UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Patent No. 6,870,034
Title: PROTEIN PURIFICATION

Inter Partes Review No. IPR2017-02029

PATENT OWNER RESPONSE

Pursuant to 37 C.F.R. § 42.120, Patent Owner, Genentech, Inc., submits this Patent Owner Response to the Petition for *Inter Partes* Review of U.S. Patent No. 6,870,034 filed by Petitioner, Boehringer Ingelheim Pharmaceuticals, Inc.

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The patent at issue, U.S. Patent No. 6,870,034 (Ex. 1001, "the Breece Patent") claims improved methods for performing protein A chromatography to purify a protein like an antibody. The research reflected in the Breece Patent arose from Genentech's effort to improve on its prior method for performing protein A chromatography, disclosed in U.S. Patent No. 6,127,526 (Ex. 1008 or "Blank"). The Breece Patent repeatedly discusses Blank and uses its method as the baseline for evaluating the Breece Patent's new purification methods. *See*, *e.g.*, Ex. 1001 at Figs. 2-6.

Boehringer's Petition challenges two of the Breece Patent's independent claims: claim 13 (reciting a washing solution with a high concentration buffer) and claim 16 (reciting a washing solution comprising salt and one of a group of organic solvents). As to claim 13, Boehringer alleges that the claimed method is anticipated by no fewer than five references (Grounds 1-5). As to claim 16, Boehringer alleges that the claimed method is anticipated by one reference (Ground 6) or rendered obvious (Ground 7).

The only consistent theme between Boehringer's arguments is a fundamental misapprehension of the technologies at issue. For example, Boehringer argues in Ground 5 that the Breece Patent's claim 13 is anticipated by Blank's purification method, the very method that the Breece Patent's inventors sought to improve upon and distinguish. Boehringer's argument that the Breece Patent might

somehow have claimed what it was improving upon should sound suspect, and upon scrutiny, falls apart because it rests on a claim construction that is inconsistent with all of the intrinsic evidence. Boehringer's four other attacks on claim 13 all rely upon art predating by several years Blank's insight that a protein A column should be washed with an intermediate washing solution to remove contaminants that had non-specifically bound to the column. These references disclose, in one form or another, passing over the column the same solution that was used to load the column. Because these methods fail to change the chemical environment inside the column, they do not anticipate claim 13's method.

Boehringer's challenges to claim 16 similarly fail to appreciate the technological context. Claim 16 recites a method for purifying a protein like an antibody and recovering it, meaning that it relates to "preparative" chromatography. Boehringer alleges in Ground 6 that this method is anticipated by a reference (Ex. 1009, "Fang") teaching an "analytical" chromatography method. While both involve chromatography, preparative and analytical chromatography involve vastly different scales and plainly different goals. With this context, it is clear that Fang does not teach a method of purifying a protein in which the wash step "removes contaminants" or in which the protein is "recovered" from the column.

Finally, Boehringer alleges in Ground 7 that claim 16 would have been obvious because it would have been obvious to replace the washing solution in Blank with the elution solution used in another type of chromatography to purify a different protein. The various motivations alleged all suffer from technical misunderstandings, and the alleged expectation of success contradicts the prior art, submitted by Boehringer, that the solution Boehringer alleges would have been obvious to use was "disqualified" from use in preparative contexts.

In short, the Petition fails to demonstrate the challenged claims are invalid, and the patentability of claims 13 and 16 should be confirmed.

BACKGROUND

A. Protein A Affinity Chromatography.

Affinity chromatography is "a highly selective mode of chromatography" and typically the first step in industrial scale antibody purification. Ex. 2002 ("Cramer") ¶¶ 19-23.[1] Affinity chromatography takes advantage of a specific

[1] Dr. Steven M. Cramer is a professor at the Rensselaer Polytechnic Institute and has more than three decades of research experience concerning methods for purifying proteins. Cramer ¶¶ 2-3. He has published nearly 200 articles in refereed journals, including a number of papers relating to the use of protein A chromatography to purify proteins like antibodies. *Id.* ¶ 4. Dr. Cramer's many

interaction between the target protein being purified and an immobilized affinity ligand in the chromatography column. *Id.* ¶ 19. Because it binds antibodies so effectively, protein A generally is regarded as the affinity ligand of choice for separating antibodies of interest from other impurities. *Id.*

A typical protein A chromatography process used in the course of antibody manufacturing involves several steps. *Id.* ¶ 19-22. First, the column containing immobilized protein A is prepared by adding to it an "equilibration" solution, intended to bring the column to a condition compatible with the protein of interest. *Id.* ¶ 20. Next, the composition containing the target antibody mixed with impurities, often called the feed material, is loaded onto a column, often after being mixed with a "loading" or "binding" solution. *Id.* As the composition passes through the column, the target antibody is separated from various other components of the mixture, because it binds specifically to the protein A immobilized in the column. *Id.* Next, a low pH solution is passed through the column to dissociate the target antibody from the protein A, eluting the antibody from the column. *Id.*

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professional achievements and awards are set forth more fully in Section I of his Declaration and in his curriculum vitae, attached thereto as Exhibit A.

In some protein A chromatography processes, an intermediate wash step between loading and elution is used. *Id.* ¶ 21-22. This step involves washing the column with a solution with a particular composition to improve purification by eluting contaminants (but not the target protein) that bound non-specifically. *Id.*

B. The Blank Patent.

Genentech has been a leader in developing antibody manufacturing techniques for some time. Years before the invention of the Breece Patent, Genentech obtained a patent on a different protein A process. That earlier patent—Blank—is directed to a protein A purification method using an intermediate wash step, and specifically, using a washing solution containing hydrophobic electrolytes, such as tetramethylammonium chloride ("TMAC") and tetraethylammonium chloride ("TEAC"). *See, e.g.*, Ex. 1008 at 8.

Blank's process includes the following steps: (i) equilibrating the column "with a suitable buffer," (ii) loading the feed material onto the column "using a loading buffer which may be the same as the equilibration buffer," (iii) washing the column "with a hydrophobic electrolyte solvent" like TMAC or TEAC and (iv) recovering the target protein "using a suitable elution buffer." *Id.* In the early 2000s, Blank's intermediate wash step using hydrophobic electrolytes like TMAC was understood to be an effective way to remove additional contaminants during protein A chromatography. Cramer ¶ 22; Ex. 2004 at 311.

C. The Breece Patent.

The Breece Patent issued on March 22, 2005 and claims priority to a provisional application filed on February 5, 2002. Ex. 1001 at 1. The patent discloses a "[a] method for purifying proteins by Protein A chromatography . . . which comprises removing contaminants by washing the solid phase with various intermediate wash buffers." *See id.* Among those intermediate wash buffers are compositions "comprising a buffer at a concentration of greater than about 0.8M," *id.* at 11, and compositions "comprising salt and solvent," *id.* Claim 13 is directed to the former, while claim 16 is directed to the latter.

The Breece Patent states clearly that its methods are improvements upon Blank's protein A chromatography method that used TMAC and TEAC to perform the wash. Example 1 of the Breece Patent specification explicitly contrasts the wash solutions of the invention with those disclosed in Blank:

> During the elution phase of the Protein A operation, any non-specifically bound CHOP will co-elute with the antibody, compromising the purity of the product pool. To remove this CHOP before the elution phase, U.S. Pat. Nos. 6,127,526 and 6,333,398 (Blank, G.) exemplify an intermediate wash step using tetramethylammonium chloride (TMAC) to remove CHOP. Although TMAC is effective at removing non-specifically bound CHOP, it is difficult to handle and dispense, is toxic, requires costly disposal as a hazardous waste, and is corrosive at high concentration and low pH.

> *The following study shows that alternative wash compositions, without the drawbacks of TMAC, can be used in an intermediate wash step*.

Ex. 1001 at 19 (emphasis added). Figures 2 through 6 of the Breece Patent all include a comparison of wash solutions of the invention with an intermediate wash solution comprising TMAC, based upon Blank. *Id.* at 4-8.

The distinctions between Blank and the Breece Patent were further highlighted during prosecution of the Breece Patent, as the Examiner expressly considered Blank when assessing the patentability of claim 13 (then claim 14 of the pending application). In a May 20, 2004 office action, the Examiner rejected another claim as anticipated by Blank. Ex. 1019 at 120. He then considered what is now claim 13, but found it was "free of the prior art of record," including Blank, on the basis that "[n]o reference teaches a washing composition having a buffer of at least about 0.8M concentration." *Id.* at 122; *see also* Ex. 2003 at 28:21–30:22.

ARGUMENT

The Petition challenges the patentability of two claims of the Breece Patent—claim 13 and claim 16.

