UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Patent No. 7,807,799
Issue Date: October 5, 2010
Title: REDUCING PROTEIN A LEACHING DURING PROTEIN A AFFINITY CHROMATOGRAPHY

Inter Partes Review No. 2016-01837

PATENT OWNER RESPONSE

Pursuant to 37 C.F.R. § 42.120, Patent Owner, Genentech, Inc. submits this Response to the Petition for *Inter Partes* Review of U.S. Patent No. 7,807,799 (the "Fahrner Patent") filed by Petitioner, Hospira, Inc.

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Over the past two decades, monoclonal antibody therapies have transformed medical treatment. Genentech has been at the forefront of this revolution, starting with the approval in 1998 of Herceptin (trastuzumab) for the treatment of breast cancer. The challenged patent, U.S. Patent No. 7,807,799 (Ex. 1001, "the Fahrner Patent"), arose from Genentech's research efforts in the early 2000s to develop better methods for manufacturing trastuzumab (Herceptin) and other therapeutic antibodies the company had in clinical development. The Petitioner, Hospira, seeks to market biosimilar trastuzumab, Exs. 2035 and 2036; and has challenged the validity of this and several other patents that cover this product.[1]

Genentech's research focused, in part, on protein A chromatography, the first "downstream" step in purifying trastuzumab from the harvested cell culture fluid ("HCCF"). Genentech's scientists learned that proteolytic enzymes in the HCCF caused protein A to leach from the chromatography column into the eluate,

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[1] *Hospira, Inc., v. Genentech, Inc.*, 2017-00731, Paper 1 (Jan. 20, 2017); *Hospira, Inc., v. Genentech, Inc.*, 2017-00737, Paper 1 (Jan. 20, 2017); *Hospira, Inc., v. Genentech, Inc.*, 2017-00739, Paper 1 (Jan. 20, 2017); *Hospira, Inc., v. Genentech, Inc.*, 2017-00804, Paper 1 (Jan. 30, 2017); *Hospira, Inc., v. Genentech, Inc.*, 2017-00805, Paper 1 (Jan. 30, 2017).

adding an impurity to eliminate from the final product. And Genentech scientists solved this problem by chilling the HCCF to a particular temperature range—a solution that is neither disclosed nor suggested in any of the art cited by Hospira. This method is claimed in the Fahrner Patent, and [redacted].[2]

Hospira apparently plans to copy Genentech's patented manufacturing methods in addition to the trastuzumab molecule itself. But the prior art cited in the Petition does not come close to justifying the relief requested in the Petition. Neither of Hospira's two anticipation references, WO '389 (Ex. 1003) and van Sommeren (Ex. 1004), disclose the Fahrner Patent's method of chilling HCCF to the claimed temperature range. All they disclose is protein A chromatography performed in laboratories with unusually broad definitions of "ambient temperature." But it is the temperature of the cell culture fluid, not the temperature of the room, that matters. And, in any event, the temperature ranges recited in the references at best only minimally overlap the claimed temperature range, and because the claimed temperature range is critical to the operability of the invention,

[2] Dr. Christopher J. Dowd is the Senior Director and Head of Purification Development at Genentech. Dowd ¶¶ 4-8.

as shown by the data in the Fahrner Patent and in new experiments performed for this proceeding, there is no anticipation.

Hospira's obviousness arguments are no more substantial. Hospira argues that "routine optimization" would result in the performance of the claimed methods. Like the invocation of "common sense," *see Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355 (Fed. Cir. 2016), "routine optimization" invites hindsight bias, and that is particularly so here. At his deposition, Hospira's expert, Dr. Todd Przybycien, admitted what the art itself makes clear, that process engineers experimenting with protein A chromatography could and did vary several different conditions with precision, *but temperature was not one of them*.

Hospira also contends that both the causes of protein A leaching and Genentech's claimed solution were obvious to the person of ordinary skill. But this is another argument hopelessly riddled with hindsight. It requires combining a reference about antibody purification with an article about the treatment of blood disorders (Ex. 1005), and a third reference about the kinetics of bacterial proteases (Ex. 1006). The notion that the person of ordinary skill would have combined the teachings of these disparate references to practice the claimed inventions is not credible.

The obviousness arguments also are belied by objective evidence from the time of the invention. Among other things, one of the inventors was selected by

the American Chemical Society to present the research disclosed in the Fahrner Patent at the 2005 National Meeting of the Division of Biochemical Technology. That simply would not have happened if, as Hospira and its expert now claim, Genentech's research team was merely engaged in "routine optimization" work.

BACKGROUND

A. Protein A Chromatography.

Affinity chromatography is the typical first step in industrial scale antibody purification, and protein A, because it binds antibodies so effectively, has emerged as the affinity ligand of choice for separating antibodies of interest from other impurities. Ex. 2008 ("Cramer") ¶¶ 21, 23.[3] A typical protein A chromatography process involves two steps. *Id.* ¶ 22. First, the HCCF composition containing the target antibody is loaded onto a column containing immobilized protein A. *Id.* ¶ 22. As the HCCF passes through the column, the target antibody is separated from the mixture because it selectively binds to the protein A. *Id.* Next, a low pH buffer is loaded onto the column to dissociate the target antibody from the protein A, eluting the now-purified antibody from the column. *Id.* Protein A columns are

[3] Dr. Steven M. Cramer is a professor at the Rensselaer Polytechnic Institute, *see* Cramer ¶¶ 2-7, Ex. A, and is acknowledged by Hospira's expert Dr. Przybycien as one of the world's leading experts on protein purification, Ex. 2010 at 31:19-24.

so efficient that they remove most of the host cell proteins and other impurities present in the HCCF in a single chromatography step. *Id.* ¶ 23, 25.

