UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENETECH, INC.,
Patent Owner.

Case IPR2017-02029
Patent 6,870,034 B2

Before LORA M. GREEN, ZHENYU YANG, and ROBERT POLLOCK, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 13 and 16 of U.S. Patent No. 6,870,034 B2 (Ex. 1001, "the '034 patent"). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") did not file a Preliminary Response to the Petition.

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of challenged claims 13 and 16. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner states that it "is not aware of any matters involving the '034 patent." Pet. 3. Patent Owner identifies Application Serial No. 11/084,729, which claimed priority to the '034 patent, but is now abandoned. Paper 4, 2. Patent Owner also identifies several district court cased that "may affect, or be affected by, a decision in this *Inter Parties* Review". Paper 6, 2; Paper 7, 2.

B. The '034 Patent (Ex. 1001)

The '034 patent issued March 22, 2005, with Timothy N. Breece, Robert L. Fahrner, Jeffrey R. Gorrell, Kathlyn Pham Lazzareschi, Philip M. Lester, and David Peng as the listed co-inventors. Ex. 1001. The patent "relates generally to protein purification," and, in particular, "to a method

for purifying C_H2/C_H3 region-containing proteins, such as antibodies and immunoadhesins, by Protein A chromatography." *Id.* at 1:10–13.

The '034 patent teaches that the ability to purify proteins on a large-scale and economically is an important issue in the biotechnology industry. *Id.* at 1:16–18. Proteins are usually made using cell cultures that have been transformed with the DNA encoding the protein of interest using recombinant methods, and the '034 patent notes that the "[s]eparation of the desired protein from the mixture of compounds fed to the cells and from the by-products of the cells themselves to a purity sufficient for use as a human therapeutic poses a formidable challenge." *Id.* at 1:17–28.

According to the '034 patent, affinity chromatography may be used in protein purification. *Id.* at 1:64–66. As taught by the '034 patent, affinity chromatography "exploits a specific interaction between the protein to be purified and an immobilized capture agent." *Id.* Protein A, which binds to proteins that contain an Fc region, such as antibodies, may, thus, be used as an absorbent in affinity chromatography. *Id.* 1:67–2:1. In that regard, the '034 patent teaches that U.S. Patent Numbers 6,127,526 and 6,333,398 to Blank "describe an intermediate wash step during Protein A chromatography using hydrophobic electrolytes, e.g., tetramethylammonium chloride (TMAC) and tetraethylammonium chloride (TEAC), to remove the contaminants, but not the immobilized Protein A or the protein of interest, bound to the Protein A column." *Id.* at 2:10–16.

The '034 patent, therefore "provides various intermediate wash buffers, other than TMAC or TEAC, for use in Protein A chromatography." *Id.* at 2:20–22. The '034 patent teaches also a method for purifying a protein that comprises a C_H2/C_H3 region, wherein the protein is absorbed to

Protein A that has been immobilized on a solid phase, the solid phase is washed with a wash solution to remove contaminants, and the protein is eluted from the solid phase. *Id.* at 2:23–55. In certain embodiments, the wash solution may comprise "a buffer at a concentration of greater than about 0.8 M" (*id.* at 2:36–37) or a "salt and solvent" (*id.* at 2:44–46).

The '034 patent defines "buffer" as "a buffered solution that resists changes in pH by the action of its acid-base conjugate components." *Id.* at 4:1–2. The '034 patent teaches that when the wash solution is a buffer "the intermediate wash step involves the use of a highly concentrated buffer solution, e.g., a buffer at a concentration of greater than about 0.8M, e.g.[,] up to about 2M, and preferably in the range from 0.8M to about 1.5M, most preferably about 1M." *Id.* at 17:45–49.