Boehringer argues in its first five Grounds that claim 13 is anticipated by certain prior art references:

-- Ground 1, asserting that claim 13 is anticipated by A.P.G. van Sommeren et al., 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 Preparative Biochemistry 135 (1992) (Ex. 1004 or "van Sommeren");

-- Ground 2, asserting that claim 13 is anticipated by Godfrey et al., 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) (Ex. 1005 or "Godfrey");

-- Ground 3, asserting that claim 13 is anticipated by U.S. Patent No. 4,801,687 (Ex. 1006 or "Ngo");

-- Ground 4, asserting that claim 13 is anticipated by U.S. Patent No. 5,098,829 (Ex. 1007 or "Aoki"); and

-- Ground 5, asserting that claim 13 is anticipated by U.S. Patent No. 6,127,526 (Ex. 1008 or "Blank").

As set forth in Section II below, not a single one of the allegedly anticipatory references discloses the invention of claim 13 of the Breece Patent, and they all therefore fail to anticipate the claim. Each of these Grounds is premised on an unreasonable construction Boehringer tepidly advanced for the claim phrase "concentration of greater than about 0.8M," Boehringer's misapplication of the definition of "buffer," or both.

Boehringer's next two Grounds challenge the patentability of claim 16. In Ground 6, Boehringer alleges that claim 16 is anticipated by Yu Fang et al., *Real-Time Isoform Analysis by Two-Dimensional Chromatography of a Monoclonal Antibody During Bioreactor Fermentations*, 816 Journal of Chromatography A 39-47 (1998) (Ex. 1009 or "Fang"). And in Ground 7, Boehringer argues that claim 16 is obvious over the combination of Blank and David H. Reifsnyder et al., *Purification of insulin-like growth factor-I and related proteins using underivatized silica*, 753 Journal of Chromatography A 73-80 (1996) (Ex. 1018 or "Reifsnyder"). These two Grounds also fail. Boehringer's arguments in support of Ground 6 misinterpret the prior art and ignore key limitations of claim 16, while its arguments in support of Ground 7 misapply the law of obviousness, declining to assess meaningfully whether and why the POSA would have been motivated to combine the prior art as Boehringer urges, let alone have a reasonable expectation of success in doing so. The validity of the challenged claims should be confirmed.

I. CLAIM CONSTRUCTION

A. "Concentration of Greater than About 0.8M"

Claim 13 requires that its recited wash buffer be "at a concentration of greater than about 0.8M." Both the Petition and Dr. Bracewell's declaration profess some confusion and uncertainty as to the proper construction of this

"concentration" limitation. *See, e.g.*, Pet. at 23-24; Ex. 1002 ("Bracewell") ¶¶ 48-49. Dr. Bracewell summarizes the issue as follows:

> The term "composition comprising a buffer at a concentration of greater than about 0.8M," found in claim 13, is ambiguous. As a matter of English construction, it may be either all of the materials dissolved in the composition (i.e., the "solutes") that are at a concentration of greater than about 0.8M, or it may be the buffering material itself that is dissolved in the composition at a concentration of greater than about 0.8M

Bracewell ¶ 48 (footnote omitted). Neither Boehringer nor Dr. Bracewell ever reaches a conclusion as to which of the alternative meanings the POSA would assign to this language. Pet. at 23-25; Ex. 2003 at 17:23-18:10. Nor do Boehringer or its expert apply the controlling claim construction rubric to assert that the correct construction of the "concentration" phrase looks to the concentration of all solutes (the "first construction"), rather than the concentration of only the buffering agent (the "second construction"). Instead, Boehringer merely proposed the "first construction" as one of two possible interpretations, while acknowledging, *sotto voce*, that it is incorrect. There is no mystery to Boehringer's approach, as this remarkably broad construction—divorced from the claim language, the specification, and the purpose of the invention—is as helpful to its anticipation case as it is devoid of support in the intrinsic record.

The Board's Institution Decision nevertheless adopted the first of the potential constructions—allowing the claimed "concentration" to apply to *all* solutes in the wash solution—reasoning that this construction, though too baseless even for Boehringer to advance, reflected the "broadest reasonable interpretation." Paper 8 at 7. The Board had not been provided the intrinsic evidence showing that this "first construction" is plainly wrong.

The requirement in this proceeding that claim language receive its "broadest reasonable construction in light of the specification of the patent," 37 C.F.R. § 42.100, does not permit "giving [the] claims a legally incorrect interpretation." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016). Rather, "claims should always be read in light of the specification and teachings in the underlying patent," *id.* (quoting *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010)), and "the Board 'should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review,'" *id.* (quoting *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)). The "first construction" of the phrase "at a concentration of greater than about 0.8M" violates each and every one of these standards. Not only is that construction inconsistent with the ordinary meaning of the phrase to the POSA, but it also conflicts with both the specification and prosecution history of the Breece Patent.

As an initial matter, it is the "second construction" (under which the recited "concentration" refers only to the concentration of any buffering agent in solution) that reflects the ordinary meaning the POSA would assign to claim 13's "concentration" phrase. As Dr. Cramer explains, "[t]he express mention of a 'buffer' before the 'concentration' language would suggest to the POSA that the recited concentration was that of a buffering agent." Cramer ¶ 35. And Dr. Bracewell appears to agree with this view, at least in his less guarded moments. When questioned about the meaning of claim 14, which recites "[t]he method of claim 13 wherein the buffer is Tris acetate," Ex. 1001 at 23, Dr. Bracewell candidly agreed that in the context of claim 14, the method requires a solution with a concentration of greater than about 0.8M Tris acetate. *See* Ex. 2003 at 71:14-73:17. He likewise acknowledged that this second construction was "the simplest way" to construe the "concentration" phrase. Ex. 2003 at 13:24–14:1 (explaining further that "the most simplest [sic] interpretation" is that the "concentration" limitation describes the concentration of "the buffering material, i.e., the . . . base acids that are there to control the pH").

But, even were this not the case, the specification of the Breece Patent would compel the same conclusion. Example 1 of the Breece Patent, for example, directly contrasts the wash solutions of the Breece Patent with those disclosed in Blank. *See* Ex. 1001 at 19 ("[Blank] exemplif[ies] an intermediate wash step using

tetramethylammonium chloride (TMAC) to remove CHOP. . . . The following study shows that alternative wash compositions, without the drawbacks of TMAC, can be used in an intermediate wash step."). And crucially, Blank discloses a wash solution with a concentration of hydrophobic electrolytes (and thus also a concentration of total solutes) greater than 0.8M. *See* Ex. 1008 at 8 (disclosing a "preferred final concentration for the hydrophobic electrolyte in the wash solvent" of "from about 0.1 to about l.0M"). The Breece Patent therefore reveals that what distinguishes its process from Blank is the concentration of buffering agent, not the concentration of any and all solutes including dissolved salts like TMAC. If the Board's initial construction were correct, the specification's repeated distinction between the wash solutions of Blank and the Breece Patent would make no sense, given Blank's disclosure of a wash with total solute concentration greater than 0.8M. Ex. 1008 at 8.

Indeed, Boehringer itself recognizes that the Board's construction cannot survive the controlling legal mandates that the specification is the single best guide to a claim term's meaning and that a construction that is inconsistent with the specification cannot be correct. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc); *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (rejecting Board's construction because at odds with the specification). In a passage that explains why Boehringer's Petition identified the solute

concentration construction but did not invite the Board to commit legal error by adopting it, Boehringer admitted:

> Under the "second construction," it is the substance that provides the buffering capacity to the composition that must be present at a concentration of greater than about 0.8M. This construction, while not as broad as the "first construction," may nonetheless be compelled by the [Breece Patent] specification's reference to [Blank].
>
> . . .
>
> [I]n order to follow the [Breece Patent's] logic that differentiates [Blank's] wash substances from the wash substances claimed in the [Breece Patent], the construction of "concentration greater than about 0.8M" must refer to only the buffering substance, alone, within the entire wash composition.

Pet. at 24-25. Boehringer is correct—the specification's disclosure means that the "'concentration greater than about 0.8M' must refer to only the buffering substance, alone," and that ends the inquiry as a matter of law. *David Netzer Consulting Eng'r LLC v. Shell Oil Co.*, 824 F.3d 989, 993 (Fed. Cir. 2017); *Indacon, Inc. v. Facebook, Inc.*, 824 F.3d 1352, 1355 (Fed. Cir. 2016). Where, as here, both parties agree that the specification is inconsistent with the adoption of a given construction, that construction necessarily is wrong. *In re Suitco Surface, Inc.*, 603 F. 3d 1255, 1260 (Fed. Cir. 2010).