A major drawback of protein A is its expense. Cramer ¶ 24. Protein A columns therefore are highly engineered to permit reuse for hundreds of purification cycles before being replaced. *Id.* This requires protein A to be immobilized on materials, such as agarose, porous glass, or polystyrene, that can withstand washing with the harsh solutions necessary to elute and clean the column. *Id.* ¶ 160; Ex. 2014 at 37, Table 1.

Another problem with this chromatography step is that some amount of protein A leaches into the eluate. *Id.* ¶ 24. Because protein A can be toxic, it must be reduced below certain levels before the purified antibodies are suitable for therapeutic use. *Id.* ¶¶ 20, 47; Ex. 2006 at 304-305. It is typically removed during additional purification steps following protein A chromatography. Cramer ¶¶ 31-38.

B. The Fahrner Patent.

In the early 2000s, Genentech scientists were researching ways to improve the processes then in use to make trastuzumab. Dowd ¶¶ 18-25.[4] While

[4] Dr. Christopher J. Dowd is the Senior Director and Head of Purification Development at Genentech. Dowd ¶¶ 4-8.

implementing and scaling up these processes, the Genentech scientists got a "curve ball," Ex. 2011 at 19—levels of leached protein A so high that downstream purification steps were unsuccessful at removing it. Dowd ¶ 19; Ex. 2011 at 20.

To solve this problem, these scientists conducted a series of experiments adjusting a number of different variables. Dowd ¶¶ 20-25; *see* Ex. 1001 at 21:56-24:50. They questioned whether the observed increase was caused by changes in the protein A detection assay; they tested whether the new protein A resin they switched to was the source of the problem; they adjusted the height of the column; they tried different buffers; and they modified the downstream processes. Dowd ¶¶ 20-23. Over months of research into this issue, Dr. Rhona O'Leary (one of the named inventors) and her team observed that the HCCF from the Herceptin v1.0 process resulted in less leaching than the HCCF from the Herceptin v1.1 process. *Id.* ¶¶ 24, 28; Ex. 2012 at 34. This observation motivated them to experiment with changing the temperature of the HCCF loaded on to the column. Dowd ¶¶ 24-25.

These efforts are described in Example 1 of the Fahrner Patent. The patent discloses temperature-controlled protein A chromatography experiments at three different scales: "small" or lab scale, pilot scale (400 L of cell culture fluid), and full-scale (12,000 L of cell culture fluid). Ex. 1001 at 20:35-21:8. Lab scale experiments are typically used to design and test protein A chromatography processes before they are scaled up to pilot and full scale. *See* Ex. 2011 at 19;

Cramer ¶¶ 39-44. But the standard laboratory equipment for chromatography optimization experiments—an ÄKTA EXPLORER liquid handler controlled by UNICORN software—had no mechanism for adjusting and controlling the temperature of the HCCF. Cramer ¶ 43; Dowd ¶ 56. Dr. Przybycien, who also uses this standard equipment in his research, conceded at his deposition that the machine cannot control temperature. Ex. 2010 at 131:20-132:18. (This helps explain why the inventors tested other variables before trying experimenting with the temperature of the HCCF and why no reference cited by Hospira discloses such experiments.) And the setup that the inventors eventually developed and disclosed in the Fahrner Patent demonstrates how difficult these experiments were to perform:

> The temperature was controlled by immersing the column and the 5 ml stainless steel upstream line in a water bath controlled to the desired temperature of the run. The inlet line acted as a heat exchanger cooling or heating the HCCF prior to entering the protein A column, similar to the effect of chilling the HCCF in a tank at manufacturing scale.

Ex. 1001, 20:36-42. Dr. Amy Laverdiere, of the named inventors, later included a diagram of this setup in her presentation to the American Chemical Society concerning this research. Ex. 2012 at 17.[5]

The Fahrner Patent's second set of experiments were done at pilot scale using HCCF that was "stored and chilled in a 400 L-jacketed tank." Ex. 1001 at 20:60-61. The jacketed tank allowed the researchers to control the temperature of the HCCF to within 1°C. *Id*. at 20:61-62. The results of experiments at pilot scale "line up exactly with lab scale results from runs performed with the same HCCF on the same lot of PROSEP vA [a particular protein A resin]." *Id*. at 23:59-62.

The Fahrner Patent's third set of experiments were run at full scale to determine whether it was possible to conduct protein A chromatography of chilled HCCF on an industrial scale. Ex. 1001 at 23:62-24:19. In these full-scale experiments, 12,000 liters of harvested cell culture fluid were held "at 15+/-3° C for the duration of loading." *Id.* at 21:7-8. The results, reported in Table 4, detected leached protein A at 10 ng/mg or less, "demonstrating that controlling temperature of the HCCF controls protein A leaching," *id.* at 23:65-67, even at the massive scale used in the industrial manufacture of therapeutic antibodies.

