenged Claims of the '799 Patent:

Ground	Reference(s)	Statutory Basis	Challenged Claims
1	WO '389 (Ex. 1003)	§ 102(b)	1 and 5
2	van Sommeren (Ex. 1004)	§ 102(b)	1, 2 and 5
3	WO '389 (Ex. 1003)	§ 103(a)	1 and 5

Ground	Reference(s)	Statutory Basis	Challenged Claims
4	WO ’389 (Ex. 1003), Balint (Ex. 1005) & Potier (Ex. 1006)	§ 103(a)	1 to 3 and 5
5	WO ’389 (Ex. 1003) & the ’526 Patent (Ex. 1007)	§ 103(a)	2, 3 and 6 to 11
6	WO ’389 (Ex. 1003), Balint (Ex. 1005), Potier (Ex. 1006) & the ’526 Patent (Ex. 1007)	§ 103(a)	2, 3 and 6 to 11
7	van Sommeren (Ex. 1004)	§ 103(a)	1, 2 and 5
8	van Sommeren (Ex. 1004) & the ’526 Patent (Ex. 1007)	§ 103(a)	3 and 6 to 11

B. The ’799 Patent

The ’799 Patent issued on October 5, 2010 from the Application No. 12/269,752 (the “’752 Application”), which was filed on November 12, 2008. The ’752 Application was filed as a continuation of U.S. Application No. 10/877,532 (the “’532 Application”), now issued as U.S. Patent No. 7,485,704 (the “’704 Patent,” Ex. 1008). The ’532 Application claimed priority to Provisional Application No. 60/490,500 (the “500 Provisional”), which was filed on July 28, 2003. International Application No. PCT/US04/20480 and European Patent No. EP1648940 (“EP ’940,” Ex. 1009), among other foreign counterparts, also claim priority to the ’500 Provisional.

The inventors listed for each of these applications and patents are Robert L. Fahrner, Amy Laverdiere, Paul J. McDonald, and Rhona M. O'Leary. The '799 Patent, '704 Patent and EP '940 appear to be assigned to Genentech, Inc. The assignment by the inventors to Genentech, Inc. is located at reel/frame 015216/0197 of the U.S. Patent & Trademark Office's patent assignment database. No assignment has been recorded for the '799 Patent.

1. The Specification

According to the '799 Patent, the invention concerns a method for reducing leaching of protein A during protein A affinity chromatography. (Ex. 1001, 1:17-18.) The disclosed method includes reducing the temperature of a composition comprising the protein subjected to protein A affinity chromatography to below room temperature, such as "about 3° C. to about 20° C., e.g. from about 10° C. to about 18° C." (*Id.* at 18:4-9.) In another aspect, the alleged invention includes adding protease inhibitor(s) and/or lowering the pH of the composition in combination with the above-mentioned temperature reduction. (*Id.* at 18:17-21.) The specification acknowledged the relationship between protease activity and protein A leaching in the following way:

> "Protease activity" refers to the enzymatic activity of one or more proteases. Such activity may be measured indirectly by measuring leaching of protein A, for instance. The activity may be reduced by reducing temperature of a composition comprising the protease(s),

> and/or by adding one or more protease inhibitors to the composition etc.

(*Id.* at 5:1-6.) The '799 Patent does not provide any explanation or data showing how or why protease activity may be measured indirectly by measuring leaching of protein A. That is of no matter, however, because the relationship between protease activity and protein A leaching was known in the prior art and is not inventive subject matter.

Most of the specification is devoted to modes of carrying out protein A chromatography, including prior art techniques for generating proteins that have a C_H2/C_H3 region (*id.* at 7:48-17:28), and prior art methods for measuring protein A leaching (*id.* at 17:50-18:3). The specification explicitly discloses that protein A chromatography was a widely used tool for purifying antibodies, and that it efficiently separates them from host cell proteins, DNA, and other small molecules. (*Id.* at 20:7-9.)

The specification includes two experimental examples. Example 1 is titled "Temperature Reduction for Reducing Protein [A] Leaching During Protein [A] Affinity Chromatography" (*id.* at 20:3-4), and Example 2 is titled "Protease Inhibitors for Reducing Protein [A] Leaching During Protein [A] Affinity Chromatography" (*id.* at 24:54-55). The materials utilized in these examples, including the target proteins (*id.* at 20:19-31), chromatography columns (*id.* at 21:56-57) and protease inhibitors (*id.* at 25:22-52, Table 5), were all well-known

and commercially available before the date of the alleged invention. After testing the target proteins at a range of temperatures, the Patentee plotted the results in Figures 1 to 3, and superimposed exponential trend-lines, asserting that "[t]his type of non-linear correlation would be consistent with temperature-activated proteolytic cleavage." (*Id.* at 22:1-3.)

The Patentee concluded that, by controlling temperature of the harvested cell culture fluid ("HCCF") that was subjected to protein A chromatography, the level of protein A in the protein A pool could be controlled, or reduced. (*Id.* at 24:36-37.) For example, trastuzumab HCCF at pilot scale 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.) All of the experimental data shown in the '799 Patent relates to a mass ratio of protein A to the purified antibody, or protein A in parts per million. (*See*, *e.g.*, *id.* at 2-3 and 7, Figs. 1-3, 8 and 9.) Nothing in the disclosure established the absolute amount of target protein purified during the experimental examples, or the nature of the relationship between protein purification and temperature, or any other parameter.

2. The Claims

The '799 Patent concludes with 12 claims directed to methods of purifying a protein comprising a C_H2/C_H3 region. Claims 1 and 12 are independent, and claims 2 through 11 ultimately depend from claim 1, which provides:

> A method of purifying a protein which comprises a 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.

The further limitations of claims 2 and 3 relate to exposing the composition to a protease inhibitor. Dependent claim 5 recites that the protein to be purified is an antibody, and claims 6 through 9 recite further limitations regarding the claimed antibody. Claim 10 depends from claim 1, and recites that the protein is an immunoadhesin. Claim 11 further limits the immunoadhesin of claim 10 to a TNF receptor immunoadhesin.

C. Summary of the Prosecution Histories

1. The '704 Patent Prosecution History

The original 19 claims of the '532 Application were directed to methods of reducing leaching of protein A during protein A affinity chromatography. Claims 1, 12 and 13 were independent, and claim 1 provided the following:

> A method of purifying a protein which comprises a C_H2/C_H3 region, comprising reducing the temperature of a composition comprising the protein and one or more impurities subjected to protein A affinity chromatography in the range from about 3°C to about 20°C, wherein protein A leaching is reduced.

(Ex. 1010, '704 Patent File History at 38.) Claim 12 recited the additional steps of measuring leached protein A in the composition, and, if protein A leaching was detected, reducing the temperature of the composition. (*Id.* at 39.)

On October 6, 2006, the Examiner issued a Non-Final Office Action rejecting all 19 claims of the '532 Application as being either anticipated or obvious based on prior art. Horenstein et al., *Design and scaleup of downstream processing of monoclonal antibodies for cancer therapy: from research to clinical proof of principle*, 275 JOURNAL OF IMMUNOLOGICAL METHODS, 99 (2003) ("Horenstein") disclosed performing the protein A liquid chromatography at room temperature, about 22° C. The Examiner stated that this teaching met the claim limitation of "about 3°C to about 20°C." (*Id.* at 50.)

On January 4, 2007, the Applicant amended several claims in response to the rejections, including removing one instance of the word "about" so that amended claims 1, 12, 13 and 17 recited performing the chromatography "in the range from about 3°C to 20°C." (*Id.* at 55.) The Applicant argued that this amendment set 20° C as the upper limit of the temperature range for conducting protein A affinity chromatography, thereby ostensibly avoiding the teachings of Horenstein. (*Id.* at 59.)

However, the Examiner found this characterization of the temperature range, as well as the Applicant's other arguments, to be unpersuasive, and issued a Final Rejection on March 20, 2007. (*Id.* at 63-72.) There, the Examiner pointed out that there was no basis in the specification for the range of "about 3°C to 20°C" defining an upper cutoff of 20°C. (*Id.* at 65.) The Examiner also rejected the

claims under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,927,044 to Stahl et al. ("Stahl"). (*Id.* at 68.) Stahl was cited for teaching purifying fusion polypeptides having C_H2/C_H3 regions using protein A chromatography at 4° C. Stahl also disclosed the use of protease inhibitors, including ethylenediaminetetraacetic acid ("EDTA"), with protein A chromatography.