The Board's Institution Decision concluded that the "first construction" was correct based upon the specification's definition of "buffer." Paper 8 at 8. While the Board is correct about the definition of "buffer," *see infra* Section I.B, the definition of "buffer" does not make the "first construction" reasonable. This can be illustrated in the context of claim 13 by replacing the word "buffer" with the specification's definition. Claim 13's washing step would then require the use of "a composition comprising a [buffered solution that resists changes in pH by the action of its acid-base conjugate components] at a concentration of greater than about 0.8M." As Dr. Bracewell conceded, the simplest understanding of this phrase is that the 0.8M concentration limitation refers to the acid-base conjugate components. Put another way, the Board appears to have erred by equating the washing solution with the "buffer." But claim 13's wash step recites the use of "a composition *comprising* a buffer." Thus, other components may be included in the washing solution, and it is not the case that the "buffer" must "include all of the solutes added to the solution," contrary to the Board's reasoning at page 8 of the Institution Decision.

The intrinsic evidence contradicting the Board's construction does not end with the specification. The Examiner's determination during prosecution that claim 13 (then claim 14 of the pending application) was "free of the prior art of record" (including Blank) because "[n]o reference teaches a washing composition

having a buffer of at least about 0.8M concentration" is clear evidence that neither the applicant nor Examiner understood the "concentration" language to apply to all solutes in the wash solution. Ex. 1019 at 122. If the "concentration" limitation of claim 13 did refer to the concentration of all solutes, as the Board's Institution Decision contemplates, the wash solution disclosed in Blank—a reference of which the Examiner plainly was aware—*would* have "a concentration of greater than about 0.8M."[2]

These discussions of Blank in the prosecution history and specification of the Breece Patent make clear that the appropriate construction of the phrase "at a concentration of greater than about 0.8M" should take into account only the concentration of the buffering agent in the composition, rather than the concentration of all solutes. That Boehringer's "first construction" is broader does not matter—the intrinsic evidence, which must be considered and which

[2] As noted above, Blank discloses a preferred concentration range for the TMAC or TEAC of "about 0.1 to about l.0M." Ex. 1008 at 8.

Boehringer's expert in part ignored,[3] renders that construction unreasonable. *See D'Agostino*, 844 F.3d at 948.

Finally, it is notable that Boehringer's "first construction" would yield absurd results. If the claimed "concentration of greater than about 0.8M" refers to the concentration of all solutes in solution, then a "composition comprising a buffer at a concentration of greater than about 0.8M" might include even solutions in which only trace amounts of buffering agent are present. Dr. Bracewell confirmed this absurd result during his deposition, testifying that under his "first construction" the POSA would have understood a 0.8M NaCl, pH 8.6 solution containing only a *single molecule* of a buffering agent (glycine) to be a "composition comprising a buffer at a concentration of greater than about 0.8M" within the meaning of claim 13. *See* Ex. 2003 at 187:5-188:22.

B. "Buffer"

The Breece Patent's specification defines a "buffer" as "a buffered solution that resists changes in pH by the action of its acid-base conjugate components."

[3] Dr. Bracewell, who professed an inability to choose between the two alternative constructions, conceded that he did not "review the file history for the [Breece Patent]" in rendering his claim construction opinions in this proceeding. Ex. 2003 at 23:12-14; 23:22-24:3.

Ex. 1001 at 12. Following decades of Federal Circuit precedent, this definition is controlling and ends the claim construction inquiry. *AstraZeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1339-40 (Fed. Cir. 2004). Thus, in the context of the Breece Patent, a buffer is a solution defined by its functionality—specifically, a buffered solution containing a buffering agent that *in fact* resists changes to pH when added to a mixture or when additional components are added to it. Cramer ¶¶ 38-40.[4]

Boehringer nominally agrees with this construction, quoting the same language from the Breece Patent's specification. Pet. at 18. But, as discussed in more detail in Section II.B below, Boehringer fails to apply this construction faithfully. *See id.* at 26-48. Each of Grounds 1-4 rely, in part, on Boehringer's replacement of the Breece Patent's express "buffer" definition ("a buffered solution that resists changes in pH") with its subtly different construction (a buffered

[4] Outside the context of the Breece Patent's controlling definition of "buffer," the term "buffer" is sometimes used casually to refer to aqueous solutions. *See*, *e.g.*, Ex. 1002 ¶ 24 (referring to "buffers with high salt concentrations, urea, detergents, and organic solvents"); Cramer ¶ 38. This casual usage of "buffer" risks confusion in view of the Breece Patent's controlling definition and should be avoided.

solution *potentially capable* of resisting changes in pH depending upon, *inter alia*, the environment to which it is added).

While the difference between these two concepts is subtle, it is critical to appreciating the invention embodied in claim 13. The Breece Patent builds upon the observation, reflected in Blank, that there are contaminants which, under the conditions of the loading buffer, are capable of binding nonspecifically to the column (or the Protein A, or the bound antibody). Without an intervening wash step, these contaminants might elute with the antibody if the eluting solution were to desorb them along with the antibody. Cramer ¶¶ 19-22. But an intermediate wash step that *changes* the conditions in the column (without eluting the antibody) can remove some of these contaminants. *Id.* Claim 13 of the Breece Patent embodies this principle by reciting a washing solution that contains a high concentration of buffer (greater than about 0.8M) that in fact resists a change to pH, requiring that the pH of the solution in the column prior to washing be different from the pH of the washing solution. By actually changing the environment within the column, *i.e.*, by changing from the pH of the loading solution to the pH of the washing solution, the intermediate wash step of claim 13 is able to dislodge some of the contaminants that bound nonspecifically under the conditions of the loading solution. *See id.*

By ignoring the requirement that the "buffer" "resists changes in pH," Boehringer is able to argue in Grounds 1 through 4 that prior art methods in which the loading solution also is used to wash the column anticipate claim 13. As one of the references, van Sommeren, explains, this use of identical load and wash solutions occurred in the early days of protein A chromatography so that "the *non-bound fraction* was washed through the column." Ex. 1004 at 138 (emphasis added). Such methods ignore the problem—a problem solved in different ways by Blank and the Breece Patent—posed by contaminants that had bound non-specifically to the column and would not be removed under the conditions of the loading solution. Cramer ¶¶ 19-22.

With the distinction between the parties' positions crystallized, it is notable that in addition to being compelled by the intrinsic evidence, Genentech's construction also comports with the testimony of Dr. Bracewell, Boehringer's own expert witness. In his Declaration, Dr. Bracewell acknowledges the Breece Patent's definition of "buffer" as a "buffered solution *that resists changes to pH* by the action of its acid-base conjugate components," Bracewell ¶ 49, and further defines a "buffered solution" as "a solution *designed to* maintain a particular pH," Bracewell ¶ 43 (emphasis added). Boehringer applies the latter meaning to the term "buffer" in its Petition, characterizing any solution "designed to" or potentially capable of resisting pH changes as a "buffer," and ignoring the Breece

Patent's requirement that the buffered solution actually resist changes to pH. But, as Dr. Bracewell states, the meaning applied by Boehringer is the definition of a "buffered solution," not a "buffer," and the Breece Patent makes clear that these are distinct concepts, even defining the latter by reference to the former—"[a] '***buffer***' is a ***buffered solution*** that resists changes in pH." Ex. 1001 at 12. While a "buffered solution" may be any solution designed to maintain a particular pH, the term "buffer" applies only to those buffered solutions that actually fulfill that role, *i.e.*, that in fact "resist[] changes to pH." The Breece Patent's definition of "buffer" is the meaning compelled by the intrinsic evidence, *see* Ex. 1001 at 12, and is controlling as a matter of law.

II. CLAIM 13 IS NOVEL (GROUNDS 1-5).

The Petition includes five Grounds (Grounds 1-5) challenging the patentability of claim 13, which recites:

> A method for purifying a protein, which comprises a C_H2/C_H3 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.

Ex. 1001 at 23. Each of these five instituted Grounds alleges anticipation.

"[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys. Inc. v Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

For the reasons that follow, the Board should reject Boehringer's challenges to claim 13. None of the five references discussed in Grounds 1–5—the "best" anticipatory references Boehringer could muster, Ex. 2003 at 118:4–14—anticipates claim 13.

A. Blank Does Not Disclose a Wash Solution with a "Concentration of Greater than About 0.8M" and Thus Does Not Anticipate Claim 13 (Ground 5).

Ground 5 contends claim 13 is anticipated by Blank, the Genentech patent directed to a first-generation protein A chromatography process using a hydrophobic salt like TMAC in its intermediate wash step. Pet. at 45-47. Boehringer contends that Blank anticipates claim 13 only under the first, overbroad construction that it proffered of the claim limitation "concentration of greater than

about 0.8M." *See* Pet. at 45 (arguing "the disclosure of the '526 patent anticipates claim 13 under Petitioner's first claim construction").