C. Challenged Claims

Petitioner challenges claims 13 and 16 of the '034, which are reproduced below:

> 13. A method for purifying a protein, which comprises a C*H*2/C*H*3 region, from a contaminated solution thereof by Protein A chromatography comprising:
>
> (a) adsorbing the protein to Protein A immobilized on a solid phase;
>
> (b) removing contaminants by washing the solid phase with a composition comprising a buffer at a concentration of greater than about 0.8M; and
>
> (c) recovering the protein from the solid phase.
>
> 16. A method for purifying a protein, which comprises a C*H*2/C*H*3 region, from a contaminated solution thereof by Protein A chromatography comprising:
>
> (a) adsorbing the protein to Protein A immobilized on a solid phase;

(b) removing contaminants by washing the solid phase with a composition comprising salt and a solvent selected from the group consisting of ethanol, methanol, isopropanol, acetonitrile, hexylene glycol, propylene glycol, and 2,2-thiodiglycol; and

(c) recovering the protein from the solid phase.

Ex. 1001, 25:41–26:6; 26:13–24.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 13 and 16 of the '034 patent on the following grounds (Pet. 7–8):

Ground	References	Basis	Claims Challenged
I	Van Sommeren[1]	§ 102(b)	13
II	Godfrey[2]	§ 102(b)	13
III	Ngo[3]	§ 102(b)	13
IV	Aoki[4]	§ 102(b)	13
V	Blank[5]	§ 102(b)	13

[1] Van Sommeren, *Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG1 Antibodies to Protein A Sepharose 4 Fast Flow*, 22:2 PREPARATIVE BIOCHEMISTRY, 135–49 (1992) ("van Sommeren") (Ex. 1004).

[2] Godfrey, *A Sensitive Enzyme-Linked Immunosorbent Assay (ELISA) for the Detection of Staphylococcal Protein A (SpA) Present as a Trace Contaminant of Murine Immunoglobulins Purified on Immobilized Protein A*, 149 JOURNAL OF IMMUNOLOGICAL METHODS, 21–27 (1992) ("Godfrey") (Ex. 1005).

[3] Ngo, U.S. Patent No. 4,801,687, issued Jan. 31, 2989 ("Ngo") (Ex. 1006).

[4] Aoki et al., U.S. Patent No. 5,098,829, issued March 24, 1992 ("Aoki") (Ex. 1007).

[5] Blank, U.S. Patent No. 6,127,526, issued Oct. 3, 2000 ("Blank") (Ex. 1008).

Ground	References	Basis	Claims Challenged
VI	Fang[6]	§ 102(b)	16
VII	Blank and Reifsnyder[7]	§ 103(a)	16

Petitioner relies also on the Declaration of Daniel G. Bracewell, Ph.D. Ex. 1002.

II. ANALYSIS

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity,

[6] Fang, *Real-Time Isoform Analysis by Two-Dimensional Chromatography of a Monoclonal Antibody During Bioreactor Fermentations*, 816 JOURNAL OF CHROMATOGRAPHY A 39–47 (1998) ("Fang") (Ex. 1009).

[7] Reifsnyder, *Purification of Insulin-Like Growth Factor-I and Related Proteins Using Underivatized Silica*, 753 JOURNAL OF CHROMATOGRAPHY A 73–80 (1996) ("Reifsnyder") (Ex. 1018).

deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Although Petitioner offers several claim constructions (Pet. 22–25), at this stage of the proceeding, we determine that only one term requires explicit construction in order to determine whether to institute a trial in this case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

i. "composition comprising a buffer at a concentration of greater than about 0.8M"

Petitioner provides two possible constructions of the above claim limitation. Pet. 23–25. Petitioner contends that it is unclear as to "what substance must be 'at a concentration of greater than about 0.8M.'" *Id.* at 23 (citing Ex. 1002 ¶ 48). Petitioner asserts that the broadest reasonable construction is that it encompasses "the total concentration of the solutes (i.e., the materials dissolved) in the buffered solution . . . must be greater than about 0.8M." *Id.* Petitioner notes that another, second possible construction, is that the concentration of the buffer itself, that is, the component specifically identified as a buffer, for example, tris, is greater than about 0.8 M. *Id.* at 23–24.

For purposes of this decision, we determine that the broadest reasonable interpretation of a "composition comprising a buffer at a concentration of greater than about 0.8M" in view of the specification is that

the total concentration of all the solutes in the buffered solution must be greater than about 0.8 M.