In response to this rejection, on June 14, 2007, the Applicant amended the temperature ranges to recite "about 3°C to about 18°C." (*Id.* at 74-75.) The Applicant argued that Horenstein was not anticipatory because it disclosed performing protein A chromatography at 22° C, which was not within the scope of the pending claims. (*Id.* at 79.) The Applicant also amended claim 1 to include additional recovering and measuring steps, similar to claim 12. (*Id.* at 74.) The Applicant asserted that the additional steps patentably distinguished the claimed method from Stahl. (*Id.* at 80.)

Following two more rejections on December 26, 2007 and July 14, 2008, the amended claims presented on November 12, 2008 were allowed. Claim 1 of the '704 Patent provides:

> 1. A method of purifying a protein which comprises a C_H2/C_H3 region comprising:
>
> a. subjecting a composition comprising said protein to protein A affinity chromatography to provide a recovered composition and measuring leached protein A in said recovered composition; and
>
> b. if greater than about 20 ng protein A per mg of said protein is measured in said recovered composition,

> then performing subsequent purification of compositions comprising said protein by protein A affinity chromatography at a temperature in the range from about 3° C. to about 18° C., such that protein A leaching is reduced.

(Ex. 1008, ’704 Patent at 35:45-59.) This claim recites subjecting a composition comprising a protein to protein A chromatography and measuring the leached protein A. If more than 20 ng/mg of protein A is measured, under the claims of the ’704 patent, the practitioner must perform a subsequent purification on other compositions at a reduced temperature in order to reduce the protein A leaching. (*See* Ex. 1010, ’704 Patent File History at 77-78.)

2. The ’799 Prosecution History

The ’752 Application was filed on November 12, 2008. Original claims 1 through 19 were cancelled, and new claims 20 to 33 were added in a preliminary amendment. New claim 20 recited:

> 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, such that protein A leaching is reduced.

(Ex. 1011, ’799 Patent File History at 4.)

The Examiner only issued one rejection during the prosecution of the ’752 Application. On October 9, 2009, she provisionally rejected the claims for double patenting based on the claims of the ’704 Patent. (*Id.* at 9.) The Examiner also

rejected the claims under 35 U.S.C. § 112, first and second paragraphs, for the phrases "a means for reducing protease activity" and "such that protein A leaching is reduced," respectively. (*Id.* at 10-11.) At the conclusion of the Office Action, the Examiner noted that Stahl and Horenstein respectively taught carrying out chromatography at both 4° C and 22° C, but that these temperatures were outside of the range required by pending claim 20. (*Id.* at 12.) Neither WO '389 nor van Sommeren was mentioned. In response, the Applicant deleted the language deemed unacceptable under § 112, and filed a terminal disclaimer over the '704 Patent. (*Id.* at 14-21.) After a minor Examiner's amendment to correct informalities, the '799 Patent proceeded to issue on October 5, 2010.

Although both WO '389 and van Sommeren were before the Examiner in the '704 and '799 Patents, neither of these references was relied upon in a rejection under § 102 or 103. The Examiner stated that the claimed feature not found in the previously *cited* prior art—i.e., Horenstein and Stahl—was the temperature range from about 10° C to about 18° C. (*Id*. at 11.) However, the Examiner failed to appreciate the disclosures in WO '389 and van Sommeren that clearly read on this claimed range.

3. The EP '940 Prosecution History

Citing an International Preliminary Report on Patentability dated January 30, 2006 (Ex. 1012, EP '940 File History at 6-14), the European Examiner also argued

that Horenstein's disclosure of performing the protein A liquid chromatograph at about 22° C encompassed the claim limitation of "about 3°C to about 20°C." (*Id.* at 10; *and see* 16-18.) In order to overcome this rejection, the European Applicant amended the temperature range to recite "from about 3°C to about 18°C." (*Id.* at 19.)

On May 14, 2012, the European Examiner stated that "no defined meaning can be attributed to 'about 3 °C' and 'about 18 °C.'" (*Id.* at 34.) In addition, WO '389 was cited for disclosing a temperature range of 18-25° C, and measuring protein A in the eluate. (*Id.*) In response, on September 21, 2012, the European Applicant amended the claims to recite "15° C" instead of "about 18° C." (*Id.* at 37-38.) The European Applicant noted that:

> The claims have been amended to refer to an upper temperature limit of 15° C based on the disclosure in Examples 1 and 2. This amendment deals with the objection raised by the ED based on prior art purification methods carried out at room temperature.

(*Id*.) The Applicant also noted the 15° C temperature used in the examples (as well as the results of reducing protein A leaching shown in the examples) can be "generalised" to the entire claimed invention instead of being limited to a particular experimental setting. (*Id*. at 39.) Similarly, on February 24, 2014, the Applicant argued temperature range of 3° C to 15° C produced the technical effect that is required for patentability, stating that "when undesirable protein A leaching

occurs at room temperature, it can be reduced through the use of a reduced temperature in the range of 3°C to 15°C." (*Id.* at 61.)

Like the claims of the '704 Patent, the claims ultimately granted in EP '940 narrowly recited multiple steps including carrying an initial chromatography step that results in greater than 20 ng leached protein A, subjecting another sample to protein A chromatography at a reduced temperature in the range from 3° C to 15° C, and measuring a reduced level of leaching ranging from 0 ng to 15 ng protein A per mg protein. (Ex. 1009, EP '940 at 20.)

D. Claim Construction (37 C.F.R. § 42.104(b)(3))

In accordance with 37 C.F.R. § 42.100(b), the Challenged Claims must be given their broadest reasonable construction in light of the specification of the '799 Patent. Except to the extent they are addressed below, the terms in the Challenged Claims are presumed to take on their ordinary and customary meaning based on the broadest reasonable construction of the claim language in view of the specification.

1. Claim 1

Claim 1 recites a method of purifying a protein that comprises a C_H2/C_H3 region by subjecting said protein to protein A affinity chromatography "at a temperature in the range from about 10° C to about 18° C." Petitioner submits that claim 1 should be construed as a method of purifying a protein, which does not

require reduction of protein A leaching. (Ex. 1002, Przybycien Decl. at ¶ 88.) In addition, the term "about" should be construed to mean ±3° C. (*Id.* at ¶ 82.)

A "method of purifying a protein" means a method of separating the protein of interest from the other proteins produced by the cell. (*See* Ex. 1001, '799 Patent at 1:53-66; Ex. 1002, Przybycien Decl. at ¶ 88.) A method of purifying a protein as recited in claim 1 is distinct from a method of purifying a protein such that protein A leaching is reduced. As discussed above, although the Applicant initially claimed a method "such that protein A leaching is reduced" during the prosecutions of both the '704 and '799 Patents, the Applicant specifically deleted this phrase from the Challenged Claims in order to overcome a rejection under § 112, second paragraph. (Ex. 1011, '799 Patent File History at 15.) Arguments and amendments made during the prosecution history must be examined to determine the meaning of terms in the claims. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). Moreover, the '704 Patent claims that do recite a reduction of protein A leaching also recite the additional steps of measuring protein A leaching and conducting a subsequent purification. (*See* Ex. 1001, '799 Patent, claim 12; Ex. 1008, '704 Patent, claims 1 and 12; Ex. 1009, EP '940, claim 1.) Interpreting "a method of purifying a protein" as recited in claim 1 of the Challenged Claims to require the reduction of protein A leaching would

impermissibly import limitations from the specification into the claims. *See Epos Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d 1338, 1341 (Fed. Cir. 2014).

As the term "about," recited in "from about 10° C to about 18° C," avoids a strict numerical boundary, "[i]t is appropriate to consider the effects of varying that parameter." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995). In construing the term "about" in its technological and stylistic context, courts may consider disclosures in the patent specification, prosecution history, and extrinsic evidence. *Id.* In this case, statements in related applications are particularly relevant in construing "about." *See Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007); *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1368-69 (Fed. Cir. 2007).