But as explained in Section I.A**Error! Reference source not found.** above, the claimed "concentration of greater than about 0.8M" refers to the concentration of any buffering agent(s) in a wash solution, rather than the concentration of all solutes therein. Blank, a reference already considered during examination of the Breece Patent, *see supra* Section I.A, cannot anticipate claim 13 because it does not disclose a wash composition containing a buffer "at a concentration of greater than about 0.8M."

The Petition relies upon the following passage of Blank, which describes the amount of hydrophobic salt (but not buffer) in its washing solution:

> 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 [sic] 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.

Ex. 1008 at 8; *see also* Pet. at 46-47. Nowhere does the Petition reference the concentration of any buffering agent(s) in the solution to which the hydrophobic electrolyte is added. Ex. 1008 at 8; Pet. at 45-48; Cramer ¶¶ 86-88. Blank merely describes the preferred concentrations of the hydrophobic electrolytes, which are not buffering agents. Ex. 1008 at 8; Cramer ¶¶ 86-88; Ex. 2003 at 36:2-11. Thus, there is no disclosure of a washing solution comprising a buffer at a "concentration of greater than about 0.8M." Cramer ¶¶ 86-88.

Even Dr. Bracewell agrees with this conclusion, explaining in his claim chart for Ground 5 that Blank discloses the "greater than about 0.8M" limitation of claim 13 only under "the first construction of this term," *i.e.*, the construction referencing the concentration of *all* solutes in the solution. Bracewell ¶ 61 (claim chart). Under the correct construction of the "concentration" limitation, it is undisputed that Blank does not anticipate claim 13.

B. Van Sommeren, Godfrey, Ngo, and Aoki Do Not Disclose the Use of a Washing Solution Comprising a "Buffer" and Thus Do Not Anticipate Claim 13 (Grounds 1-4).

Grounds 1, 2, 3, and 4 of the Petition allege that claim 13 is anticipated by van Sommeren, Godfrey, Ngo, and Aoki, respectively. Each of these papers and patents were published nearly a decade or more before the Breece Patent's priority

date, *see* Ex. 1004 (published June 1992), Ex. 1005 (published 1992), Ex. 1006 (issued Jan. 31, 1989), Ex. 1007 (issued Mar. 24, 1992), and each discloses a protein A chromatography method that rinses the column with a solution identical to the loading solution, *see* Ex. 1004 at 9, Ex. 1005 at 3, Ex. 1006 at 4, Ex. 1007 at 11. As Boehringer indicates, such processes were commonly found in the prior art. Pet. at 19. And it is precisely this inadequate "washing" that distinguishes the prior art, including van Sommeren, Godfrey, Ngo, and Aoki, from the method of claim 13. Applying the proper construction of the term "buffer," none of these references anticipate claim 13.

Godfrey (Exhibit 1005) exemplifies this problem inherent in each of Boehringer's anticipation challenges. Godfrey discusses an assay designed to measure the amount of protein A leached from a column and further details test chromatography runs conducted to assess the performance of this assay. *See* Ex. 1005 at 1-3; Cramer ¶¶ 60-61, 63; Ex. 2003 at 143:4-145:14. Boehringer cites the disclosures concerning those test runs as the basis for its anticipation argument. Pet. at 34-37. Godfrey describes its chromatography process as follows:

> Prosep A, high capacity, and Protein A-Sepharose CL-4B (preswollen) were suspended in washing buffer (glycine, 1 M; sodium chloride, 0.15 M; pH 8.6), and the fines removed (Sepharose only). They were then poured into disposable columns (2 ml, 8 mm diameter) and purged with 5 vols. of elution buffer (citric acid, 0.1 M, pH 3) and an equal volume

> of PBS. The columns were then loaded with murine IgGl 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.

Ex. 1005 at 3.

In Godfrey's load step, 20 ml of supernatant containing the target antibody is dialysed against 100 column volumes of wash solution—a solution comprising 1M glycine and 0.15M sodium chloride at pH 8.6. Drs. Bracewell and Cramer both agree that, following this step, one would expect the composition in the protein A column also would have a pH of 8.6. Cramer ¶¶ 64-67; Ex. 2003 at 149:9-150:8, 152:17-153:15, 153:21-154:6. As Dr. Cramer explains, by dialyzing the supernatant against the glycine wash solution, the combined solution would most likely have a pH 8.6. Cramer ¶¶ 64-67; *see also* Ex. 2003 at 149:9-19 ("There's 100 column volumes used . . . 100 volumes of washing buffers, a very large volume, so we don't know, but we might assume, that it's at the wash buffer condition just because we've given so many dia volumes to exchange there."). Indeed, shifting the pH of the supernatant to that of the loading solution is the purpose of mixing the two. Cramer ¶ 58. Both Dr. Cramer and Dr. Bracewell also agree, however, that the POSA could not have been certain about the pH of the

liquid in the column, as the introduction of the supernatant theoretically could alter the composition's pH. Cramer ¶¶ 64-67; Ex. 2003 at 149:9-150:8, 152:17-153:15, 153:21-154:6. Various unknown factors, including the exact composition of the supernatant, the supernatant's pH prior to dialysis, and the precise state of the column prior to loading, would make such a determination impossible. Cramer ¶¶ 64-67.

The POSA's inability to ascertain the pH of the composition in column following Godfrey's load step defeats Boehringer's anticipation challenge—if Godfrey does not disclose that the pH of the composition in column following the load step is different than the pH of the wash solution, it does not disclose that the wash solution actually "resists changes in pH." *Id.* ¶¶ 60-67. And, as explained above, a wash solution that does not resist changes in pH is not a "buffer" as that term is defined in the Breece Patent. *See supra* Section I.B. Here, there is no question that Godfrey does not contain an express disclosure of a composition in the column at a different pH than the pH of the wash solution—at best, it is ambiguous, and "[a]mbiguous references do not anticipate a claim." *Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017).

Nor does the reference provide such a disclosure inherently. Even if Boehringer had not already waived any inherent anticipation argument,[5] the facts here foreclose such a theory. Where inherent anticipation is argued, "[t]he mere fact that a certain thing *may result* from a given set of circumstances is not sufficient. Rather, the inherent result *must inevitably result* from the disclosed steps." *U.S. Water Servs., Inc. v. Novozymes A/S*, 843 F.3d 1345, 1350 (Fed. Cir. 2016) (emphases added). "A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present." *Akamai Technologies, Inc. v. Cable & Wireless Internet Svcs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003). For all the reasons discussed above, and as Dr. Bracewell acknowledges, the pH of the composition in the column prior to the wash step would not necessarily be different than the pH of the wash solution. Cramer ¶¶ 60-

[5] The Petition contains no suggestion that Godfrey or any other reference inherently anticipates claim 13, thus waiving any such argument at this late stage. *See, e.g.*, *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) ("[T]he expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute. While the Board's requirements are strict ones, they are requirements of which petitioners are aware when they seek to institute an IPR.").

67; Ex. 2003 at 149:9-150:8, 152:17-153:15, 153:21-154:6. Indeed, the POSA actually would expect it to be at the *same* pH as the wash solution itself, pH 8.6. Cramer ¶¶ 66-67; *see also* Ex. 2003 at 149:9-19. Godfrey thus does not disclose use of a washing solution comprising a "buffer."

This same issue plagues the rest of Boehringer's anticipation challenges to claim 13. Van Sommeren describes a protein A chromatography process using the same binding solution at each of the equilibration, load, and intermediate wash steps. Ex. 1004 at 9. This process was tested with fifteen separate binding solutions, *id.* at 9-11, and Boehringer contends that the disclosure of twelve of these solutions being used in van Sommeren's method anticipates claim 13, Pet. at 26-34; *see also* Bracewell ¶¶ 55-56. But both Dr. Bracewell and Dr. Cramer agree that van Sommeren does not provide enough information concerning its protein A process for the POSA to determine the pH of the composition in the column following the load step. Cramer ¶¶ 53-59; Ex. 2003 at135:16–136:5, 157:8-20.

Ngo likewise discloses a protein A method using an identical solution at the equilibration, load, and wash steps (1.0M K_2HPO_4 and 0.05M Tris at pH 8.5). Ex. 1006 at 4. But, again, the POSA would not be able to discern whether the wash solution disclosed by Ngo comprises a "buffer" within the meaning of the Breece Patent. As both Dr. Cramer and Dr. Bracewell agree, the POSA would not be able to determine whether the composition in the column prior to the wash step was at a

different pH than the wash solution itself. Cramer ¶¶ 68-73; Ex. 2003 at 163:25-164:15.