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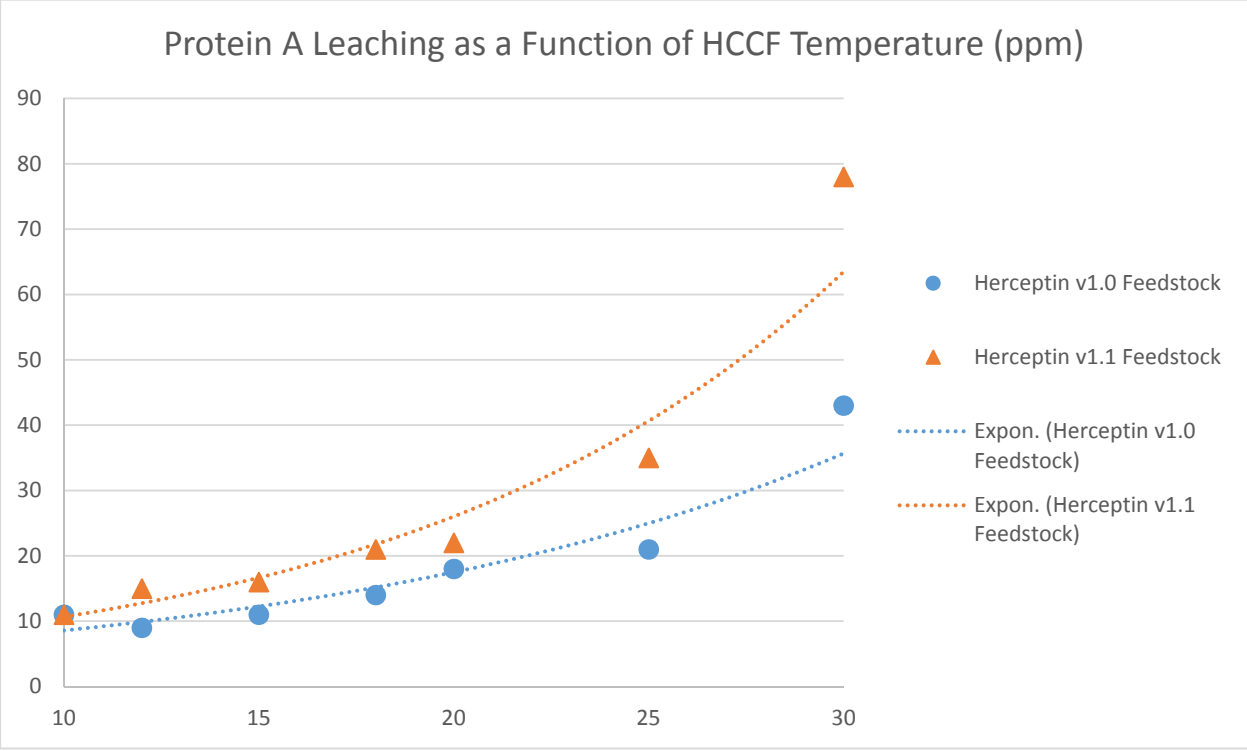
[5] Dr. Dowd's declaration includes photographs of his efforts to assemble an apparatus to perform these experiments. Dowd ¶¶ 56-60.

Figures 1-3 and 8-9 of the Fahrner Patent include data from these experiments. The trastuzumab data from Figure 1, replotted below for clarity, demonstrate the exponential trend in leaching observed by the inventors:



Cramer ¶ 113. As mentioned, Dr. Laverdiere was later invited to present these data to her colleagues in the Biochemical Technology division at the National Meeting of the American Chemical Society in March 2005. Dowd ¶ 27; Cramer ¶¶ 176-79; Ex. 2012 at 23.

C. The Petition.

The Petition relies on declaration testimony from Dr. Przybycien that the POSA would consider all the challenged Fahrner Patent claims (all claims except Claims 4 and 12) anticipated by or obvious over various combinations of Exhibits

1002 through 1007. All but one of these references were considered during prosecution. Ex. 1001 at 1; Ex. 2010 at 14:10-23.

During his deposition, Dr. Przybycien was candid about how he performed his analysis. First, he read the patent. Ex. 2010 at 11:13-19. At that point, he "had formed an opinion fairly rapidly after looking at the patent itself, just in terms of what I thought its novelty was." *Id.* at 18:8-18. He then read four references (Exhibits 1003, 1004, 1005, and 1007) from the file history, and after that spent "five, six hours" conducting his own literature search for any references of "remote relevance." Ex. 2010 at 13:8-18:7. Despite this searching, he found only one new reference that he considered worth citing, Ex. 1006, an article about proteolysis in bacterial cells, *see infra* § IV.B. Although none of the references Hospira provided him, nor any that he found on his own, disclosed or suggested chilling the HCCF purified by protein A chromatography, Dr. Przybycien adhered to the conclusion he had reached after reading just the patent itself that it was invalid. Ex. 2010 at 18.

ARGUMENT

I. HOSPIRA MISCONSTRUES THE CLAIMS.

Hospira has challenged Claim 1, reproduced below, and various claims that depend from Claim 1:

> A method of purifying a protein which comprises a C_H2/C_H3[6] region, comprising subjecting a composition comprising said protein to protein A chromatography at a temperature in the range from about 10° C to about 18° C.

A claim subject to *inter partes* review must be given its "broadest reasonable construction in light of the specification in which it appears." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-46 (2016).

Hospira proposes two unreasonable constructions—one that is unreasonable because it is too narrow ("method of purifying a protein"), and one that is too broad ("about"). Hospira also interprets the claimed temperature range unreasonably by applying it to the room in which the method is performed, not—as the Fahrner Patent plainly claims—to the composition being purified.

A. "Method of Purifying a Protein"

The Board's Institution Decision construed the phrase "method for purifying a protein" as not requiring a reduction in protein A leaching. Paper No. 19 at 7-8. Genentech agrees with this construction.