Specifically, the specification defines "buffer "as "a buffered solution that resists changes in pH by the action of its acid-base conjugate components." Ex. 1001, 4:1–2. That is, the specification defines the "buffer" as the "buffered solution," which would include all of the solutes added to the solution, and not just the concentration of the solute specifically identified as the buffer.

B. Anticipation by van Sommeren

Petitioner asserts that claim 13 is anticipated by van Sommeren. Pet. 26–34. Petitioner presents a claim chart demonstrating where each limitation of claim 13 may be found in van Sommeren. *Id.* at 32–34.

i. Overview of van Sommeren (Ex. 1004)

van Sommeren teaches that purification of immunoglobulins (IgG), such as mouse monoclonal antibodies, "using affinity chromatography with protein A as ligand is very popular because of its simplicity, speed and efficiency." Ex. 1004, 135.[8] van Sommeren teaches:

> A protein A Sepharose 4 Fast Flow column (0 10, h 13 mm) was equilibrated with binding buffer. The cell culture supernatant was diluted with an equal volume of binding buffer and filtered through a 0.2 μm pore size membrane filter. Subsequently a volume containing a fixed amount of mab was loaded onto the column. The non-bound fraction was washed from the column with binding buffer. The fraction bound to the column was desorbed with 0.1 M citric acid (pH 5.0).

Id. at 138.

[8] Unless otherwise noted, the referenced page number is the page number in the original reference, and not the page number added by the parties.

van Sommeren looked at the effects of binding buffer composition on the binding capacity of protein A. *Id.* at 139. The different binding buffers looked at by van Sommeren are shown in Table 2, reproduced below:

TABLE II

Ionic Strength (mole/l) of the Binding Buffers and their Effect on Binding Capacity (mg IgG/ml gel) of Protein A Sepharose 4 Fast Flow for Mabs OT-hCG-1C and OT-hCG-4D

Binding buffer	Ionic Strength	Binding capacity Mab 1C	Mab 4D
0.1 M sodium phosphate pH 8.1	0.3	0.5	0.7
0.1 M $Na_2B_4O_7$, 0.15 M NaCl pH 8.5	---	0.6	0.6
0.25 M glycine, 0.1 M tris and 0.1 M K_2HPO_4 pH 8.9	0.3	0.2	0.4
0.5 M glycine, 0.5 M NaCl pH 8.9	0.6	1.1	0.9
0.5 M glycine, 1.0 M NaCl pH 8.9	1.1	1.4	1.5
0.5 M glycine, 2.0 M NaCl pH 8.9	2.1	2.8	2.6
0.5 M glycine, 3.0 M NaCl pH 8.9	3.1	4.2	5.5
1.5 M glycine, 0.5 M NaCl pH 8.9	0.7	2.3	2.2
1.5 M glycine, 1.0 M NaCl pH 8.9	1.2	3.1	3.5
1.5 M glycine, 2.0 M NaCl pH 8.9	2.3	4.1	7.1
1.5 M glycine, 3.0 M NaCl pH 8.9	3.4	4.6	10.3
0.025 M glycine, 1.2 M K_2HPO_4 pH 9.0	3.6	8.7	20.7
0.025 M glycine, 1.2 M K_2HPO_4 pH 10.0	3.6	7.1	19.1
0.1 M tris, 1.0 M Na_2SO_4 pH 7.5	3.1	7.2	16.8
0.1 M tris, 1.5 M $(NH_4)_2SO_4$ pH 7.5	4.5	8.9	19.6

Chromatographic conditions: column dimensions Ø 10, h 13 mm; ambient temperature; flow rate 76 cm/h; sample: 5 ml 2.0 mg/ml mab 1C and 2 ml 14.5 mg/ml mab 4D.

Id. at 140.

ii. Analysis

Claim 13 is drawn to a method of purifying a protein that has a C_H2/C_H3 region using Protein A that is immobilized on a solid support,

comprising the steps of absorbing the protein to the solid support, removing contaminants by washing with a buffer composition ("washing solution" or "washing buffer") wherein the buffer is present at a concentration of about 0.8 M of higher, and recovering the protein from the solid phase.