Finally, Aoki is directed to a monoclonal antibody specific to a thrombin-binding substance (TM), and Example 2 of that patent discloses a process for the preparation of the anti-TM antibody, including a protein A chromatography step that uses the same solution (1.5M glycine at pH 8.9) at each of the equilibration, load, and wash phases. Ex. 1007 at 1, 11; Cramer ¶¶ 74-75; Ex. 2003 at 165:5-166:14. Boehringer contends the disclosures of Aoki's Example 2 anticipate claim 13. Pet. at 42-45; *see also* Bracewell ¶ 60. This argument too fails because the POSA would not view the protein A wash solution described by Aoki as comprising a "buffer." Dr. Bracewell and Dr. Cramer agree the POSA would not understand from Aoki whether the composition in column prior to the wash step had a different pH than that of the wash solution itself. Cramer ¶¶ 76-79; Ex. 2003 at 168:11-169:24.

In each of these cases, the POSA would expect the pH of the composition in the column following the load step likely would be at the pH of the binding solution used—indeed, the very point of a buffered solution is to maintain its pH—but the POSA could not be certain of that. Cramer ¶¶ 58-59, 66-67, 73, 79. And what the POSA even more certainly could not determine is that the pH of the composition in the column prior to washing had a different pH than the wash

solution, a prerequisite of any finding of anticipation. *Id.* ¶¶ 55-59, 64-67, 70-73, 78-79.

III. CLAIM 16 IS NOT INVALID (GROUNDS 6-7).

The remaining grounds concern claim 16, which recites:

> A method for purifying a protein, which comprises a C_H2/C_H3 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 at 23.

As discussed above, *see* Background Section C, the Breece Patent disclosed several different intermediate washes that could be used in lieu of the Blank Patent's intermediate wash step. While claim 13 relates to the "high concentration buffer" embodiment, claim 16 relates to a distinct embodiment, the "salt and solvent" embodiment, *see* Ex. 1001 at Fig. 5. In claim 16's method, the intermediate wash step uses salt (to disrupt electrostatic interactions) and one of a group of solvents (to disrupt hydrophobic interactions). Cramer ¶ 90.

A. Claim 16's Method is Novel Over Fang (Ground 6)

Boehringer alleges in Ground 6 that claim 16 is anticipated by Fang (Ex. 1009). Fang does not disclose processes for the industrial purification of antibodies. Cramer ¶ 98-100. Rather, it discloses a specialized process that concatenates a protein A column and an anion exchange column in order to separate, for analytical purposes, a particular antibody and a variant of that antibody that differs by the sulfation of a single tyrosine residue. *Id.* ¶¶ 91, 98-100. Because the objective of Fang's process ultimately is not to purify an antibody as part of making a drug, it materially differs from claim 16's process.

1. Fang Discloses a Highly Specialized Analytical Technique.

Boehringer's terse explanation of Fang, *see* Pet. at 48-49, elides the different purpose for which it discloses using Protein A chromatography. The paper concerns a particular antibody, "HuDREG-55," a "humanized IgG4 monoclonal antibody that binds to human L-selectin." Ex. 1009 at 1. The authors observed "during purification of HuDREG-55" that the affinity purified antibody, *i.e.*, the composition resulting from protein A chromatography, could be separated into two components: (1) the unmodified antibody; and (2) a variant resulting from the

sulfation of a tyrosine residue in the light chain. *Id.*[6] The authors hypothesized that differences in cell culture conditions might affect the ratio of variants. *Id.* at 2. Accordingly, they developed an analytical technique capable of separating these two closely-related species in order to determine which species was favored under particular culture conditions. *Id.* at 2.

The Fang paper has nothing to do with the industrial purification of antibodies for therapeutic use. Cramer ¶¶ 98-100. The analytical apparatus used in the paper, the "Integral microanalytical workstation," is not used for the purification of antibodies. Ex. 1009 at 2; Cramer ¶ 99. Dr. Bracewell conceded—eventually—that this type of workstation was for "analytical purposes" and that he had never heard of it being used in the manufacture of a therapeutic antibody. Ex. 2003 at 211:2-213:15. That makes sense because the Fang process analyzes a sample of 500 µl, Ex. 1009 at 2, "an amount literally millions of times less than the thousands of liters of cell culture fluid purified in a typical industrial protein A chromatography process," Cramer ¶ 99.

[6] Boehringer's quotes in its claim chart this background statement about "purification of HuDREG-55." *See* Pet. at 50 (quoting Ex. 1009 at 1). This statement about purification is unrelated to the analytical method disclosed in Fang. Cramer ¶ 91, 97-100, 144.

Fang discloses arranging the Integral workstation to connect a protein A column to an anion exchange chromatography column via an 8 µl "pancake" mixer. Ex. 1009 at 2-3. Table 2 summarizes the steps of Fang's optimized analytical method. *Id.* at 3. During the steps defined in Table 2, a defined number of column volumes ("CVs") of solutions comprising mixtures of "1A," "1B," "2A," and "2B" (defined in Table 1, *id.* at 2-3) are pumped through the apparatus. The outlet of the apparatus was monitored, and the results are depicted in chromatograms (Figures 1-5). The chromatograms depict the intensity of the absorbance at 280 nm of the solution coming off the column. Cramer ¶ 94 ("Because amino acids with aromatic rings have peak absorbance at 280 nm, measuring absorbance at 280 nm is a widely-used technique for measuring the amount of protein in a solution."). On the second y-axis, the chromatograms depict the composition of the solvent being pumped through the column at different points in time. *Id.*

2. Fang Does Not Disclose "Removing Contaminants."

Claim 16 requires that the intermediate wash step "remov[e] contaminants," specifically, by washing the solid phase with particular compositions of salt and solvents. As explained below, Fang's chromatograms make perfectly clear that its protein A wash step does not remove contaminants.

The Petition alleges that the "removing contaminants by washing" step of claim 16 is anticipated by step 3 of Fang's analytical method, the "Column 1 wash." *See* Pet. at 51-52. As set forth in Fang Table 1, the Column 1 wash composition is a 60:40 mixture of 1A:2A, both of which contain 2.5 percent isopropanol and some amounts of potassium chloride and potassium phosphate.

The Petition fails to allege where in Fang there is any disclosure that this composition "removes contaminants." *See* Pet. at 51-52. The Petition's silence on this point results from the fact that every single chromatogram in Fang shows no detectable level of protein eluting from the two-column apparatus during this wash step. Cramer ¶¶ 94-95. Reproduced below is Figure 5 of Fang, with yellow highlighting emphasizing the portion of the method during which step 3, the "column 1 wash" is occurring. The gray line indicates that the 60:40 column 1 wash composition is being pumped through the column, the thick black line at 0 indicates that no protein is being detected at the outlet of the column. Cramer ¶ 94.

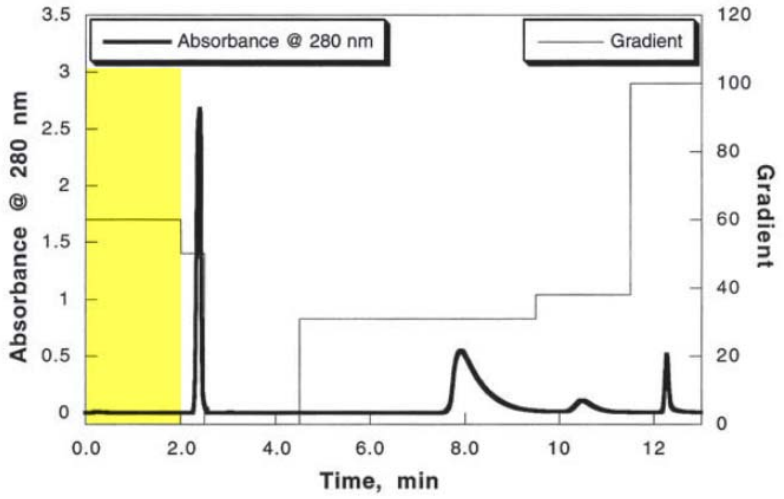

Fig. 5. Dual-column separation obtained for a HuDREG-55 mixture of two isoforms after reducing the ionic strength of the solvents used for the protein A column. The solvent mixture used for elution of column 1 was 50% 1A–50% 2A (with 1A and 2A being 75 m*M* potassium chloride, 25 m*M* potassium phosphate and 2.5% isopropanol, pH values of 7.3 and 1.7, respectively), for 0.5 min. The solvent mixture used for the binding step of column 2 was 100% 1B, for 2 min. Solvents 1B and 2B were 50 m*M* Tris, pH 8.5, and 50 m*M* Tris, 1 *M* NaCl, chloride, pH 8.5, respectively.