Petitioner submits that the term "about" would be understood to mean "±3° C." (*See* Ex. 1002, Przybycien Decl. at ¶ 81-82.) "About" was not explicitly defined in the specification, but it is apparent from the Examples disclosed in the specification that the Patentee considered "±3° C" to reflect typical temperature fluctuations during protein A chromatography. For example, the specification at column 21, lines 7-8 states that "[f]ive harvests were recovered through the protein A step. The HCCF was collected and held at 15 +/-3°C. for the duration of loading." (Ex. 1001, '799 Patent at 21:6-8; *see also*, *id.* at 23:61-63; 24:43-45.) Moreover, 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. (Ex. 1002, Przybycien Decl. at ¶ 82.)

During prosecution of the applications for the '704 Patent and EP '940, the Patentee implicitly acknowledged that "about" means at least ±2° C but less than ±4° C. As discussed above, the original claims recited a temperature range of "from about 3° C to about 20° C." The claims were rejected by the Examiner as anticipated by Horenstein, which disclosed performing protein A chromatography at 22° C. The Patentee acquiesced by amending the claims to recite "about 18° C" in order to overcome this rejection. Thus, the Patentee interpreted the term "about 20° C" to encompass 22° C, while the term "about 18° C" apparently excluded 22° C. This interpretation is consistent with construing "about" to mean "±3° C," as suggested by the specification. (Ex. 1002, Przybycien Decl. at ¶ 82.)

The remaining terminology employed in claim 1 consists of common technical terms, and the meaning of these terms needs no further construction.

2. Claims 2 and 3

Claim 2 further limits claim 1 by reciting the step of exposing the composition to a protease inhibitor. The term "exposing" is only used in the claims of the '799 Patent. However, it is clear from the specification that "exposing" the composition to a protease inhibitor means adding the protease inhibitor and composition together. (Ex. 1001, '799 Patent at 5:5, 18:19; Ex. 1002,

Przybycien Decl. at ¶ 100.) The term "protease inhibitor" is explicitly defined to be "a compound or composition which reduces, to some extent, the enzymatic activity of protease(s)"—a definition that comports with the customary meaning well known to those of ordinary skill in the art. (*See* Ex. 1002, Przybycien Decl. at ¶¶ 44.)

Claim 3 depends from claim 2, and specifies that the protease inhibitor is EDTA or 4-(2-aminoethyl)-benzenesulfonyl-fluoride, hydrochloride ("AEBSF"). These terms have a common technical meaning, and need no further construction.

3. Claims 5 to 9

Claim 5 further limits claim 1 by reciting that the protein is an antibody. Claims 6 and 8 additionally recite specific antigens to which the antibody binds, while claims 7 and 9 recite specific known antibodies. The terms "bind," "antibody," "antigen," and the particular antigens and antibodies recited are all common technical terms which are either defined in the specification, or require no further construction.

4. Claims 10 and 11

Claim 10 further limits claim 1 by reciting that the protein is an immunoadhesin. Claim 11 further recites that the immunoadhesin is a TNF receptor immunoadhesin. These terms are common technical terms in the art, and the specification reflects the widely held understanding that an immunoadhesin

"designates antibody-like molecules which combine the 'binding domain' of a heterologous 'adhesin' protein . . . with the effector functions of an immunoglobulin constant domain." (Ex. 1001, '799 Patent at 6:53-57.) The terms found in claims 10 and 11 require no further construction.

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") is presumed to be aware of all pertinent art, think along the line of conventional wisdom, and possess ordinary creativity in the pertinent field. A person of ordinary skill in the art is possessed of "common sense" and is "not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). The education level of a person of ordinary skill in the art would likely include at least a graduate degree, such as a Ph.D., and several years of postgraduate training or practical experience in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others. (Ex. 1002, Przybycien Decl. at ¶ 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.*)

VII. TECHNICAL BACKGROUND AND THE PRIOR ART

As stated in the '799 Patent, and as is well known in the art, proteins of interest are produced by cells, including cells engineered by the insertion of

recombinant plasmids. Protein A chromatography had been widely used for decades before the alleged invention of the '799 Patent as a way of isolating proteins of interest from other proteins produced by cell lines. (Ex. 1002, Przybycien Decl. at ¶¶ 11, 33 and 80; *see also*, H. 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).)

Protein A affinity chromatography is a type of adsorption chromatography based on the specific and reversible interaction of a biologically functional pair of molecules: the bacterial Ig Fc receptor protein A, and the C_H2/C_H3 region, which is present on numerous proteins of biological interest. (Ex. 1007, '526 Patent at 1:65-2:5.) When a composition comprising a mixture of the target protein and undesired components contacts a column having protein A immobilized on it, the target protein binds to the immobilized protein A with a high affinity, and the remaining components that do not bind can be removed. (Ex. 1002, Przybycien Decl. at ¶¶ 33, 41.) Several parameters can affect the performance of the chromatography column, including temperature, pH, the nature of the target protein, and the presence of impurities such as proteases. (Ex. 1004, van Sommeren at 6; Ex. 1002, Przybycien Decl. at ¶ 70.)

A. WO ’389 (Ex. 1003)

WO ’389, titled *Antibody Purification*, is the publication of an international patent application by SmithKline Beecham Corporation on behalf of Shadle et al. (Ex. 1003.) The WO ’389 inventors recognized that while protein A affinity column chromatography is widely used, “elution of antibody from such columns can result in leaching of residual Protein A from the support.” (*Id.* at 6.) The disclosed invention involves purifying an IgG antibody by sequentially subjecting a medium containing the antibody to: (1) protein A chromatography, (2) ion exchange chromatography, and (3) hydrophobic interaction chromatography. (*Id.*) Example 1 consists of these three purification steps, and “[a]ll steps are carried out at room temperature (18 - 25 °C).” (*Id.* at 15.)

WO ’389 was published on August 24, 1995, more than one year before July 28, 2003, the earliest possible priority date of the ’799 Patent. Therefore, it is available as prior art under 35 U.S.C. § 102(b).

B. Van Sommeren (Ex. 1004)

Van Sommeren reports the results obtained from varying several parameters while conducting protein A chromatography on mouse monoclonal IgG_1 antibodies, including temperature, flow rate, and composition of a binding buffer. (Ex. 1004 at 6.) Specifically, the effect of temperature during protein A chromatography, “4°C versus ambient temperature (AT) (20-25°C),” produced

varying results for several antibodies that were purified. (*Id.* at 16.) Van Sommeren disclosed that it was already known that temperature could have a significant effect on the protein A binding capacity of certain antibodies. (*Id.* at 17.) Van Sommeren also teaches that proteolytic activity in starting materials—i.e., the HCCF—and purified fractions resulted in contamination. (*Id*. at 18-19.) As a remedy for this contamination, van Sommeren suggests that addition of pepstatin A, a protease inhibitor. (*Id.* at 19.)

As it was published more than one year before the priority date of the '799 Patent, van Sommeren is available as prior art under 35 U.S.C. § 102(b).

C. Balint (Ex. 1005)

Evidence for Proteolytic Cleavage of Covalently Bound Protein A from a Silica Based Extracorporeal Immunoadsorbent and Lack of Relationship to Treatment Effects, by J.P. Balint, Jr. and F.R. Jones ("Balint"), discloses studies conducted to evaluate potential causes of the release of covalently bound protein A from a silica-based extracorporeal immunoadsorbent matrix—a clinical application of protein A chromatography. (Ex. 1005 at 4.) Initial investigations showed that protein A was released from the matrix in a linear fashion with time, indicating some factor beyond mere binding of the IgG antibody to the immunoadsorbent is responsible for the leakage. (*Id.* at 7.) Using several conventional protease inhibitors, including EDTA, the endogenous proteolytic activity was reduced, and

so was the concomitant release of protein A. (*Id.* at 7-8.) The authors of Balint concluded that leakage of protein A was due to inherent endogenous proteolytic activity, which cleaved protein fragments from the matrix. (*Id*. at 8.)

Balint was published in 1995, more than one year before the priority date of the '799 Patent. Accordingly, Balint is prior art under 35 U.S.C. § 102(b).

D. Potier (Ex. 1006)

Temperature-dependent changes in proteolytic activities and protein composition in the psychrotropic bacterium Arthrobacter globiformis S_I55, by Potier et al. ("Potier"), discloses research regarding temperature-dependent changes in proteolytic activities in the bacterium *Arthrobacter globiformis S_I55*. (Ex. 1006 at 5.) The authors studied the variation in proteolytic activities in extracts of *A. globiformis S_I55* after a sudden increase in temperature, as well as the effect of growth temperature on proteolytic activities. (*Id.* at 7-9.) Their experiments showed that degradation caused by proteolysis increased with temperature and increased faster at higher temperatures. (*Id*.)