Petitioner contends[9] that van Sommeren discloses the steps of claim 13. Petitioner notes that "van Sommeren explores . . . the effect of the composition of the binding buffer on the binding strength between protein A and an IgG antibody." Pet. 26. The binding buffer, Petitioner asserts, has the same composition as the washing buffer that is used to wash the non-bound proteins from the solid support after the protein of interest has been absorbed. *Id.* According to Petitioner, van Sommeren tested 15 different buffers, including buffers containing 1.5 M glycine. *Id.* at 26, 28–30. Petitioner relies on Flynn[10] only for its teaching that glycine is a buffer, with a pH buffering range of approximately 8.8 to 10.8. *Id.* at 28 (citing Ex. 1017, Table V). Thus, Petitioner contends, van Sommeren anticipates claim 13. *Id.* at 32 (citing Ex. 1002 ¶ 55).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that van Sommeren discloses the method steps of claim 13. Based on that showing,

---

[9] We adopt Petitioner's statement (Pet. 8–9) as to the level of skill of the ordinary artisan for purposes of this Decision. We note that the applied prior art also reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

[10] Gordon L. Flynn, *Buffers—pH Control within Pharmaceutical Systems*, 34 PDA J. PHARM. SCI. AND TECH. 139–162 (1980) ("Flynn") ("Ex. 1017).

Petitioner has sufficiently demonstrated a reasonable likelihood that claim 13 is anticipated by van Sommeren.

C. Anticipation by Godfrey

Petitioner asserts that claim 13 is anticipated by Godfrey. Pet. 34–37. Petitioner presents a claim chart demonstrating where each limitation of claim 13 may be found in Godfrey. *Id.* at 35–37.

i. Overview of Godfrey (Ex. 1005)

Godfrey teaches that the "utility of immobilized protein A (SpA) preparations for the affinity purification of antibodies for therapeutic applications is widely acknowledged." *Id.* at 21. Godfrey also discloses an assay that may be used to evaluate the leakage of Protein A murine IgG1 is purified using protein A immobilized on agarose. *Id.*, Abstract.

In addition, Godfrey teaches a method of purifying murine IgG1. *Id.* at 23. In that method, protein A immobilized on sepharose is suspended in a washing buffer that comprises 1 M glycine and 0.15 M sodium chloride at a pH of 8.6, and poured into a disposable column. *Id.* According to Godfrey:

> The columns were then loaded with murine lgGl containing bioreactor supernatant (20 ml, at approximately 1 mg/ml, dialysed against 100 vols. of washing buffer), and washed with 10 vols. of washing buffer. Purified antibodies were eluted in 5.5 column vols. of elution buffer, the first 0.5 vols. were discarded prior to collection of the affinity purified fraction. This purification process was carried out four times in all, regenerating the columns with 5 column vols. of eluting buffer and re-equilibrating with an equal volume of washing buffer between each run.

Id.

ii. Analysis

Petitioner contends that Godfrey discloses the steps of claim 13. Petitioner notes that "Godfrey describes an assay developed to measure the

amount of protein A that elutes with the target antibody during the elution step of protein A chromatography." Pet. 34. Petitioner notes that Godfrey teaches a washing buffer that is used to wash contaminants from the solid phase that has glycine at a concentration of 1 M. *Id.* at 36. Petitioner relies on Flynn only for its teaching that glycine is a buffer, with a pH buffering range of approximately 8.8 to 10.8. *Id.* Petitioner notes that glycine would, therefore, have some buffering capacity at a pH of 8.6. *Id.* (citing Ex. 1002 ¶ 58). Thus, Petitioner contends, Godfrey anticipates claim 13. *Id.* at 34 (citing Ex. 1002 ¶ 58).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that Godfrey discloses the method steps of claim 13. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 13 is anticipated by Godfrey.

D. Anticipation by Ngo

Petitioner asserts that claim 13 is anticipated by Ngo. Pet. 37–41. Petitioner presents a claim chart demonstrating where each limitation of claim 13 may be found in Ngo. *Id.* at 38–41.

i.Overview of Ngo (Ex. 1006)

Ngo teaches "a process for the purification of monoclonal and polyclonal antibodies, such as immunoglobulins." Ex. 1006, 2:6–8. The method steps of Ngo include mixing the immunoglobulins with a buffer solution having a pH of approximately 7.5 to 10, and contacting the solution with immobilized protein A. *Id.* at 2:9–19. The immobilized immunoglobulins are then washed with the buffer solution, and then

removed from the immobilized protein A using a buffer solution with a pH of around 3 to 6. *Id.* at 2:21–28.