Ex. 1009 at 5 (Figure 5) (highlighting added). In fact, it is not until well into the subsequent elution step (step 4, 50:50 mixture) that contaminants are detected at the outlet of the column and thus "removed." Cramer ¶ 94.

An anticipatory reference must disclose "each and every" limitation of a challenged claim. *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 868 (Fed. Cir. 2015) (quoting *Am. Calcar, Inc. v. Am. Honda Motor Corp.*, 651 F.3d 1318, 1341 (Fed. Cir. 2011)). Because Boehringer does not even allege that Fang's column 1 wash "removes contaminants," and because in fact Fang shows no protein detected at the column outlet during the "column 1 wash," Cramer ¶¶ 94-95, Fang does not disclose that its wash step "remov[es] contaminants," and claim 16's "removing contaminants" language cannot reasonably be understood to

encompass a step in which no contaminants are detected leaving the column. Fang thus cannot anticipate claim 16.

3. Fang Does Not Disclose "Recovering the Protein from the Solid Phase."

Consistent with a typical industrial protein A process, the final step of claim 16 is "recovering the protein from the solid phase." Claim 16 recites a "method for purifying a protein," and its final step of "recovering the protein" is essential to fulfilling that purpose. Yet the Petition's conclusory treatment of this limitation consists, in its entirety, of a short statement in its claim chart: "*See* Table 2, listing step 4 as 'column 1 elution to column 2.'" Pet. at 52.

This barebones contention misinterprets Fang. At step 4 of Fang's analytical process, the antibody is not "recovered from the solid phase"—it is believed either to be trapped in the pancake mixer or beginning to adsorb to the anion exchange column. Cramer ¶ 97. Boehringer's utter failure to explain how the antibody is "recovered" during step 4 precludes it from carrying its burden of persuasion that Fang discloses the method recited in claim 16 of Breece.

While the Petition's allegation of anticipation rests on citing a single sentence in Fang, to be clear, nowhere does Fang state that the antibody was "recovered" following its analytical process. *See generally* Ex. 1009; Cramer ¶ 97. Fang nowhere suggests that the solution coming out of the column was collected,

which makes sense because the purpose of Fang's method is not to purify an antibody but to measure the relative areas under the curve of the two peaks associated with the two isoforms of HuDREG-55 in order to study the effect of cell culture conditions. Cramer ¶ 98. The total volume of the sample solution used in Fang—500 microliters—is so trivial that the POSA would not have understood the point of trying to recover the HuDREG-55 isoforms from Fang's micro-analytical workstation. Cramer ¶ 99. Because an anticipatory reference must disclose "each and every" limitation of a challenged claim, *Ineos*, 783 F.3d at 868, the Petition's failure to identify any disclosure in Fang of claim 16's recovery step precludes Boehringer from meeting its burden of persuasion as to Ground 6. And any suggestion by Boehringer that merely eluting the protein from the first column to the second column is the same as "recovering the protein" results from an unreasonable interpretation of the "recovery" limitation in view of the purpose of the claimed method to purify the protein.

B. The Board's Institution Was Improper.

Boehringer alleges in Ground 7 that claim 16 is obvious over the combination of the '526 patent (Ex. 1008 or Blank) and Reifsnyder (Ex. 1018), and it is hard to imagine how Boehringer could have been clearer in framing the ground. *See* Pet. at 8 ("In **Ground 7** Petitioner challenges claim 16 as obvious over the '526 patent and Reifsnyder"); 52 ("**GROUND 7 – CLAIM 16 IS**

OBVIOUS OVER THE '526 PATENT AND REIFSNYDER"); 58 ("Claim 16 is therefore obvious over the '526 patent and Reifsnyder.").

The Board nevertheless instituted trial on a ground of its own making, "Obviousness over Blank, Reifsnyder, and Fang." Paper 8 at 18. It did so despite recognizing that "Petitioner does not explicitly include Fang when introducing the obviousness ground." *Id.* at n.11. As a preliminary matter, the Board is not authorized to invent new grounds for instituting trial. *See* 37 CFR § 42.108. This limit on the Board's authority is particularly clear following the Supreme Court's ruling in *SAS Institute, Inc. v. Iancu*, explaining that "the petitioner's petition, not the Director's discretion, is supposed to guide the life of the litigation." *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018). This trial should proceed on the Ground 7 defined by Boehringer—the '526 patent combined with Reifsnyder—not the Ground 7 defined by the Board.

The Board concluded that "there is no prejudice to Patent Owner to include Fang in the statement of the obviousness ground." Paper 8 at 18-19, n.11. Patent Owner respectfully disagrees because it lacks clear notice of the Ground to which it is responding. As explained further below, the concept of "Blank, Reifsnyder, and Fang" as an obviousness combination does not make sense. Both parties agree that Blank teaches a state-of-the-art protein A chromatography process for purifying therapeutic antibodies, *see* Background Section B. Boehringer postulates

three scenarios in which Blank's high-salt intermediate wash might be ineffective. Pet. at 53-54. According to Boehringer, the POSA would then have replaced Blank's high-salt wash with the ethanol/salt wash taught in Reifsnyder and practiced claim 16. Pet. at 56.

Fang adds nothing to the argument framed by Boehringer. It teaches an isopropanol/salt wash, which according to Boehringer could have been used in lieu of Reifsnyder's ethanol/salt wash, not in addition to Reifsnyder's ethanol/salt wash. Pet. at 56. Yet the Board has instituted trial (in violation of 37 CFR § 42.108) on a combination of references that the Petition does not explain and which does not make sense, depriving Patent Owner of adequate notice.

In view of *SAS*, Patent Owner responds to the argument as presented in the Petition by Boehringer.

C. Claim 16 Is Not Obvious (Ground 7).

Boehringer also alleges that the method of claim 16 would have been obvious to the POSA because it would have been obvious to replace Blank's high-salt wash with the ethanol/salt wash taught in Reifsnyder.[7] This argument is wrong

[7] Boehringer's expert, Dr. Daniel Bracewell, defines the person of ordinary skill in the art as follows:

because the motivations Boehringer ascribes to the POSA do not make sense in the context of its argument. This argument is also wrong because Boehringer provides no basis to believe the POSA would have had a reasonable expectation of success in recovering the target protein following the use of Reifsnyder's washing conditions.

1. Obviousness Requires the POSA To Have Had a Reason to Practice the Claimed Method and a Reasonable Expectation of Success in Doing So.

> [A] person of ordinary skill in the art would have experience with protein manufacturing and purification. This person would understand the mechanics of and the science behind protein A chromatography because that is one of the common steps performed during protein purification. This person would also have hands on experience with other protein purification methods, including other types of chromatography. The relevant experience could be gained by formal education, such as by a Ph.D., in chemical engineering, physical chemistry, analytical chemistry, biotechnology, biochemistry, or a related field, along with at least three years' post-education experience.

Bracewell ¶ 28. Genentech does not dispute this recitation of the level of ordinary skill for purposes of this proceeding.

Boehringer's obviousness challenge requires it to demonstrate that "the difference between the subject matter [of the claims] and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is determined as of the time of the invention, from the viewpoint of the POSA. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000), and, in assessing obviousness, the Board must determine whether the POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418-19 (2007). In other words, for a claim to be obvious, the POSA would have to have been motivated or had reason, based on what was known in the prior art, to make the claimed invention by putting together all of the elements of the claim in the particular way the claims recite, as well as a reasonable expectation of success in doing so. *KSR*, 550 U.S. at 418-19; *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008).

2. The Alleged Motivations Do Not Make Sense.

The Petition alleges that the method of claim 16 would have been obvious because the POSA would have had reason to replace the high-salt solution used in Blank's intermediate wash step with another solution. Pet. at 53. Specifically, it

argues that "in some cases . . . the use of certain types of salts are not desirable for various reasons," *id.*, and identifies three such cases, *id.* at 53-55. None of these reasons makes sense in the context of the Blank patent.

a. Boehringer's first rationale warrants one line of discussion: "some antibodies form chemical interactions with some salts used in buffers. (Ex. 1015 (Gagnon) at 185-86.)" Tellingly, Boehringer's expert declaration is not cited, and Dr. Bracewell's discussion of the POSA's alleged motivations nowhere mentions this argument. *See* Ex. 1002 ¶ 71.