Potier was published in 1990, more than one year before the priority date of the '799 Patent. Accordingly, Potier is prior art under 35 U.S.C. § 102(b).

E. The '526 Patent (Ex. 1007)

U.S. Patent No. 6,127,526 (the "'526 Patent"), titled *Protein Purification by Protein A Chromatography*, lists Gregory S. Blank as the inventor, and Genentech,

Inc. as the assignee. The ’526 Patent is concerned with methods for purifying proteins of interest that comprise a C_H2/C_H3 region, and therefore are amenable to purification by protein A chromatography. (Ex. 1007, ’526 Patent at 2:63-65.) The ’526 Patent also discloses specific examples of proteins that may be purified, including humanized anti-HER2 antibody, humanized anti-IgE antibody, chimeric anti-CD20 antibody, and TNF receptor immunoadhesion. (*Id.* at 13:67-14:5.) The ’526 Patent describes steps for addressing contaminants in the protein preparation that adhere to the glass or silica surface of the solid phase. The ’526 Patent discloses an intermediate wash step, which serves to remove the contaminants, but not the immobilized protein A or the bound protein of interest. (*Id.* at 2:8-28.) In addition, the ’526 Patent discloses that a buffer used to equilibrate the solid phase could include EDTA. (*E.g.*, *id.* at 3:35, 14:28-30.) EDTA is known to be effective as a protease inhibitor. (Ex. 1002, Przybycien Decl. at ¶¶ 16, 17, 73, 77.)

The ’526 Patent issued in 2000, more than one year prior to the priority date of the ’799 Patent. Therefore, the ’526 Patent is prior art under 35 U.S.C. § 102(b).

VIII. STATEMENT OF THE REASONS FOR THE RELIEF REQUESTED (37 C.F.R. §§ 42.104(b)(4) and (5))

A. Ground 1: WO '389 Anticipates Claims 1 and 5

WO '389 anticipates claims 1 and 5 as shown in the chart and discussed below. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 90-95.)

Claim Limitations	Disclosed in WO '389
1. A method of purifying a protein which comprises a C_H2/C_H3 region,	"9. A method for the purification of an IgG antibody . . ." (Ex. 1003 at 42)
comprising subjecting a composition comprising said protein to protein A affinity chromatography	"9. A method for the purification of an IgG antibody . . . comprising sequentially subjecting the medium to (a) Protein A affinity chromatography." (Ex. 1003 at 42)
at a temperature in the range from about 10 °C. to about 18 °C.	"The process in its most preferred embodiment consists of three purification steps (Protein A affinity, cation exchange, and hydrophobic interaction chromatography) . . . All steps are carried out at room temperature (18 – 25 °C)." (Ex. 1003 at 15)
5. The method of claim 1 wherein the protein is an antibody.	"9. A method for the purification of an IgG antibody . . ." (Ex. 1003 at 42)

WO '389 discloses that "Staphylococcal Protein A is known to bind certain antibodies of the IgG class." (Ex. 1003 at 4.) IgG is a protein comprising a C_H2/C_H3 region. (Ex. 1002, Przybycien Decl. at ¶ 90.) The '799 Patent confirms that "[i]n a particularly preferred embodiment, the adhesin amino acid sequence is fused to (a) the hinge region and C_H2 and C_H3 or (b) the C_H1, hinge, C_H2 and C_H3

domains, of an IgG heavy chain." (Ex. 1001, '799 Patent at 14:66-15:2.) In one aspect, the invention of WO '389 provides for the purification of an IgG antibody from conditioned cell culture medium comprising subjecting the medium to protein A chromatography. (Ex. 1003, WO '389 at 6, 42.) Therefore, WO '389 discloses a method that uses protein A chromatography to purify an antibody having a C_H2/C_H3 region as claimed in claims 1 and 5.

The process taught by WO '389 in its most preferred embodiment includes a purification step using protein A affinity chromatography, which is carried out at 18-25° C. (*Id.* at 15.) The disclosed range of 18 to 25° C overlaps with the claimed range of about 10° C to about 18° C. There is no evidence that the claimed range is critical to a method of purifying a protein using protein A affinity chromatography. (Ex. 1002, Przybycien Decl. at ¶¶ 88-89.) Also, although the claims do not require any reduction in protein A leaching, there is likewise no evidence that the claimed range is critical to a method of reducing protein A leaching. (*Id.* at ¶ 87.) For at least these reasons, the temperature range of 18 to 25° C anticipates the claimed range of about 10° C to about 18° C.

Anticipation of a patent requires that a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). Where the patent claims a range, it is anticipated by prior art disclosing a point within the range. *Titanium*

Metals Corp. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985). And, where the prior art discloses an overlapping range, it anticipates 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). For example, criticality has been found where only a narrow range of temperature 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.*, 411 F.3d 991 (Fed. Cir. 2006). Criticality of a claimed range may also be established by evidence of unexpected results. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). The unexpected results must be commensurate in scope with the claimed range. *Id.* at 1331.

Although the specification of the '799 Patent discusses reducing protein A leaching, the Challenged Claims, including independent claim 1, do not recite a maximum level of leaching or an objective degree of protein A leaching reduction. The claimed method should not be construed to include a reduction of protein A leaching, given that this term was removed from the claims in order to overcome a

rejection based on § 112, second paragraph. (Ex. 1002, Przybycien Decl. at ¶ 88.) Instead, the claims should be construed as simply running protein A chromatography at about 10° C to about 18° C.

A person of ordinary skill in the art would understand the temperature range of about 10° C to about 18° C is not critical to the operability of protein A chromatography, nor does the recited temperature range produce any surprising, unknown, or unexpected result. (*Id.* at ¶¶ 85-89, 93-95.) The Patentee has broadly claimed methods of purifying proteins, including methods performed at broader temperature ranges than "about 10° C to about 18° C," but it never proffered any evidence regarding the effect of temperature on separating the protein of interest from other proteins produced in the cell. (*Id.* at ¶ 51.) All of the experimental data in the '799 Patent relates to protein A leaching, which does not directly reflect the level of purification obtained by conducting chromatography. (*Id.*) Any relationship between temperature and purification would be predictable to one of ordinary skill in the art, and the claimed range does not represent a critical region where purification is unexpectedly enhanced. (*Id.* at ¶¶ 85-89.) Unlike the case of *Atofina*, the prior art amply demonstrates that protein A chromatography is effective at a wide range of temperatures above and below the claimed temperature range. (*Id.* at 84.)

Even if the Challenged Claims were interpreted to require the reduction of protein A leaching, a POSA would still not consider the claimed range to be critical. The Patentee limited the claims to about 10 °C to about 18 °C in order to avoid rejections based on prior art cited during the '704 Patent's prosecution. (*Id.* at ¶¶ 52-65, 85.) The Patentee also claimed or attempted to claim other arbitrary ranges for the same reasons, including "about 3° C to 20° C," "about 3° C to about 18° C" and "3° C to 15° C." (*Id.* at ¶ 86.) Thus, the temperature range of about 10° C to about 18° C cannot be critical if these other arbitrary ranges also encompass the alleged invention. (*Id.* at ¶¶ 87, 89.)

In fact the results disclosed in the '799 Patent prove that the range of about 10° C to about 18° C is not critical. The data reported in the '799 Patent does nothing more than confirm what would be expected by a POSA: lower temperatures result in less leaching of protein A. (*Id.* at ¶ 93.) Relying on this principle, the patentee disclosed a method of conducting chromatography at temperatures as low as 3° C, even though its lowest temperature trials were conducted at 10° C. (Ex. 1001, '799 Patent at 2-3, Figs. 1-3; 18:8.) The Patentee admits that protein A leaching for most of the antibodies tested was only slightly affected even at temperatures over the range extending to 30° C. (*Id.* at 21:61-64.) Furthermore, the patent does not provide any evidence that these marginal

improvements in protein A leaching improved the overall purification process. (Ex. 1002, Przybycien Decl. at ¶ 87.)