Hospira, however, asked the Board to go further and narrow the claim so that "purifying a protein" actually *excludes* the reduction of leached protein A.

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[6] "C_H2/C_H3" refers to a portion of the constant region of an antibody heavy chain.

Hospira proposes: "A 'method of purifying a protein' means a method of separating the protein from the other proteins *produced by the cell*." Pet. 18 (emphasis added). This is nonsensical. Cramer ¶¶ 50-54. It is certainly true that some impurities are indeed "produced by the cell"—*e.g.*, host cell proteins and DNA. But several other known impurities, like small molecules (*e.g.*, nutrients from the cell culture media), aggregated forms of the antibody, and viruses, are not necessarily "produced by the cell." *See* Cramer ¶ 20. Likewise, leached protein A is uniformly considered an impurity even though it is not "produced by the cell." *Id.* It appears *during* purification as a byproduct of the first chromatography step, but, just like the others, it needs to be purified from the final product, *i.e.*, reduced to or below safe levels. The specification certainly describes it as such—an "impurity" that must be removed *in addition to* "proteins from the host cell producing the desired protein," Ex. 1001 at 4:56-59—and Dr. Przybycien has testified to the same point. Ex. 2010 at 69:6-8.

It is just as baffling for Hospira to suggest that the claimed invention does not purify the HCCF of this impurity. For example, Hospira argues, Pet. 18, that because Genentech deleted a certain limitation during prosecution, Hospira's narrowing construction that excludes leached protein A should be adopted. This makes no sense, and would have made no sense to the POSA, Cramer ¶¶ 55-56, because deleting a limitation necessarily *broadens* a claim. Relatedly, all of the

figures in the Fahrner Patent assess purity based on the amount of protein A measured in the eluate, not some other impurities. Dr. Przybycien did not even try to resist the point. He acknowledged that protein A is an impurity that must be removed to make a therapeutic product. Ex. 2010 at 69:6-71:25.

To the extent any doubt remained about the proper construction of this term, Claim 12 should extinguish it. Claim 12 recites a "method of purifying a protein" in which multiple steps are performed to reduce levels of leached protein A. Cramer ¶ 53. The POSA would have understood that the contaminant at issue in Claim 12 is leached protein A and that Claim 12 recites a "method of purifying a protein" to reduce this contaminant. Hospira's proposed construction makes no sense, particularly in the context of this claim.

The Court should reject Hospira's construction to the extent it proposes this additional "produced by the cell" limitation. The "broadest reasonable interpretation" of the claims cannot be one that is so narrow as to exclude the very impurity problem that the methods claimed in the Fahrner Patent solve.

B. Temperature of the Composition Being Purified

Although the Institution Decision indicates that construction is required only for the two terms Hospira identified, *see* Paper No. 19 at 10 (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795 (Fed. Cir. 1999)), Hospira's

anticipation arguments raise another claim construction issue—to what does the claimed temperature range apply?

Hospira's anticipation arguments implicitly construe that range as claiming the temperature of the room where the chromatography happened—that is the only thing Hospira's two anticipation references (Exhibits 1003 and 1004) disclose. *See* Section II *infra*. But, as Hospira's expert concedes, Ex. 2010 at 116:8-118:16. the only reasonable construction of the claims is that they refer to the temperature of the HCCF subjected to purification, not of the room in which the method is performed. This conclusion flows directly from the claim language—the method is for "purifying a protein . . . comprising *subjecting a composition* comprising said protein . . . at a temperature in the range from about 10° C. to about 18° C." (emphasis added) The claim makes clear that "it is the composition being purified that is 'at a temperature.'" Cramer ¶ 59.

"[C]laims should always be read in light of the specification and teachings in the underlying patent." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016) (quoting *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010)). Here the specification could hardly be clearer that it is the temperature of the composition being purified that is the subject of the claimed invention:

> Preferably, the method comprises reducing the *temperature of the composition* subjected to the protein A affinity chromatography, e.g.

> where the *temperature of the composition* is reduced *below room temperature*, ... The *temperature of the composition* may be reduced prior to and/or during protein A affinity chromatography thereof. However, according to the preferred embodiment of the invention, the method comprises lowering the *temperature of the composition* prior to subjecting the composition to protein A affinity chromatography, e.g., by lowering the *temperature of harvested cell culture fluid* (HCCF) which is subjected to chromatography.

Ex. 1001 at 18:4-17 (emphasis added). The specification, replete with other references to the temperature of the HCCF,[7] explains in detail how the inventors controlled that condition and how that particular variable affected the level of

[7] *See also, e.g.*, Ex. 1001 at 2:24 ("reducing the temperature of a composition"), 5:3-4 ("activity may be reduced by reducing temperature of a composition"), 18:4-16 ("reducing the temperature of the composition subjected to the protein A affinity chromatography . . . lowering the temperature of the composition prior to subjecting the composition to protein A affinity chromatography, e.g. by lowering the temperature of harvested cell culture fluid (HCCF)"), 20:40 ("cooling or heating the HCCF"), 20:61 ("[t]he temperature of the HCCF"), 21:7-8 ("[t]he HCCF was collected and held at 15+/-3° C."), 24:36 ("controlling the HCCF temperature").

protein A leaching. *See, e.g.*, Ex. 1001 at 20:36-43; 20:61-64; 21:7-8; Cramer ¶¶ 59-63. For example, the lab-scale experiments included the elaborate set up described above, with a water bath and a heat exchanger, to ensure that similarity "to the effect of chilling the HCCF in a tank at manufacturing scale." Ex. 1001 at 20:35-43. Experiments conducted at larger scale used a jacketed holding tank to ensure "[t]he temperature of the HCCF was controlled to within 1° C." *Id.* at 20:59-63. The temperatures of these compositions—not the ambient temperature of the laboratory—are what are implicated by Claim 1.