The underlying reference makes plain why Boehringer's expert would not endorse this allegation. The cited passage of Gagnon explains that on occasion, sufficiently-charged antibodies are able to "form stable crosslinks with polyvalent anions." Ex. 1015 at 185. A polyvalent anion has a charge of -2 or more. Cramer ¶ 120. The intermediate wash step exemplified in Blank uses TMAC (tetramethylammonium chloride) or TEAC (tetraethylammonium chloride). Cramer ¶ 121. The chloride ion has a charge of -1; it is a monovalent anion and it is incapable of causing stable crosslinks to form between antibodies to create an aggregate. *Id.* Because the problem identified in Gagnon—that a polyvalent anion may cause aggregation—is physically inapplicable to the intermediate wash step taught by Blank that uses monovalent salts, the POSA would not have been

motivated by Gagnon to change Blank's intermediate wash step. Cramer ¶¶ 120-22.

b. Boehringer's second rationale similarly misapprehends the underlying technology. It focuses on the analytical chromatography methodology disclosed in Fang. Pet. at 53-54. The analytical apparatus in Fang connected a protein A column to an anion exchange column. Cramer ¶¶ 91, 125. The anion exchange column binds to proteins via electrostatic interactions, and proteins are eluted from such columns by using high-salt solutions. Cramer ¶ 125. Thus, Fang observed that a solution of isopropanol and 100 mM salt was preferable to a solution of isopropanol and 200 mM salt because the latter was so salty that it prevented binding to the anion exchange column that had been connected to the protein A column. Cramer ¶ 123; Pet. at 54.

At most, this observation would encourage the POSA to be mindful of the amount of salt in the eluate from a protein A column before applying that eluate to a downstream anion exchange column. Cramer ¶ 126. But the issue at hand concerns the saltiness of the solution used for *washing* the protein A column, not the saltiness of the solution used for *eluting* the antibody from the Protein A column. Only the latter solution is conceivably subject to further downstream processing on an ion exchange column; the former solution (which comprises contaminants and not antibody) is discarded as waste. Cramer ¶¶ 124-26. Thus,

no matter how much TMAC or TEAC were used in in the intermediate wash step of Blank's method, that salt could not interfere with later downstream processing. Cramer ¶¶ 124-26. Accordingly, the POSA would not have been motivated to modify Blank by a fear that a salty washing solution would impair downstream processing.

As technically inconceivable as Boehringer's argument is, it also rests on sleight of hand, as it does not explain why the POSA would have been motivated to modify *Blank's* method. Rather, it explains why someone might be motivated to modify the amount of salt used in Fang's concatenated-column analytical set-up. But as explained above, the salty washing solution in Blank's method is discarded and not part of the antibody-containing solution that is recovered from the column. While Boehringer's second rationale might encourage the POSA to modify Fang, Ground 7 concerns why the POSA would have modified Blank. And this purported motivation is inapplicable to Blank.

c. Boehringer's final rationale is simply unsupported. It argues that "in other cases, high concentrations of salt, used to disrupt electrostatic interactions, are not successful in washing proteins that are bound to glass or silica columns." Pet. at 54. But Boehringer cites no evidence that the high-salt wash used in the Blank patent would fail to remove contaminants. The inventors of the Breece patent were certainly not motivated by such a concern. They described the Blank

patent's high-salt wash as "effective" for removing contaminants, *see* Ex. 1001 at 2:10-16, 18:45-49, and depicting it as the baseline for all of their studies, *see id.* at Figs. 2-6 (bold black line corresponds to TMAC washing solution). One contemporaneous review article from the time touted TMAC's efficiency as an intermediate wash. Ex. 2004 at 311.

Failing to find a single example in the Protein A chromatography literature suggesting that the Blank patent's high-salt wash would be ineffective at removing contaminants, Boehringer cites Reifsnyder, a paper describing a different type of chromatography (non-specific adsorption chromatography) being used to purify different proteins (not antibodies). Pet. at 54-55. Per Boehringer, "Reifsnyder teaches 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.*

Again, Boehringer cites no expert testimony to support its reading of the reference. Dr. Bracewell's testimony regarding Reifsnyder says no such thing. He states only that "in Reifsnyder, a solution with salt and ethanol worked better than a high concentration TMAC solution." Ex. 1002 ¶ 72. He does not explain further what happened in Reifsnyder, but Dr. Cramer does. Cramer ¶¶ 102-17. He explains Reifsnyder's teaching in detail, making clear that "better" in this context refers to the ethanol/salt solution's ability to *elute* only the particular protein of

interest (and *not* other contaminants) while TMAC eluted both the protein of interest and more hydrophobic contaminants. Cramer ¶¶ 116, 128-32 (explaining Ex. 1018 at 76-79); *see also id.* ¶¶ 102-115, 117. Reifsnyder does not suggest that TMAC was ineffective at removing contaminants from a silica column; to the contrary, to the contrary, Reifsnyder suggests by using TMAC to regenerate the column that TMAC was superior at removing contaminants. Cramer ¶¶ 114, 116, 130.

Simply put, there is no evidence supporting Boehringer's attorney argument that the POSA would have been motivated by an alleged lack of efficacy. As Dr. Cramer explains, the POSA would have understood Blank's wash step to remove contaminants effectively and would not have understood Reifsnyder to suggest that an ethanol/salt solution would be more effective (or even equally effective) at desorbing contaminants. Cramer ¶¶ 113-16, 128-32. To the contrary, the POSA would have understood Reifsnyder to teach that a TMAC solution was the most effective solution for desorbing proteins from a silica column. Cramer ¶ 117, 130-32.

* * *

Because the Petition's alleged motivations for modifying the intermediate wash step of the Blank patent are not credible, claim 16's validity should be confirmed.

3. The Alleged Expectation of Success Does Not Address Claim 16 as a Whole.

Even if the POSA had cause to modify Blank's purification method and chose to look to Reifsnyder, the POSA could not have reasonably expected success. The crux of Boehringer's argument is that the POSA "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." Pet. at 55-56. Dr. Bracewell testifies similarly, explaining that the POSA "would have had a reasonable expectation of success that using a solution of a salt and a solvent such as ethanol would successfully desorb the contaminant proteins from the column in protein A chromatography." Bracewell ¶ 70.

This argument is focused too narrowly. Boehringer and Dr. Bracewell have explained why the POSA might have reasonably expected success at removing contaminants, but that is only the second step of claim 16's three-step process. They have not explained why the POSA would have reasonably expected success in performing claim 16's method of purifying a protein, which includes both removing contaminants *and* recovering the protein that had adsorbed to the protein A. The law requires that claim 16 be analyzed as a whole. "Focusing on the

obviousness of substitutions and differences, instead of on the invention *as a whole*, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990) (emphasis added); *see also* 35 U.S.C. § 103(a) (2006) (a patent may not issue if "the differences between the claimed invention and the prior art are such that the claimed invention *as a whole* would have been obvious." (emphasis added)). Boehringer's failure of proof on this point should be dispositive.

In fact, the fundamental, mechanical differences between the adsorption chromatography in Reifsnyder and protein A chromatography would have precluded the POSA from having a reasonable expectation of success.

Adsorption chromatography (used in Reifsnyder) and protein A affinity chromatography (used in Blank) use fundamentally different mechanisms to purify a protein of interest. The simplest difference is that the former is a non-specific method of chromatography, the latter is a specific method of chromatography. This difference manifests in the composition of the columns. Reifsnyder's chromatography column was made of silica. Cramer ¶¶ 102-03. A protein A column may also be made of silica (or glass), to which an affinity ligand, protein A, has been covalently attached. Cramer ¶¶ 19, 137.

This difference in the columns' compositions dictates the differences in the techniques' mechanisms. In adsorption chromatography, there is only one

mechanism of interaction that matters: the non-specific interactions between the protein/contaminants and the column. Cramer ¶ 135. In protein A chromatography, there are two mechanisms of interaction that matter: the specific (but non-covalent) interactions between the protein A ligand the protein of interest and the undesired, non-specific interactions between contaminants and the column (or between contaminants and the ligand, or between contaminants and bound antibody). Cramer ¶¶ 136-38. Critically, it was understood that the specific interaction between protein A and the C_H2/C_H3 region was driven primarily by hydrophobic interactions, *see* Ex. 1015 at 158, Cramer ¶ 136, the same type of interactions believed to be involved in the non-specific binding of contaminants to the column, as Dr. Bracewell admits, *see* Ex. 1002 ¶ 41.