POSAs were aware that reactions between protein A and proteases are temperature-dependent well before the date of the alleged invention. (*Id.* at ¶¶ 16, 87.) The temperature dependence of chemical reaction rate is well-described by the commonly used exponential relationship of the Arrhenius equation. (*Id.* at ¶¶ 49, 87.) As such, the effect of temperature on protein A leaching (which is essentially proteolysis) at the claimed range is predictable, based on the predictable course of temperature-activated proteolysis. (*Id.* at ¶ 93.) A POSA would have expected an intermediate temperature range to demonstrate intermediate reductions of protein A leaching, which is borne out by empirical evidence. (*Id*.) Therefore, WO '389 anticipates claims 1 and 5.

B. Ground 2: Van Sommeren Anticipates Claims 1, 2, and 5

The disclosures set forth in van Sommeren anticipate claims 1, 2 and 5 as shown in the chart below. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 96-100.)

Claim Limitations	**Disclosed in Van Sommeren**
1. A method of purifying a protein which comprises a C_H2/C_H3 region,	"The purification of immunoglobulins (IgG) . . ." (Ex. 1004 at 6)

Claim Limitations	**Disclosed in Van Sommeren**
comprising subjecting a composition comprising said protein to protein A affinity chromatography	"The purification of immunoglobulins (IgG), in particular mouse monoclonal antibodies (mabs), using affinity chromatography with protein A as ligand is very popular . . ." (Ex. 1004 at 6)
at a temperature in the range from about 10 ° C. to about 18 ° C.	"The effect of temperature, 4 °C versus ambient temperature (AT) (20-25 °C), was studied for the mabs OT-hCG-1C, 4D, 3A, 6A and 7B and OT-HIV-4A and 4B . . ." (Ex. 1004 at 16)
2. The method of claim 1 further comprising exposing the composition subjected to protein A affinity chromatography to a protease inhibitor.	"Whether or not degradation of the IgG molecule occurs, depends among other factors on pH and subclass of the mab. However, if required, the activity of cathepsin D can be inhibited by addition of pepstatin A." (Ex. 1004 at 19)
5. The method of claim 1 wherein the protein is an antibody.	"The purification of immunoglobulins (IgG) . . ." (Ex. 1004 at 6)

Petitioner advances arguments based on two anticipating references because of the differences between the teachings of WO '389 and van Sommeren concerning, among other claimed features, temperature ranges for conducting protein A chromatography. Claim 1 of the '799 Patent recites the temperature range "from about 10° C to about 18° C." As discussed in detail above, WO '389 discloses the temperature range of 18 to 25 °C, which explicitly overlaps with the claimed range. As set forth in the chart above, and in detail below, van Sommeren

discloses conducting protein A chromatography at 4° C and at 20 to 25° C. While both of these references anticipate claims 1 and 5, and van Sommeren additionally anticipates claim 2, the differences in the teachings and context of each reference necessitate distinct sets of invalidity arguments.

Van Sommeren discloses each and every limitation of claims 1, 2 and 5. *See In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). It discloses that purifying antibodies, including IgG, using protein A chromatography "is very popular because of its simplicity, speed and efficiency." (Ex. 1004, van Sommeren, at 6.) As discussed above, IgG antibodies are proteins that comprise a C_H2/C_H3 region. Therefore, van Sommeren discloses a method that uses protein A chromatography to purify an antibody having a C_H2/C_H3 region as provided in claims 1 and 5.

Van Sommeren also discloses conducting protein A chromatography on antibodies at 4° C and at 20 to 25° C. (*Id.* at 16.) A POSA would immediately appreciate from this disclosure that protein A chromatography could be conducted at temperatures between 4° C and at 20 to 25° C as well. (Ex. 1002, Przybycien Decl. at ¶ 97.) Protein A chromatography works when proteins of interest bind to immobilized protein A. (*Id.*) As Dr. Przybycien explains in his Declaration, a POSA would expect any changes in protein A binding to smoothly increase or decrease with changes in temperature. (*Id.*) By disclosing the purification of

antibodies at 4° C and at 20 to 25° C, van Sommeren teaches a broad span of workable temperatures that encompasses the claimed range of about 10° C to about 18° C. (*Id.*) As discussed below, the claimed range of about 10° C to about 18° C is not critical to conducting protein A chromatography, or to reducing protein A leaching.

Additionally, the higher range of temperatures disclosed in van Sommeren, 20 to 25° C, independently overlaps the claimed range of about 10° C to about 18° C. As discussed above, examples disclosed in the '799 Patent show that the Patentee considered "±3° C" to reflect typical temperature fluctuations during protein A chromatography. In addition, during prosecution of the '704 Patent, the Patentee made amendments indicating that a temperature differential of ±3° C was encompassed by "about." (Ex. 1010, '704 Patent File History at 74-75.) Therefore, the upper range of 20-25° C also overlaps with the claimed range of about 10° C to about 18° C because the "about" in "about 18° C" means "±3° C." (Ex. 1002, Przybycien Decl. at ¶ 98.)

Where the prior art discloses an overlapping or broader range, it anticipates unless the claimed range is critical to the operability of the claimed invention. *Ineos USA LLC*, 783 F.3d at 871; *ClearValue, Inc.*, 668 F.3d at 1344-45. The claimed temperature range of about 10° C to about 18° C is not critical to the operability of the claimed invention, or to the reduction of protein A leaching for

the same reasons as discussed above regarding WO '389. (*See* Section VIII(A).) For example, the Patentee cannot show that purification of proteins at the claimed temperature is unexpectedly enhanced. There is no demonstrated difference in the level of purification achievable at the claimed temperature range of about 10° C to about 18° C versus the prior art temperature ranges of 4° C to 20-25° C, or 20-25° C. (Ex. 1002, Przybycien Decl. at ¶¶ 87, 89.) Accordingly, claims 1 and 5 are anticipated by van Sommeren.

In addition, van Sommeren explicitly discloses the use of a protease inhibitor, pepstatin A, to reduce the activity of proteases known to cause degradation in the composition comprising the protein of interest. (Ex. 1004 at 19.) This anticipates claim 2, which recites exposing the composition subjected to protein A affinity chromatography to a protease inhibitor. (Ex. 1002, Przybycien Decl. at ¶¶ 99, 100.) Therefore, in addition to claims 1 and 5 as discussed above, claim 2 is also anticipated by van Sommeren.

C. Ground 3: WO '389 Renders Claims 1 and 5 Obvious

A patent claim is invalid under 35 U.S.C. § 103(a) if 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 pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). In view of the disclosures of WO '389 as discussed above, it would have been obvious for a person of ordinary skill in the art to perform protein A

chromatography on an antibody at within the claimed range of about 10 °C to about 18° C. (Ex. 1002, Przybycien Decl. at ¶¶ 101-104.)

In cases involving overlapping ranges, courts have consistently held that even a slight overlap in range establishes a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that the claimed ranges were encompassed by overlapping ranges disclosed in a single prior art reference). "[T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious . . ." *Id.* at 1330. If the applicant can show criticality in the claimed range by evidence of unexpected results, the overlapping ranges may be patentable. *Id.* However, 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)). Furthermore, a court may take into account the creative steps that a person of ordinary skill in the art would employ. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

WO '389 teaches that protein A chromatography may be used to purify antibodies out at "about 18° C." Since the claimed range is not critical, the claims are obvious simply because of the overlap at "about 18°C." Also, a person of ordinary skill in the art at the time of the alleged invention would have known that

performing protein A chromatography at temperatures of about 18° C, or even at lower temperatures within the claimed range, would purify a target protein. (Ex. 1003, WO '389 at 13; Ex. 1002, Przybycien Decl. at ¶¶ 103-104.) It would have been obvious to a person of ordinary skill in the art to use protein A chromatography for purifying antibodies at various temperatures based on widely known principles of chemical kinetics to achieve a desired result, such as lowering temperature to reduce proteolysis. (Ex. 1002, Przybycien Decl. at ¶¶ 102-104.)

WO '389 also discloses that while protein A chromatography is widely used to purify antibodies, it can lead to leaching of residual protein A from the chromatography column. (Ex. 1003 at 6.) The temperature for conducting protein A chromatography is clearly a "result-effective variable," rendering optimization of the overlapping temperature range "within the grasp of one of ordinary skill in the art." *In re Applied Materials*, 692 F.3d at 1295. Given 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. (Ex. 1002, Przybycien Decl. at ¶ 103.) Claims 1 and 5 are therefore obvious in view of WO '389 alone.