The Petition seems to acknowledge that "controlling temperature of the harvested cell culture fluid" is the point of the invention. Pet. 10. And Dr. Przybycien agrees that the POSA would interpret the claims that way, that the "intent" of the invention "was to bring the *cell culture fluid* below room temperature before subjecting it to chromatography," and that the "focus[]" was on "controlling the temperature of the cell culture fluid." Ex. 2010 at 117:6-118:16.

> Q. And you understand, at least in claim one, that . . . it talks about temperature range of the cell culture fluid between 10 and 18 degrees? You understand that?
>
> A. I do.

Id. at 53:7-12.

Neither of Hospira's allegedly anticipating references disclose the temperatures of the compositions being purified. Cramer ¶¶ 74-79; 87-93. They instead disclose the "room temperature" or "ambient temperature" of the facility in which the experiments were done. *Id.* While Hospira's petition may elide this distinction, the Board should not. It should construe the claims consistent with their plain language and the repeated, clear teaching of the specification as requiring that the composition being purified be at the claimed temperature range.

C. "About 10° C to About 18° C"

Hospira argues that the claimed temperature range "about 10 °C to about 18 °C" should be construed as extending three degrees in both directions (i.e., 7°C to 21°C). But nearly doubling the claimed range this way ignores the plain, commonly understood meaning of the term "about" and impermissibly "contradicts the manner in which these terms are used in the patent specification." *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1241 (Fed. Cir. 2001).

1. Starting with the claim language, *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), "about" is a common term. Cramer ¶ 65. It is given its "ordinary meaning" of "approximately" unless its "technologic and stylistic context" requires otherwise, "depend[ing] on the technological facts of the particular case." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995) (range of "about 5:1 to about 7:1" means "approximately" within those

endpoints); *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1369-70 (Fed. Cir. 2005). "About" should be construed as "approximately" if it is "not defined either explicitly or by implication by the specification." *Ferring B.V. v. Watson Labs., Inc.*, 764 F.3d 1382, 1389 (Fed. Cir. 2014).

2. It is undisputed that the specification contains no "explicit" definition of "about." Nor does the specification define the term "about" as Hospira proposes "by implication." To the contrary, the person of ordinary skill would understand the invention disclosed in the specification as something quite different from the construction Hospira is proposing. Cramer ¶¶ 66-67. The specification makes clear—and Dr. Przybycien acknowledges—that the purpose of this limitation is to claim protein A chromatography conducted "below room temperature." Ex. 1001 at 18:4–9; Ex. 2010 at 117:6-118:16. And the specification makes it clear that "about 20° C" means "below room temperature." Ex. 1001 at 18:4-8. *A fortiori* so does "about 18° C." But a construction equating "about" with ±3° C, so that the high end of the range is 21° C, extends the claimed range to a point that, according to Dr. Przybycien, every reasonable scientist would consider "room temperature." Ex. 2010 at 135:10-14; Cramer ¶¶ 66-67. The claimed invention cannot be conducted "below room temperature" but somehow also encompass room temperature, as Hospira's position necessitates. A construction that is "contradicted by the patent's specification" is unreasonable and should be rejected.

Source Vagabond Sys. Ltd. v. Hydrapak, Inc., 753 F.3d 1291, 1300 (Fed. Cir. 2014).

Hospira argues that the full-scale experiment disclosed in Example 1 demonstrates "that the Patentee considered '±3 °C' to reflect typical temperature fluctuations during protein A chromatography." Pet. 19. This falls far short of an implicit definition of the claim language—the word "about" is not even used. It also ignores the context of the claim, where the word "about" modifies the endpoints of the range "about 10° C to about 18° C." Cramer ¶¶ 67-69. The full-scale experiment involved controlling the temperature of the HCCF so that it was within the range of "about 10° C to about 18° C," even if its temperature were to fluctuate. The POSA would not have understood this full-scale experiment, which exemplifies the performance of the claimed method of chilling HCCF prior to protein A chromatography, as impliedly defining the word "about" so that the claimed methods encompass the purification of room temperature cell culture fluid. *See* Cramer ¶¶ 68-69.

3. Hospira concludes with a curious argument that Genentech, in narrowing its claims during prosecution, somehow defined "about" so broadly that the claims must be read to contradict the specification. Pet. 20. According to Hospira, during prosecution (of other patents) Genentech "implicitly acknowledge[d]" that "about" means "at least ±2°C but less than ±4°C," because it

amended claims in response to a reference disclosing protein A chromatography at 22° C. Pet. 20. In fact, Genentech made it clear it did *not* "acquiesce[] to the rejection" in making its initial amendment in the prosecution of the '704 patent ("about 3°C to 20°C"), Ex. 1010 at 55, 59, or in making its subsequent amendment ("about 3°C to about 18°C"), *id.* at 74, 76 ("All amendments and cancellations were made without prejudice or disclaimer."). The same is true of its amendment during prosecution of EP '940. Ex. 1012 at 21 ("Any amendments made during the prosecution of this application are intended solely to expedite prosecution of the application and are not to be interpreted as acknowledgement of the validity of any objection raised earlier in prosecution, nor as acknowledgement that any citation made against the application is material to the patentability of the application prior to amendment.").