Ngo provides multiple examples of its method. Example 5 is reproduced below:

> To a 3 ml column was added 1 ml of immobilized protein A (Protein A Avid-Gel TM, BioProbe International, Inc., Tustin, Calif.). The column was equilibrated with 10 ml of a 0.05 Tris (hydroxymethyl) aminomethane (Tris) buffer, pH 8.5 containing 1.0M K_2HPO_4. A quantity of 1 ml of mouse monoclonal antibody from ascites fluid was diluted with 1 ml of buffer and applied to the column. Then the column was washed with 5–10 ml of buffer. The immunoglobulins which were absorbed on the column were eluted with 5 ml of 0.01M acetic acid-sodium acetate buffer, pH 3.5. The yield of immunoglobulins obtained was 2.9 mg.

Id. at 6:25–36.

ii.Analysis

Petitioner contends that Ngo discloses the steps of claim 13. In particular, Petitioner contends that a "number of examples in [Ngo] anticipate claim 13; for purposes of this Petition, Petitioner relies on Example 5." Pet. 38. Petitioner notes that Ngo teaches a washing buffer that is used to wash contaminants from the solid phase that has Tris at a concentration of 0.05 M and K_2HPO_4 at a concentration of 1.0 M. *Id.* at 39–40. Petitioner relies on Flynn only for its teaching that K_2HPO_4 is a buffer, with a pH buffering range of approximately 6.2 to 8.2. *Id*. at 40–41. Petitioner notes that K_2HPO_4 M would, therefore, have some buffering capacity at a pH of 8.5. *Id*. at 41 (citing Ex. 102 ¶ 59). Thus, Petitioner contends, Ngo anticipates claim 13. *Id.* at 38 (citing Ex. 1002 ¶ 59).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments

are supported by the current record, and reasonably demonstrate that Ngo discloses the method steps of claim 13. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 13 is anticipated by Ngo.

E. Anticipation by Aoki

Petitioner asserts that claim 13 is anticipated by Aoki. Pet. 41–45. Petitioner presents a claim chart demonstrating where each limitation of claim 13 may be found in Aoki. *Id.* at 42–45.

i.Overview of Aoki (Ex. 1007)

Aoki relates "to monoclonal antibodies capable of specifically interacting with a human-derived thrombin-binding substance and also to their utilization." Ex. 1007, 1:14–16.

Example 2 of Aoki is drawn to preparation of such an antibody, which Aoki refers to an anti-TM antibody. *Id.* at 2:27–29. According to Aoki:

> To 4.8 ml of the supernatant [collected from a hybridoma], an equal amount of 1.5M glycine buffer (pH 8.9) containing 3M of sodium chloride was added. The resultant mixture was subjected to chromatography on a column packed with 5 ml of "Protein A Sepharose CL-4B" (trade name) which had been equilibrated with the same buffer. After washing the column thoroughly with the same buffer, the column was eluted with 0.1M citrate buffer (pH 4.0). The eluate was collected in 3-ml portions in test tubes which contained l ml of 1M tris-HCl buffer (pH 8 .0). A_{280} was measured to collect protein fractions. After dial[y]zing the protein fractions against water, they were lyophilized to obtain an anti-TM monoclonal antibody.

Id. at 11:33–46.

ii. Analysis

Petitioner contends that Aoki discloses the steps of claim 13. In particular, Petitioner notes that Aoki teaches a wash buffer used in the

purification of the antibody that contains 1.5 M glycine buffer containing 3 M sodium chloride at a pH of 8.9. Pet. 43–44. Petitioner relies on Flynn only for its teaching that glycine is a buffer, with a pH buffering range of approximately 8.8 to 10.8. *Id*. at 44 (citing Ex. 1002 ¶ 60). Thus, Petitioner contends, Aoki anticipates claim 13. *Id.* at 42 (citing Ex. 1002 ¶ 60).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that Aoki discloses the method steps of claim 13. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 13 is anticipated by Aoki.