D. Ground 4: WO '389, Balint and Potier Render Claims 1 to 3 and 5 Obvious

Claims 1 to 3 and 5 are obvious under 35 U.S.C. § 103 in view of WO '389, and further in view of Balint and Potier as shown in the chart below. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 105-108.)

Claim Limitations	**Disclosed in WO '389, Balint and Potier**
1. A method of purifying a protein which comprises a C_H2/C_H3 region,	"9. A method for the purification of an IgG antibody . . ." (Ex. 1003 at 42)
comprising subjecting a composition comprising said protein to protein A affinity chromatography	"9. A method for the purification of an IgG antibody . . . comprising sequentially subjecting the medium to (a) Protein A affinity chromatography." (Ex. 1003 at 42)
at a temperature in the range from about 10 ° C. to about 18 ° C.	"The process in its most preferred embodiment consists of three purification steps (Protein A affinity, cation exchange, and hydrophobic interaction chromatography) . . . All steps are carried out at room temperature (18 - 25°C)." (Ex. 1003 at 15) "Prevention of this proteolytic activity also significantly inhibited the release of covalently bound SpA from the immunoadsorbent matrix upon contact with plasma or serum samples." (Ex. 1005 at 4) "The temperature dependence of the rate of chemical reactions is well-described by the commonly used exponential relationship of the

Claim Limitations	**Disclosed in WO '389, Balint and Potier**
	Arrhenius equation. Not surprisingly, the amount of protein A leached per mg of target protein generally follows an exponential trend as well." (Ex. 1002 at ¶ 87) "The temperature shift from 10 to 32° C resulted in increased amounts of ATP-stimulated proteolysis (up to 80%), such that within 1 h, the cells possessed about twice the initial ATP-stimulated activity present prior to the temperature change." (Ex. 1006 at 9)
2. The method of claim 1 further comprising exposing the composition subjected to protein A affinity chromatography to a protease inhibitor.	"To assess the effect of conventional protease inhibitors, a cocktail was prepared with protease inhibitors obtained from Boehringer Mannheim." (Ex. 1005 at 6.)
3. The method of claim 2 wherein the protease inhibitor is EDTA or 4-(2-aminoethyl)-benzenesulfonyl-fluoride, hydrochloride (AEBSF).	"Six water soluble protease inhibitors were utilized and dissolved in 1 ml of water; antipaindihydrochloride (3 mg/ml), (4-amidinophenyl)-methanesulfonylfluoride (1 mg/ml), aprotinin (0.5 mg/ml), EDTA-Na_2 . . ." (Ex. 1005 at 6)
5. The method of claim 1 wherein the protein is an antibody.	"9. A method for the purification of an IgG antibody . . ." (Ex. 1003 at 42)

In addition to the teachings of WO '389 as discussed above regarding Grounds 1 and 3, which render claims 1 and 5 anticipated and/or obvious, Balint teaches that protein A leaching following affinity chromatography "is due to

inherent endogenous proteolytic activity which cleaves protein fragments from the matrix." (Ex. 1005 at 4.) As discussed above, and explained by Dr. Przybycien, it was generally known in the prior art that lower temperatures tend to reduce the activity of proteases. (Ex. 1002, Przybycien Decl. at ¶¶ 87, 105.) Potier also explicitly discloses that degradation due to protease activity increases with rising temperature, which was generally known in the prior art. (Ex. 1006 at 7, 9; Ex. 1002, Przybycien Decl. at ¶ 105.) Therefore, a POSA would have understood that lowering temperature reduces the activity of proteases, and consequently reduces protein A leaching. (Ex. 1002, Przybycien Decl. at ¶ 105.) Understanding this, before the time of the alleged invention, a POSA would have opted to perform the protein A chromatography at lower temperatures in order to reduce protein A leaching. (*Id*.)

A POSA would have been motivated to practice the protein A chromatography at intermediate temperatures such as the claimed range, rather than the coldest available range. (*Id.* at ¶ 104.) 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. (*Id*.) 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.*) Therefore, claim 1 is obvious over WO '389, and further in view of Balint and Potier.

Claim 2 recites exposing the composition subjected to purification to a protease inhibitor, and claim 3 specifically recites that the protease inhibitor is either EDTA or AEBSF. Balint explicitly discloses the use of protease inhibitors, including EDTA, to lower the observed activity of proteases during protein A chromatography. A POSA would have been motivated to combine the use of EDTA as taught by Balint with the obvious method of practicing protein A chromatography at an intermediate temperature encompassed by the combined teachings of WO '389, Balint and Potier. (*Id.* at ¶ 108.) A POSA would have made this combination in order to further reduce the leakage of protein A—thereby preserving costly column materials while obtaining effective purification of the target antibody. (*Id.*) A POSA would have had a reasonable expectation of success for making this combination, based on the well-characterized properties of the protease inhibitors taught by Balint. (*Id.*) The combined teachings of WO '389, Balint and Potier as applied to claim 1, in addition to the disclosure in Balint regarding EDTA, therefore render both claim 2 and claim 3 obvious.

Claim 5 further limits the method of claim 1 by reciting that the purified protein is an antibody. WO '389 is entitled "Antibody Purification," and specifically relates to using protein A chromatography to purify antibody molecule

proteins, such as the IgG antibody. (Ex. 1003 at 1, Abstract.) Therefore, claim 5 is also obvious in view of the combined teachings of WO '389, Balint and Potier as set forth above with regard to claim 1. (Ex. 1002, Przybycien Decl. at ¶ 105.)

For at least these reasons, claims 1 through 3 and 5 would have been obvious over of WO '389, and further in view of Balint and Potier.

E. Ground 5: WO '389 and the '526 Patent Render Claims 2, 3 and 6 to 11 Obvious

Claims 2, 3 and 6 to 11 are obvious under 35 U.S.C. § 103 in view of WO '389 as set forth above with regard to claims 1 and 5, and further in view of the '526 Patent as discussed below. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 109-115.) Claims 2 and 3 provide:

Claim Limitations	**Disclosed in WO '389 and the '526 Patent**
2. The method of claim 1 further comprising exposing the composition subjected to protein A affinity chromatography to a protease inhibitor.	The teachings of WO '389 relevant to claim 1 are set forth above in Grounds 1 and 3. "The equilibration buffer of the example was 25 mM Tris, 25 mM NaCl, 5 mM EDTA, pH 7.1." (Ex. 1007 at 3:34-35)
3. The method of claim 2 wherein the protease inhibitor is EDTA or 4-(2-aminoethyl)-benzenesulfonyl-fluoride, hydrochloride (AEBSF).	"The solid phase for the Protein A chromatography is equilibrated with a suitable buffer. For example, the equilibration buffer may be 25 mM Tris, 25 mM NaCl, 5 mM EDTA, pH 7.1." (Ex. 1007 at 14:27-30)

Independent claim 1, from which claims 2 and 3 depend, is anticipated and/or rendered obvious by WO ’389 as described in Grounds 1 and 3. (*See* Sections VIII(A) and (C).) Like WO ’389, the ’526 Patent discloses using protein A chromatography to purify a target protein. (Ex. 1007 at 1, Abstract.) 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.*) For at least these reasons, claims 2 and 3 would have been obvious in view of the combination of WO ’389 and the ’526 Patent.

As discussed above with regard to Grounds 1 and 3, claims 1 and 5 are anticipated or obvious in view of WO ’389 alone. Claim 1 recites that the type of protein that is subjected to protein A chromatography according to the claimed method has a C_H2/C_H3 region, and claim 5 recites that this protein is an antibody. Claims 6 through 9 limit the type of antibody that is subjected to protein A chromatography according to the claimed method.