The POSA would not have read any "implicit" acknowledgement into Genentech's actions given Genentech's explicit rejection of the Examiner's positions. Cramer ¶ 70. "Because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *HTC Corp. v. IPCom GmbH & Co., KG*, 667 F.3d 1270, 1276 (Fed. Cir. 2012). Here, the only clarity in the file history is that Genentech and the Examiner disagreed about the Examiner's rejections and that

Genentech mooted that disagreement by prosecuting narrower claims that the Examiner subsequently allowed. There is simply nothing in this exchange that compels Hospira's unreasonably broad construction of "about."

* * *

"Although it is rarely feasible to attach a precise limit to 'about,' the usage can usually be understood in light of the technology embodied in the invention." *Modine Mfg. Co. v. U.S. Intern. Trade Com'n*, 75 F.3d 1545, 155 (Fed. Cir. 1996). The default rule is that "about" means "approximately." If the Board concludes that more precision is appropriate, the broadest answer consistent with the specification would construe "about" as no more than ±1° C given the specification's emphasis that "about 20° C" is "below room temperature."

In sum, the specification makes clear to the POSA that the invention concerns a method of protein A chromatography in which "the temperature of the composition is reduced below room temperature." Ex. 1001 at 18:6-7. Hospira's proposed construction of "about" is so broad that it contradicts the specification's description of the invention. Because it contradicts the specification, it cannot be a "reasonable" construction and must be rejected. *Source Vagabond*, 753 F.3d at 1300.

II. NONE OF THE CLAIMS ARE ANTICIPATED.

The Institution Decision determined there was a "reasonable likelihood" that WO '389 and van Sommeren are anticipating references. They are not. Neither discloses chilling the harvested cell culture fluid. And, even if they did, the experimental evidence disclosed in the Fahrner Patent and in the accompanying Dowd Declaration demonstrate that the claimed range is critical to the operability of the invention, defeating any anticipation challenge based on any glancing overlap with the "room temperature" ranges disclosed in these two references.

A. WO '389 Discloses the Temperature of the Lab, not the Temperature of the Composition.

Exhibit 1003, a PCT application filed in 1995, discloses purification experiments SmithKline Beecham Corporation (SKB) conducted during the development of two therapeutic antibodies. Cramer ¶ 73.

SKB's "downstream" purification process started with bind-and-elute protein A affinity chromatography, followed by two viral inactivation steps, cation exchange chromatography, and hydrophobic interaction chromatography (HIC). Ex. 1003 at 16-19; Cramer ¶¶ 80-82. It nowhere discloses or suggests chilling the harvested cell culture fluid prior to protein A chromatography.

The patent is directed in part to the use of an optimized HIC step to reduce leached protein A to acceptable levels. Cramer ¶¶ 80-82. There is no disclosure that this leaching is caused by proteolysis, or that the inventors tried any means to

prevent leaching from occurring as opposed to eliminating leached protein A during the allegedly inventive HIC step.

Hospira argues that WO '389 anticipates Claim 1 and Claim 5[8] because it discloses "[a]ll steps are carried out at room temperature (18° – 25° C)." Ex. 1003 at 13. But Dr. Przybycien concedes (and Dr. Cramer agrees) that this reference does not disclose the temperature of the composition subjected to protein A chromatography. Ex. 2010 at 82:19-22; *see also* Cramer ¶¶ 74-79. "Room temperature" as used in this reference refers to the temperature of the *laboratory* where each "step" in process was performed. "Room temperature" does not refer to the temperature of the cell culture fluid.

> Q. You see in sort of toward the end of the first paragraph, I think it's line 13 or 14, it says "all steps carried out at room temperature (18 to 25 degrees Celsius); do you see that?
>
> A. I do see that, yes.
>
> Q. Okay. So, that is referring to the temperature of the lab where this experiment was conducted; correct?
>
> A. Yes.

[8] Claim 5 depends from Claim 1 and limits the protein being purified to an antibody. Ex. 1001, Col 35: 57-58.

Ex. 2010 at 82:13-22. Where the temperature *of a composition* was important at a particular step, WO '389 discloses that fact. For example, WO '389 discloses that during the two viral inactivation steps, the solution was "held in sterile containers at 4° C, or frozen *and* held at -70° C." Ex. 1003 at 14-15. There is no similar disclosure of the temperature of the HCCF when it is loaded on to the protein A column. Cramer ¶ 77. The reference is completely silent on this point, as Dr. Przybycien concedes. Ex. 2010 at 89:16-90:5. WO '389 therefore does not anticipate.

Hospira has not argued that Exhibit 1003 inherently anticipates Claim 1. *See* Pet. 28-33. But even if the Board were to find this argument not waived,[9] Hospira could not succeed. 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

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[9] *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.").

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).

As for "inevitability," Dr. Cramer makes clear that it is not inevitable that the HCCF would have cooled to "room temperature," let alone 18°C, before being purified. Cramer ¶ 78. Dr. Przybycien agrees. He conceded that the HCCF purified in WO '389 would not inevitably be at the same temperature as the lab. He agreed that bioreactors operate at about 37° C, and the cell-culture fluid is about that temperature when it is harvested. Ex. 2010 at 66:17-24. WO '389 does not disclose the extent to which the HCCF was held before being loaded on to the protein A column, and if so where and for how long. Those details *are* provided for other steps in SKB's purification process. *See* Ex. 1003 at 14 (solution "held at pH 3.5 for at least thirty minutes" before the first viral inaction step), 15 (solution held for "thirty minutes" in second viral inactivation step); *see also* id at 19, 29. As Dr. Przybycien acknowledged, Ex. 2010 at 90:2-92:4, the POSA who read WO '389 would have no way of knowing whether the HCCF was allowed to chill to "room temperature" before being subjected to Protein A chromatography.