These differences in interactions impose different goals. *See* Cramer ¶¶ 135-40. In Reifsnyder's adsorption chromatography, the goal is to select conditions that cause the protein of interest (and hydrophobic contaminants) to bind to the column while less hydrophobic contaminants flow through. *Id.* ¶ 135. Binding to the column is a feature, not a bug. The conditions are then altered to elute the protein of interest while more hydrophobic contaminants remain bound to the column. *Id.* In protein A chromatography, the goal is to select conditions that do *not* encourage binding to the column, because the intent is to cause everything except the protein of interest to flow through the column. *Id.* ¶ 137. Loading

conditions are chosen to permit adsorption of the antibody to protein A, and washing conditions are acceptable only to the extent that they *maintain* the adsorption of the antibody to protein A. *Id.*

This imperative to maintain adsorption of the antibody to the protein A during washing is the critical issue overlooked by the Petition's allegations regarding expectation of success. The Petition nowhere explains why the POSA would have expected that conditions designed to disrupt hydrophobic interactions and elute proteins off of a silica column also would have been reasonably expected to have no effect on the primarily-hydrophobic interaction between the protein A ligand and the antibody of interest. *See generally* Pet. at 56-57.

As Dr. Cramer explains, the POSA could not reasonably have had such an expectation. The overlap in the mechanisms between (i) the interaction between contaminating proteins and the column and (ii) the interaction between the antibody and the protein A ligand means that solution conditions chosen to disrupt the former interaction could not reasonably have been expected by the POSA to avoid impacting the latter. Cramer ¶¶ 135-40; *see also* Ex. 1015 at 160 (describing solutions of organic solvents like methanol as being used to *elute* the antibody from protein A).

The potential for a solution comprising an organic solvent and salt to denature the protein of interest also would have precluded the POSA from having a

reasonable expectation of success because such denaturation would have prevented the POSA from "recovering the protein," as required by claim 16. Cramer ¶¶ 145-55. The POSA would have understood that organic solvents could denature proteins; indeed, it was hypothesized that the structural changes caused by such denaturing are what permitted reverse-phase liquid chromatography to separate closely-related proteins.[8] *Id.* ¶ 147; Ex. 2005 at 3908. When discussing elution conditions, the Gagnon chapter cited by Petitioner explicitly warns of this risk, noting: "antibodies can be dissociated with moderate concentrations of stronger organic solvents, such as methanol (20-30% v:v), but *the probability of permanent antibody denaturation disqualifies them from preparative applications*." Ex. 1015 at 160 (emphasis added). Boehringer and Dr. Bracewell nowhere explain why they contend that the POSA would have reasonably expected success using a wash solution that the art described as "*disqualified*" from use in preparative applications (*i.e.*, purification methods in which one wishes to recover the protein, like claim 16, and in distinction to analytical methods like those disclosed in Fang, *see* Cramer ¶¶ 16-18, 27-28, 98-100, 144-47). Boehringer and Dr. Bracewell also fail

[8] Reverse-phase liquid chromatography is a type of adsorption chromatography in which feed components are separated "based on hydrophobic interactions with a non-polar stationary phase or resin." Cramer ¶ 27.

to grapple with Gagnon's teaching that such organic solvent solutions dissociate the antibody from the protein A ligand, disqualifying them from being used as washing solutions. Cramer ¶¶ 144-55.

Even Dr. Bracewell acknowledges, "as a side note," that organic solvents can have a denaturing effect on proteins. Ex. 1002 ¶ 72. He contends that this acknowledged risk would *not* have affected the POSA's expectations of success based on citations to snippets of two patents that cannot bear the weight he puts on them. Ex. 1002 ¶ 72; Cramer ¶¶ 148-54.

The first is Blank, which explains that various forms of chromatography may be used downstream of protein A chromatography, including reverse phase HPLC. Ex. 1008 at 14:64-15:5. Blank, however, does not disclose the conditions for reverse phase HPLC that could be acceptable. Cramer ¶ 150. This generic disclosure would not assuage the POSA's concern that the ethanol/salt solution disclosed in Reifsnyder would have a denaturing effect on an antibody and/or the protein A on the column, and it would not have changed the POSA's expectations. *Id.* ¶¶ 149-50.

The second is another Genentech patent, Exhibit 1013 (U.S. Patent No. 6,265,542 or "Fahrner & Reifsnyder"), expanding upon Reifsnyder's prior work using reverse phase chromatography to purify IGF-1 (Ex. 1018). Dr. Bracewell simply mischaracterizes this document.

He states that "the '542 patent teaches that hexylene glycol is preferred to other organic solvents because it is not flammable and not denaturing to proteins," citing Ex. 1013 at 3:16-18. Ex. 1002 ¶ 72. But the Fahrner & Reifsnyder patent does not say that. Cramer ¶¶ 151-52. The cited passage reads: "Hexylene glycol, with a flashpoint of about 93 °C, produced essentially the same yield, purity, and throughput as acetonitrile and with *less* denaturing effect." Ex. 1013 at 3:16-18 (emphasis added). (For comparison, Fahrner & Reifsnyder had previously explained that acetonitrile was "somewhat of a denaturant," hence their desire to identify a solvent with less denaturing effect. *Id.* at 3:6-12.) Dr. Bracewell's substitution of "not denaturing" for "less denaturing" is as unsupported as it is brazen.

He further states that the Fahrner & Reifsnyder patent "teaches that ethanol, methanol, and isopropanol are also not denaturing to the antibodies discussed in the patent," citing Ex. 1013 at 2:48-55. Ex. 1002 ¶ 72. Again, Fahrner & Reifsnyder simply does not say that. Cramer ¶¶ 153-54. The cited passage in fact reads:

> There is a need in the art for an efficient reversed-phase liquid chromatography protocol for selectively separating molecules such as peptides, polypeptides, and non-peptidyl compounds from other molecules using a solvent that is less toxic, less expensive, less denaturing, and less flammable than flammable solvents often used as

> eluents for reversed-phase chromatography, such as acetonitrile, ethanol, methanol, and isopropanol.

Ex. 1013 at 2:48-55. In the context of this passage, acetonitrile, ethanol, methanol, and isopropanol are the problematic solvents that can denature proteins, not the proposed solution to the problem (which Fahrner & Reifsnyder claimed was hexylene glycol). Cramer ¶ 154.

Setting aside what Fahrner & Reifsnyder teach about the denaturing effect of organic solvents on antibodies, the patent concerns reverse phase chromatography and sheds no light on the effect of organic solvents on the protein A ligand. But just as the POSA would have been concerned about the effect of an organic solvent on the antibody's structure, the POSA also would have been concerned about its effect on the protein A ligand which, if it were to unfold or denature during the washing step, might release the antibody that the POSA had been trying to retain. Cramer ¶ 140, 145-47, 155. None of the references cited by Dr. Bracewell concern the effect of organic solvents on protein A, and Dr. Bracewell nowhere suggests that the POSA would have had a reasonable expectation that the protein A would not denature when washed with an organic solvent/salt solution like the ethanol/salt solution used in Reifsnyder's chromatography process.

Finally, the use of isopropanol/salt solutions in Fang does not change this analysis, because Fang relates to an analytical chromatography method in which

recovery of the protein is not the goal. Cramer ¶ 97-100, 144. The field recognized that the denaturing effect organic solvents can have on proteins is irrelevant in the context of analytical chromatography, where the purpose is not recovery of the protein, but separation and quantification of the components of the sample. Ex. 2005 at 3915 (observing that "when analysis and not purification is the desired goal, irreversibly altered protein structure can also be successfully employed"). The POSA would not have expected the solutions used in Fang not to have affected the antibody's structure because analytical separation, and not recovery, was the purpose of Fang's method. Cramer ¶ 97-100, 144; Ex. 1009 at 40 ("The following report details the development and implementation of a two-dimensional chromatography method *to analyze* cell culture supernatants during a fermentation run.") (emphasis added).

* * *

In sum, none of the reasons outlined in the Petition would have motivated the POSA to modify the washing solution used in the intermediate wash step of Blank's protein A process, let alone, to look to Reifsnyder or Fang for a solution comprising a mixture of organic solvent and salt. And, even if the POSA were inclined to use such a solution in a protein A chromatography process, the POSA could not reasonably have anticipated success in practicing claim 16's purification method in view of the prior art's teachings that such solutions can denature

proteins and disrupt the hydrophobic interactions that keep the antibody bound to the protein A ligand.

CONCLUSION

For the foregoing reasons, the Board should reject Boehringer's challenges and confirm the patentability of claims 13 and 16 of the Breece Patent.

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CERTIFICATION OF WORD COUNT
(37 C.F.R. § 42.24(d))

In accordance with 37 C.F.R. § 42.24, as amended, the undersigned certifies that this Patent Owner Response complies with the applicable type-volume limitations of 37 CFR §§ 42.24(a)(i) and 42.24(b)(2). Exclusive of the portions exempted by 37 CFR 42.24(a), this Patent Owner Response contains 13,452 words as counted by the word processing program used for its preparation (Microsoft Word 2013).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the above-captioned *Patent Owner Response* and all Exhibits and other documents filed together with this *Patent Owner Response* were served on June 18, 2018 by filing these documents through the Patent Review Processing System as well as delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

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