F. Anticipation by Blank

Petitioner asserts that claim 13 is anticipated by Blank. Pet. 45–48. Petitioner presents a claim chart demonstrating where each limitation of claim 13 may be found in Blank. *Id.* at 46–48.

i. Overview of Blank (Ex. 1008)

Blank teaches a method of purifying a protein that contains a C_H2/C_H3 region using protein A chromatography. Ex. 1008, 1:11–14.

As to the washing buffer, Blank teaches:

> The next step performed sequentially entails removing the contaminants bound to the solid phase by washing the solid phase with a hydrophobic electrolyte solvent in an intermediate wash step. In preferred embodiments, the hydrophobic electrolyte in this wash solvent is TEMAC and/or TEAC. While a single hydrophobic electrolyte may be present in the wash solvent, in certain embodiments, two or more such electrolytes may be used. The hydrophobic electrolyte is preferably added to a pH buffered solution having a pH in the range from about 4 to about 8, and preferably in the range from about 5 to about 7. Suitable buffers for this purpose include

> Tris, phosphate, MES, and MOPSO buffers. The preferred final concentration for the hydrophobic electrolyte in the wash solvent is in the range from about 0.1 to about l.0M, and preferably in the range from about 0.25 to about 0.5M.

Id. at 14:40–55.

Blank has a single example, Example 1. *Id.* at 15:15. The washing buffer used in that example had 25 mM Tris, 25 mM NaCl, and 5 mM EDTA at a pH of 7.1. *Id.* at 15:33–34; 15:38–39.

ii. Analysis

Petitioner contends that Blank discloses the steps of claim 13. In particular, Petitioner notes that Blank teaches a wash buffer used in the purification of the antibody that contains a total concentration of solute of "up to about 1.0M. which is 'greater than about 0.8M.'" Pet. 47. Petitioner relies on Flynn only for its teaching that Tris, one of the specific buffers suggested by Blank, is a buffer, with a pH buffering range of approximately 7.1 to 9.1. *Id*. (citing Ex. 1002 ¶ 61). Thus, Petitioner contends, Blank anticipates claim 13. *Id.* at 45.

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that Blank discloses the method steps of claim 13. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 13 is anticipated by Blank.

G. Anticipation by Fang

Petitioner asserts that claim 16 is anticipated by Fang. Pet. 48–52. Petitioner presents a claim chart demonstrating where each limitation of claim 16 may be found in Fang. *Id.* at 50–52.

i. Overview of Fang (Ex. 1009)

Fang discloses the monoclonal antibody, HuDREG-55, noting that it is "a humanized IgG4 monoclonal antibody that binds to human L-selectin, an adhesion molecule associated with neutrophil interactions along activated endothelium at inflamed sites." Ex. 1009, 39.

Fang discloses the separation of isoforms of the HuDREG-55 antibody, wherein the first column used is a column that has been packed with protein A immobilized to a particle solid support, and the second column is an anion-exchange column. *Id.* at 40. Table 1 of Fang, reproduced below, shows the mobile-phase solutions used in both the affinity step, as well as the ion-exchange step.

Table 1
Optimized chromatographic conditions employed during two-dimensional analyses of cell culture supernatants

Parameter	Affinity step	Ion-exchange step
Column	Protein A	Anion-Exchange
Packing	Poros PA immunodetection	Poros HQ/H
Size	3 cm×2.1 mm	3 cm×2.1 mm
Mobile phase solvent	1A, 25 m*M* potassium phosphate, 75 m*M* potassium chloride, 2.5% isopropanol, pH 7.3	1B, 50 m*M* Tris, pH 8.5
	2A, 25 m*M* potassium phosphate, 75 m*M* potassium chloride, 2.5% isopropanol, pH 1.7	2B, 50 m*M* Tris, pH 8.5, 1 *M* NaCl
Gradient	Step	Step
UV detection	280 nm	280 nm
Flow-rate	1.5 ml/min	1.5 ml/min

Id.