Claim Limitations	**Disclosed in WO '389 and the '526 Patent**
6. The method of claim 5 wherein the antibody binds an antigen selected from the group consisting of HER2, vascular endothelial growth factor (VEGF), IgE, CD20, CD40, CD11a, tissue factor (TF), prostate stem cell antigen (PSCA), interleukin-8(IL-8), epidermal growth factor receptor (EGFR), HER3, HER4, α4β7 and α5β3.	The teachings of WO '389 relevant to claims 1 and 5 are set forth above in Grounds 1 and 3. "Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as . . . CD20 . . . members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor . . ." (Ex. 1007 at 6:13-16)
7. The method of claim 5 wherein the antibody is selected from the group consisting of Trastuzumab, humanized 2C4, humanized CD11a antibody, and humanized VEGF antibody.	"Preferred molecular targets for antibodies encompassed by the present invention include . . . 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 . . ." (Ex. 1007 at 6:13-20)
8. The method of claim 5 wherein the antibody binds HER2 antigen.	"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 . . ." (Ex. 1007 at 6:13-16)
9. The method of claim 8 wherein the antibody is Trastuzumab or humanized 2C4.	"Protein A chromatography was the initial chromatography step in the purification of the C_H2/C_H3 region-containing protein; humanized anti-HER2 antibody (humAb4D5-8) . . ." (Ex. 1007 at 15:22-24, Example 1)

Claims 10 and 11 also ultimately depend from claim 1, further limiting the purified protein to an immunoadhesin.

Claim Limitations	**Disclosed in WO '389 and the '526 Patent**
10. The method of claim 1 wherein the protein is an immunoadhesin.	The teachings of WO '389 relevant to claim 1 are set forth above in Grounds 1 and 3. "In preferred embodiments, the protein is an antibody (e.g. an anti-HER2, anti-IgE or anti-CD20 antibody) or an immunoadhesin . . ." (*Id.* at 2:38-39.)
11. The method of claim 10 wherein the immunoadhesin is a TNF receptor immunoadhesin.	"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 2:38-39.)

Protein A chromatography can be used to purify any protein having a C_H2/C_H3 region. (Ex. 1007, '526 Patent at 2:63-67.) Dr. Przybycien explains that the types of antibodies amenable to protein A chromatography were well known in the prior art. (Ex. 1002, Przybycien Decl. at ¶¶ 113, 115.) Each of the proteins recited in the claims includes a C_H2/C_H3 region. (*Id*. at ¶ 113)

The '526 Patent discloses the purification of proteins, including antibodies, that have a C_H2/C_H3 region. (Ex. 1007, '526 Patent at 2:28-40.) The '526 Patent teaches that members of the ErbB receptor family of antibodies, such as HER2, HER3 and HER4 receptors, are preferred molecular targets for protein A

chromatography. (Ex. 1007 at 6:13-16.) It therefore provides the features recited in claims 6 and 8, which recite that the antibody binds HER2 antigen. (Ex. 1002, Przybycien Decl. at ¶ 114.)

The '526 Patent discloses that preferred molecular targets for antibodies purified by its method include anti-CD11a and VEGF (*id.* at 6:18-20), which are also recited in the *Markush* group of claim 7. Claim 9 depends from claim 8, and recites that the antibody is trastuzumab or humanized 2C4, both prior art anti-HER2 antibodies having a C_H2/C_H3 region. (*See* Ex. 1001, '799 Patent at 7:33-46.) Trastuzumab is "humAb4D5-8," the antibody purified in Example 1 of the '526 Patent. (Ex. 1007 at 15:22-24.) Claims 6 through 9 are therefore rendered obvious by the teachings of WO '389 in view of the '526 Patent. Similarly, the '526 Patent teaches that in a preferred embodiment, the protein may be an immunoadhesin, such as a TNF receptor immunoadhesin. (*Id.* at 2:38-39.) Claims 10 and 11 are also rendered obvious by WO '389 in view of the '526 Patent for this reason. (Ex. 1002, Przybycien Decl. at ¶¶ 114, 115.)

There is nothing new about using protein A chromatography to purify C_H2/C_H3 region-containing proteins, including those specifically identified by the limitations of claims 6 through 11. (Ex. 1007, '526 Patent at 15:22-25, Example 1; Ex. 1002, Przybycien Decl. at ¶ 115.) It would have been obvious to use the protein A chromatography method of WO '389 to purify the antibodies and

immunoadhesins identified in the ’526 Patent in order to obtain useful proteins at a high level of purity. Accordingly, claims 2, 3 and 6 through 11 would have been obvious over WO ’389 in view of the ’526 Patent.

F. Ground 6: Claims 2, 3 and 6 to 11 Would Have Been Obvious Over WO ’389, and Further in View of Balint, Potier, and the ’526 Patent

To the extent that the Board finds that claims 1 to 3 and 5 would not have been obvious under 35 U.S.C. § 103 in view of WO ’389 alone, Petitioner submits that these claims would have been obvious over WO ’389 in combination with the teachings of Balint and Potier as set forth in Ground 4. As described in Section VIII(E), it would have been obvious to a POSA before the priority date of the ’799 Patent to combine the reduced-temperature protein A chromatography method rendered obvious by WO ’389, Balint and Potier with the teachings of the ’526 Patent as set forth in Ground 5. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 116-118.)

Like WO ’389, the ’526 Patent discloses using protein A chromatography to purify a target protein. (Ex. 1007 at 1, Abstract.) 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 ¶ 117.) Therefore, it would have been obvious to combine the obvious method of conducting protein A chromatography at reduced temperatures, with the teachings of the '526 Patent regarding EDTA, in order to optimize the chromatography process while using only common excipients widely known in the prior art. Therefore, claims 2 and 3 would have been obvious over WO '389 in combination with Balint and Potier as applied to claim 1, and further in view of the '526 Patent.

Likewise, claims 6 through 9 would have been obvious over WO '389 in combination with Balint and Potier as applied to claim 5, and further in view of the '526 Patent's disclosure regarding purifying the specific claimed antibodies using protein A chromatography. (Ex. 1007, '526 Patent at 2:28-40, 6:13-20, and 15:22-24.) Claims 10 and 11 would have been obvious over WO '389 in combination with Balint and Potier as applied to claim 1, and further in view of the '526 Patent's disclosure regarding purifying immunoadhesins using protein A chromatography. (*Id.* at 2:38-39.) Detailed reasons for combining the teachings of the '526 Patent regarding protease inhibitors, antibodies and immunoadhesins are provided in the discussion of Ground 5, and are equally applicable here. There is nothing new about using protein A chromatography to purify C_H2/C_H3 region-containing proteins, including those specifically identified by the limitations of claims 6 through 11. (Ex. 1002, Przybycien Decl. at ¶ 118.) It would have been

obvious to use the protein A chromatography method of WO ’389 to purify the antibodies and immunoadhesins identified in the ’526 Patent in order to obtain useful proteins at a high level of purity. Therefore, claims 2, 3 and 6 to 11 are rendered obvious by WO ’389 in combination with Balint, Potier, and further in view of the ’526 Patent.

G. Ground 7: Van Sommeren Renders Claims 1, 2, and 5 Obvious

As discussed above regarding Ground 2, 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, and this claimed range is not critical to the invention. Van Sommeren also anticipates claim 2 because it explicitly teaches exposing the composition to be purified to a protease inhibitor. Van Sommeren also renders claims 1, 2 and 5 obvious for these same reasons. Additionally, even if the disclosed ranges of 4° C to 20 to 25° C, or 20 to 25° C were not deemed anticipatory, other disclosures in van Sommeren render the claimed range of about 10° C to about 18° C obvious. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 119-122.)

Specifically, van Sommeren teaches at least two motivations for reducing the temperature at which protein A chromatography is conducted. First, van Sommeren discloses that conducting protein A chromatography at the lower temperature of 4° C improves the binding of certain antibodies with protein A.

(Ex. 1004 at 12.) A POSA 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. (Ex. 1002, Przybycien Decl. at ¶ 119.) Second, van Sommeren discloses that contamination due to proteolysis was a known problem. (Ex. 1004 at 18-19.) It would have been obvious for a POSA 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. (Ex. 1002, Przybycien Decl. at ¶ 120.)

The temperatures disclosed in van Sommeren, 4° C and 20 to 25° C, are merely the convenient temperatures found in laboratory settings—i.e., the temperatures found in a refrigerator or cold room, and ambient temperature of the general working area. These same temperatures are found throughout the prior art because of this convenience, and not because researchers actively sought to avoid intermediate temperatures. (Ex. 1002, Przybycien Decl. at ¶¶ 34-35, 121.) As outlined above at Section VIII(B), the results obtained at the claimed temperature range would have been expected. It would have been obvious to practice the claimed method to purify antibodies at a temperature in the range from about 10° C to about 18° C with a reasonable likelihood of success, based only on the teachings of van Sommeren. These teachings render both claim 1 and claim 5 obvious.