Q. It's not inevitable that it's at room temperature, correct?

A. That's correct.

Id. at 90:18-20.

Claim 1 requires the temperature of the "composition" being purified to be between "about 10° C to about 18° C." Because WO '389 does not disclose that the composition being purified in its process is at this temperature range, either directly or inherently, this reference cannot anticipate Claim 1.

B. Van Sommeren Discloses Protein A Purification at "Ambient Temperature" – the Opposite of the Claimed Invention.

Exhibit 1004 ("van Sommeren"), published thirteen years before the priority date,[10] discloses the impact of different variables—temperature, flow rates, and composition of buffers—on the binding capacity of a particular protein A resin. Binding capacity is a measure of the maximum amount of protein that can bind to the column; protein in excess of the column's binding capacity will not bind but rather will flow through the column. Cramer ¶¶ 26-28. Bioprocessing engineers as of the priority date focused on binding capacity when developing protein A purification processes. *Id.* ¶¶ 25-26. Higher binding capacity improved yields, reduced the time needed for this step, and thereby lowered production costs. *Id.*

[10] Hospira appears not to challenge that the claims are entitled to the July 28, 2003 priority date of the Fahrner provisional application, *see* Ex. 1002 § V, nor does it appear relevant to any instituted Ground. In any event, the claims are entitled to claim priority to the provisional application, Ex. 2013. Cramer ¶ 15.

For their binding experiments, the van Sommeren authors conducted chromatography on mouse monoclonal antibodies produced from hybridomas. Ex. 1004 at 7; Cramer ¶ 97. Among their experiments, they studied the column's dynamic binding capacity at two different temperatures—4°, the temperature of the laboratory's cold room, and 20°-25°, the "ambient temperature" of the lab. *Id.* at 15, 16; Cramer ¶¶ 45, 85-99. The authors concluded that "the temperature effect" on binding capacity was of "minor significance." Ex. 1004 at 18; Cramer ¶¶ 100-102.

Hospira makes several arguments concerning this reference, each of which is mistaken.

1. As with WO '389, Hospira argues that van Sommeren's disclosure of protein A chromatography at "ambient temperature" anticipates Claims 1 and 5 on the theory that the lower end of van Sommeren's room temperature range (20°-25°) overlaps with the top of the claimed range ("about 10° C to about 18° C"). Pet. 36. (This argument fails out of the box unless the Board accepts Hospira's proposed construction of "about.") Hospira, however, again conflates the temperature of the composition with the temperature of the lab, and thus ends up comparing apples and oranges. As Dr. Cramer explains, van Sommeren discloses the temperature of the *lab space* where the experiments were conducted, not the temperature of the HCCF subjected to purification. Cramer ¶¶ 94-99. Thus, even

if the Board adopted Hospira's unreasonably overbroad construction of "about," van Sommeren still does not anticipate because it does not disclose the temperature of the composition being purified.

2. Because Hospira's Petition conflated the temperature of the composition with the temperature of the lab, Hospira did not address whether the composition would "inevitably" have been at the "ambient temperature" disclosed in van Sommeren when it was purified. *See* Pet. 33-37. If the Board adopts Genentech's construction of "about," the inquiry can stop because "about 18° C" does not extend to 20° C. Cramer ¶¶ 88-89. But even if the Board were to consider this unbriefed issue *and* conclude that Hospira's construction of "about" were correct, Hospira's argument must still be rejected because it is not inevitable that the cell culture fluid in van Sommeren would have been at "ambient temperature" when run through the protein A column. As with the HCCF in WO '389, the composition in van Sommeren was (as the authors disclosed) obtained from a cell culture process performed around 37°C. Ex. 1004 at 7; Cramer ¶ 97. Van Sommeren never discloses cooling this composition. Cramer ¶ 97. There is no way to know from van Sommeren what temperature the composition was when it was loaded on to the column. Cramer ¶¶ 97-98. Accordingly, the method disclosed in van Sommeren cannot inherently anticipate the claimed methods, even under Hospira's proposed construction of "about."

3. Finally, Hospira also argues that by disclosing the performance of protein A chromatography in a cold room and at ambient temperature, van Sommeren somehow discloses to the POSA chilling the HCCF to any point between those temperatures. Pet. 35. No such disclosure appears in van Sommeren, and the POSA would not have understood the reference in that way. Cramer ¶¶ 87-93. On the contrary, the POSA would have understood van Sommeren to teach, based upon its conclusion that temperature had a minor effect on binding capacity, that protein A chromatography should be performed at ambient temperature, not at any and all points between a refrigerator and a lab. Cramer ¶ 91. Hospira's suggestion that the POSA would have somehow understood van Sommeren to disclose chilling the cell culture fluid to any temperature between the lab and the refrigerator is belied by Hospira's failure to cite a single prior art reference in which that was done and by Dr. Przybycien's failure, despite five to six hours of literature research, to find such an example, Ex. 2010 at 13:4-18:7.

* * *

In sum, the methods disclosed in van Sommeren bear no relationship whatsoever to the methods claimed in the Fahrner Patent. The Patent Office considered van Sommeren during prosecution, Ex. 1001 at 1, and its decision to grant the claims in view of it was plainly correct.