According to Table 2 of Fang, the solution used to wash the HuDREG-55 antibody on the protein A column before elution to the anion-exchange column was 60% solution 1A and 40% 2A. *Id.* at 41, Table 2 (Column 1 wash).

ii. Analysis

Petitioner contends that Fang discloses the steps of claim 16. Specifically, Petitioner asserts that "Fang discloses the purification of HuDREG-55, an IgG_4 antibody, by protein A chromatography." Pet. 48. Petitioner asserts that in the method of Fang, the impure antibody is loaded onto a protein A column, the column is washed to remove loosely bound proteins, and the antibody of interest is eluted. *Id.* at 48–49.

According to Petitioner, Fang discloses a solution of potassium phosphate/potassium chloride/isopropanol solution that is used as the wash solution during the protein chromatography. *Id.* at 49 (citing Ex. 1008, Table 1, Table 2). Petitioner contends that solution is "within the scope of claim 16's wash composition 'comprising salt and a solvent selected from the group consisting of ethanol, methanol, isopropanol, acetonitrile, hexylene glycol, propylene glycol, and 2,2-thiodiglycol.'" *Id.* (citing Ex. 1002 ¶ 64. Thus, Petitioner contends, Fang anticipates claim 16. *Id.* at 50 (citing Ex. 1002 ¶ 64).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that Fang discloses the method steps of claim 16. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 16 is anticipated by Fang.

H. Obviousness over Blank, Reifsnyder, and Fang[11]

Petitioner asserts that claim 16 rendered obvious by the combination

[11] We note that Petitioner does not explicitly include Fang when introducing the obviousness ground. Pet. 52. Petitioner, however, does rely on Fang in

of Blank (Ex. 1008, discussed above), Reifsnyder, and Fang (Ex. 1009, discussed above). Pet. 52–58.

i. Overview of Reifsnyder (Ex. 1018)

Reifsnyder discloses:

> Adsorption chromatography using underivatized porous glass can be an effective capture step for the purification of recombinant proteins. Classical desorption techniques using chaotropic agents or harsh chemical solvents often result in elution of inactive material and may not be economical at the process scale. More recently, elution schemes have used tetramethylammonium chloride (TMAC) to obtain biologically active material. A TMAC elution was shown to be effective in the initial purification steps for the recovery of recombinant human insulin-like growth factor-I (rhIGF-l) from an *Escherichia coli* fermentation broth. However. TMAC also elutes other, more hydrophobic, proteins that are difficult to remove in subsequent purification steps. This paper describes the capture of IGF-1 from a crude fermentation broth and a more specific elution using a combination of ethanol and NaCl rather than TMAC. This elution also can be used with other proteins including an IGF-1 binding protein (BP3) expressed in mammalian cell culture.

Ex. 1018, Abstract.

ii. Analysis

Petitioner notes that Blank is drawn to the purification of antibodies using protein A chromatography. Pet. 55. According to Petitioner, Blank "illustrates that methods from one type of chromatography may be successfully used in other types of chromatography." *Id*. In particular,

---

the statement of the obviousness ground. *See, e.g., id.* at 53–54, 56 (discussing Fang in the obviousness ground). Thus, we conclude that there is no prejudice to Patent Owner to include Fang in the statement of the obviousness ground.

Petitioner notes that Blank uses a high concentration TMAC, i.e., salt, solution. *Id.* Petitioner contends that TMAC was previously used to wash proteins that were bound to silica and glass chromatography columns, and its use in TMAC in protein A chromatography "developed as an extension of its old use of breaking electrostatic interactions between proteins and silica or glass columns in other types of adsorption chromatography." *Id.* (citing Ex. 1002 ¶ 71).

Petitioner relies on Reifsnyder for teaching "that an ethanol-salt solution successfully washed proteins that are bound to silica column with strong hydrophobic interactions when even high concentrations of the salt TMAC could not." *Id.* at 54–55 (citing Ex. 1002 ¶ 71; Ex. 1018, 76-77). Thus, Petitioner asserts, Reifsnyder teaches that high concentrations of salt, which disrupt ionic interactions, may not be useful "in washing proteins that are bound to glass or silica columns with hydrophobic interactions." *Id.* at 54.