Furthermore, as explained above with regard to Ground 2, the limitation of claim 2 regarding the use of protease inhibitors is also taught by van Sommeren. For at least these reasons, claims 1, 2 and 5 would have been obvious in view of van Sommeren alone.

H. Ground 8: Van Sommeren and the '526 Patent Render Claims 3 and 6 to 11 Obvious

Claims 3 and 6 to 11 are obvious under 35 U.S.C. § 103 in view of van Sommeren as applied to claims 1, 2 and 5 in Grounds 2 and 7, and further in view of the '526 Patent as outlined below. (*See also* Ex. 1002, Przybycien Decl. at ¶¶ 123-126.)

Claim Limitations	**Disclosed in van Sommeren and the '526 Patent**
3. The method of claim 2 wherein the protease inhibitor is EDTA or 4-(2-aminoethyl)-benzenesulfonyl-fluoride, hydrochloride (AEBSF).	The teachings of van Sommeren relevant to claims 1 and 2 are set forth above in Grounds 1 and 7. "The equilibration buffer of the example was 25 mM Tris, 25 mM NaCl, 5 mM EDTA, pH 7.1." (Ex. 1007 at 3:34-35) "The solid phase for the Protein A chromatography is equilibrated with a suitable buffer. For example, the equilibration buffer may be 25 mM Tris, 25 mM NaCl, 5 mM EDTA, pH 71." (Ex. 1007 at 14:27-30)

Claim 2 recites using a protease inhibitor during protein A chromatography, and claim 3 recites that the protease inhibitor is EDTA or AEBSF. As discussed above, van Sommeren recognized that protease activity could lead to contamination of the HCCF. (Ex. 1004 at 18-19.) Van Sommeren also disclosed that for protein A chromatography, the problem of protease activity could be alleviated by the addition of a protease inhibitor. However, it did not explicitly disclose the use of EDTA. The '526 Patent discloses using EDTA—a well-known protease inhibitor. (Ex. 1007, '526 Patent at 3:35, 14:30.) It would have been obvious to a POSA before the time of the alleged invention to use EDTA as the protease inhibitor in protein A chromatography as taught by van Sommeren, in order to solve the known problem of protein A leakage, with a reasonable likelihood of success. (Ex. 1002, Przybycien Decl. at ¶ 124.) EDTA is a widely available component with well-characterized properties, and its use would have been routine. (*Id.*) For at least these reasons, claim 3 would have been obvious over van Sommeren in view of the '526 Patent.

Claims 6 through 11, which recite specific antibodies and immunoadhesins that may be purified using protein A chromatography, are obvious in view of van Sommeren as applied to claims 1 and 5, and further in view of the '526 Patent as set forth below. Claims 6 through 9 are reproduced below:

Claim Limitations	**Disclosed in van Sommeren and the '526 Patent**
6. The method of claim 5 wherein the antibody binds an antigen selected from the group consisting of HER2, vascular endothelial growth factor (VEGF), IgE, CD20, CD40, CD11a, tissue factor (TF), prostate stem cell antigen (PSCA), interleukin-8(IL-8), epidermal growth factor receptor (EGFR), HER3, HER4, α4β7 and α5β3.	The teachings of van Sommeren relevant to claims 1 and 5 are set forth above in Grounds 2 and 7. "Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as . . . CD20 . . . members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor . . ." (Ex. 1007 at 6:13-16)
7. The method of claim 5 wherein the antibody is selected from the group consisting of Trastuzumab, humanized 2C4, humanized CD11a antibody, and humanized VEGF antibody.	"Preferred molecular targets for antibodies encompassed by the present invention include . . . 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 . . ." (Ex. 1007 at 6:13-20)
8. The method of claim 5 wherein the antibody binds HER2 antigen.	"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 . . ." (Ex. 1007 at 6:13-16)
9. The method of claim 8 wherein the antibody is Trastuzumab or humanized 2C4.	"Protein A chromatography was the initial chromatography step in the purification of the C_H2/C_H3 region-containing protein; humanized anti-HER2 antibody (humAb4D5-8) . . ." (Ex. 1007 at 15:22-24, Example 1)

Claims 10 and 11 ultimately depend from claim 1, further limiting the purified protein to an immunoadhesin.

Claim Limitations	**Disclosed in van Sommeren and the '526 Patent**
10. The method of claim 1 wherein the protein is an immunoadhesin.	The teachings of van Sommeren relevant to claim 1 are set forth above in Grounds 2 and 7. "In preferred embodiments, the protein is an antibody (e.g. an anti-HER2, anti-IgE or anti-CD20 antibody) or an immunoadhesin . . ." (*Id.* at 2:38-39.)
11. The method of claim 10 wherein the immunoadhesin is a TNF receptor immunoadhesin.	"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 2:38-39.)

Protein A chromatography can be used to purify proteins that have a C_H2/C_H3 region. (Ex. 1007, '526 Patent at 2:63-67.) Dr. Przybycien explains that the types of antibodies amenable to protein A chromatography were well known in the prior art. (Ex. 1002, Przybycien Decl. at ¶ 125.) Each of the proteins recited in the claims includes a C_H2/C_H3 region. (*Id*. at ¶¶ 113, 125)

Claim 5 recites that the purified, C_H2/C_H3 region-containing protein is an antibody, and it is anticipated and/or obvious in view of van Sommeren alone as discussed above with regard to Grounds 2 and 7. Claims 6 through 11 of the '799 Patent explicitly recite, in different ways, C_H2/C_H3 region-containing antibodies

and immunoadhesins that can be purified using protein A chromatography. As discussed above, there is nothing new about using protein A chromatography to purify C_H2/C_H3 region-containing proteins. (Ex. 1007, '526 Patent at 15:22-25, Example 1; Ex. 1002, Przybycien Decl. at ¶ 126.) It 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. (Ex. 1002, Przybycien Decl. at ¶¶ 115, 126.) Therefore, claims 3 and 6 through 11 would have been obvious in view of van Sommeren in combination with the '526 Patent.

IX. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

Analysis of secondary considerations, including long-felt need, failure of others, unexpected results, commercial success, copying, licensing, and industry praise, may assist a court in avoiding hindsight bias. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). However, a showing of secondary considerations must be commensurate to the showing of obviousness—a weak showing of secondary considerations cannot overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). In addition, the patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-

12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and *novel* in the claim. *In re Kao*, 639 F.3d 1057, 1068, 1072 (Fed. Cir. 2011) (emphasis in original) (finding that the only element not expressly disclosed in the prior art was an inherent property, and concluding that evidence of secondary considerations did not outweigh the strong showing of obviousness).

Here, there is no evidence of any of the aforementioned secondary factors that could outweigh the strong case of prima facie obviousness under Section 103(a) for the Challenged Claims. (Ex. 1002, Przybycien Decl. at ¶ 127.) As discussed above, and explained in the Declaration of Dr. Przybycien, the claimed range of about 10° C to about 18° C is not critical to the operability of the claimed method. (*Id*. at ¶¶ 85-89.) In addition, the degree of purification and level of protein A leakage at the claimed range would have been predictable to one of ordinary skill in the art. (*Id.* at ¶¶ 87-89.) Accordingly, there is no nexus between any secondary consideration and any element recited in the claims.

X. CONCLUSION

For all of the reasons described above and in the concurrently filed Declaration of Todd Przybycien, Ph.D., claims 1 to 3 and 5 to 11 of the ’799 Patent are invalid. Accordingly, this petition demonstrates a reasonable likelihood that

Petitioner will prevail with respect to at least one of the Challenged Claims pursuant to 35 U.S.C. § 314(a).

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Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of this Petition for *Inter Partes* Review of U.S. Patent No. 7,807,799 and all Exhibits filed together with this Petition were served on the official correspondence address for U.S. Patent No. 7,807,799 shown in PAIR, and on the correspondence address for the Assignee, Genentech, Inc.:

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CERTIFICATE OF COMPLIANCE PURSUANT TO 37 C.F.R. § 42

I hereby certify that this Petition complies with the word count limitation of 37 C.F.R. § 42.24(a)(1)(i) because the Petition contains 13,565 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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