Petitioner relies on Fang as an example of when the use of a wash solution with high salt may be undesirable. *Id.* at 53. Petitioner notes that salts are used in wash solutions to wash non-specifically bound proteins off of a protein A chromatography column. *Id.* (citing Ex. 1004; Ex. 1002 ¶ 42). Petitioner notes further, however, that the use of certain salts may not be desirable, such as in situations where the antibodies interact with the salts used in the buffer. *Id.* (citing Ex. 1015, 185–186). Fang is such as example, Petitioner asserts, as a "salt concentration of 200 mM interfered with a later chromatography step while a salt concentration of 100 mM did not." *Id.* (citing Ex. 1009, 42–43; Ex. 1002 ¶ 71). That is, Petitioner asserts, Fang exemplifies a situation in which the composition and amount of salts in the

washing solution must be optimized for specific circumstances. *Id.* at 54 (citing Ex. 1002 ¶ 71).

Petitioner contends that the ordinary artisan confronted with a situation in which high salt wash solutions do not work in protein A chromatography, would have known of other wash buffers that were known to be used in other types of adsorption chromatography. *Id.* at 55 (citing Ex. 1002 ¶ 69). Petitioner asserts that the ordinary artisan "would have expected that other solutions that were used to elute proteins bound to silica or glass chromatography columns during other types of chromatography would also work to elute the proteins that were bound to the silica or glass column in protein A chromatography." *Id.* at 55–56. Thus, according to Petitioner, the ordinary artisan "who needed a wash solution for protein A chromatography when a high-salt concentration solution did not work well would have been motivated to use the ethanol-salt solution taught in Reifsnyder to wash proteins from silica or glass chromatography columns during protein A chromatography." *Id.* at 56 (citing Ex. 1002 ¶ 71).

In particular, Petitioner avers that "Reifsnyder teaches that the ethanol-salt solution was able to wash proteins that were strongly bound with hydrophobic interactions to a silica column even when high concentration TMAC could not," and that Fang teaches that "using alcohols, in that case isopropanol, along with salt successfully works as a wash buffer for protein A chromatography." *Id.* (citing Ex. 1018, 76–77; Ex. 1008, 40). Petitioner asserts, therefore, that the ordinary artisan would have had a reasonable expectation of success of using a wash solution that included both a solvent, such as ethanol or isopropanol, along with a salt, as a wash solution in protein A chromatography. *Id.* at 56–57 (citing Ex. 1002 ¶ 70).

Moreover, Petitioner asserts, "there are a finite number of materials that were known and used to wash and elute proteins that are bound to silica or glass chromatography columns during adsorption chromatography," contending that the use of a salt and a solvent "was an 'identified and predictable' composition for this purpose." *Id.* at 57 (citing Ex. 1002 ¶ 69).

We have reviewed Petitioner's evidence and arguments and determine, at this stage in the proceeding, that such evidence and arguments are supported by the current record, and reasonably demonstrate that the combination of Blank, Reifsnyder, and Fang renders the method steps of claim 16 obvious. Based on that showing, Petitioner has sufficiently demonstrated a reasonable likelihood that claim 16 is obvious over the combination of Blank, Reifsnyder, and Fang.

III. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 13 and 16 of the '034 patent are unpatentable.

Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final decision as to patentability of the claim for which *inter partes* review is instituted. Our final decision will be based on the full record developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. §314(a), an *inter partes* review is hereby instituted on the following grounds:

Claim 13 is anticipated by van Sommeren;

Claim 13 is anticipated by Godfrey;

Claim 13 is anticipated by Ngo;

Claim 13 is anticipated by Aoki;

Claim 13 is anticipated by Blank;

Claim 16 is anticipated by Fang; and

Claim 16 as rendered obvious by the combination of Blank, Reifsnyder, and Fang;

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

PETITIONER:

Ira J. Levy
Sarah Fink
GOODWIN PROCTER LLP
ilevy@goodwinlaw.com
sfink@goodwinlaw.com

PATENT OWNER:

David I. Berl
Thomas S. Fletcher
WILLIAMS & CONNOLLY LLP
dberl@wc.com
tfletcher@wc.com