C. The Claimed Temperature Range is Critical Based on the Reduction in Protein A Leaching.

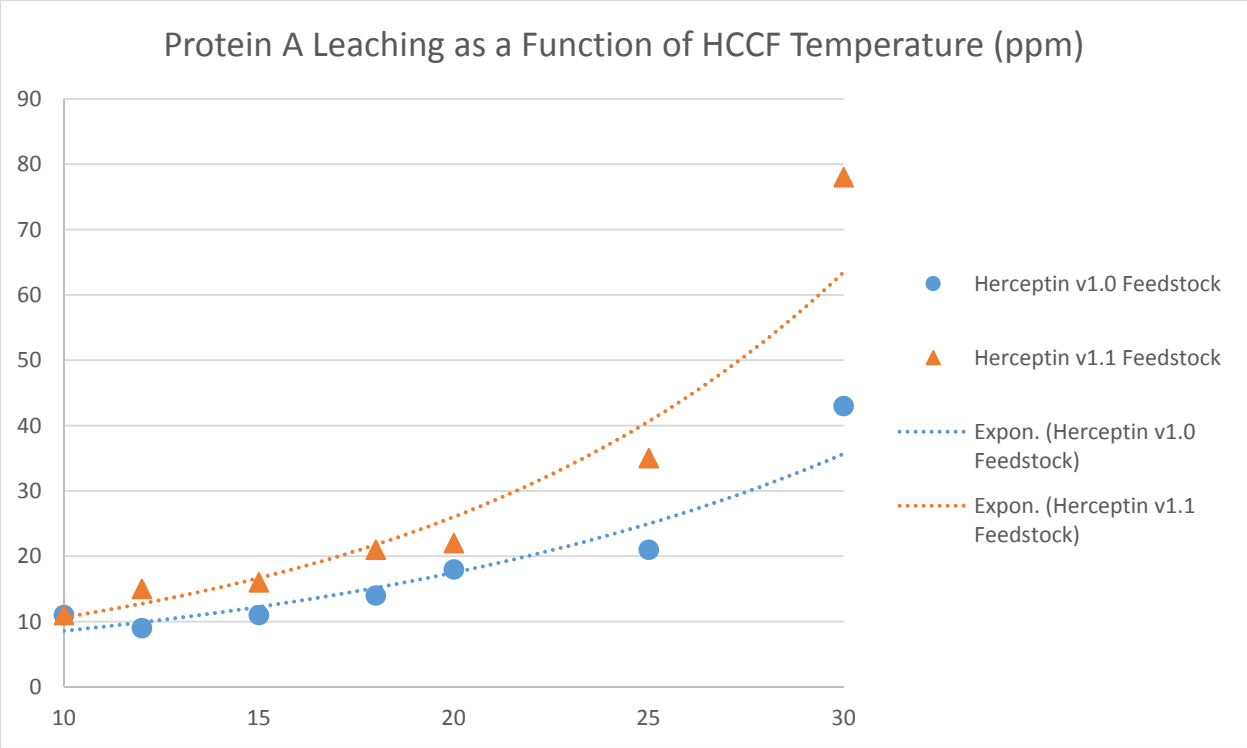
Finally, even if WO ’389 and van Sommeren are interpreted to disclose the temperature of the cell culture fluid, and even if the Board accepted Hospira’s proposed construction of “about” to expand the claimed range by as much as 3°C, there is still no anticipation because the claimed range of “about 10° C. to about 18° C.” is critical to the methods claimed in the Fahrner Patent.

The disclosure of a temperature range is just that, a disclosure of a range. It is not a disclosure of a specific temperature within the range. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006). Thus, where the prior art discloses a range of values and a challenged claim recites an overlapping range, the prior art does not anticipate *per se*. Rather, it “is only anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges.” *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015). If there is a “considerable difference between the claimed range and the range in the prior art,” there is no anticipation. *Atofina*, 441 F.3d at 999; *see also Warner Chilcott Co. v. Teva Pharm. USA, Inc.*, 89 F. Supp. 3d 641, 654 (D.N.J. 2015), *aff’d*, 642 F. App’x 996 (Fed. Cir. 2016). These considerations generally distill to a question of “criticality.” Where the claimed range is not “critical,” there is “no considerable difference between how the method would

operate within the claimed range and within the range disclosed in the prior art." *See Ineos USA LLC*, 783 F.3d at 870. And where the claimed range is not "critical," it suggests the POSA "would have envisioned that the claimed value was an acceptable choice within the prior art." *Warner Chilcott Co.*, 89 F. Supp. 3d at 654.

Here, the claimed range of about 10° C to about 18° C is critical. There is a considerable difference between how the claimed method operates over it compared to the prior art ranges of 18-25°C (WO '389) and 20-25°C (van Sommeren). As Dr. Cramer explains, "the purification method recited in claim 1 operates differently when performed at the claimed temperature range of about 10 °C to about 18 °C compared to the temperature ranges recited in [WO '389] (18-25 °C) and [van Sommeren] (20-25 °C)." Cramer ¶ 115. "In particular, the extent of protein A leaching is relatively flat within the claimed range of about 10 °C to about 18 °C, whereas the extent of protein A leaching in the ranges of 18-25 °C and 20-25 °C tends to increase more sharply per degree relative to the claimed range." *Id.* These differences in how the claimed method operates over the claimed temperature range and those ranges disclosed in the prior art is readily apparent from the results disclosed in the Fahrner Patent as well as those generated by Dr. Christopher Dowd.

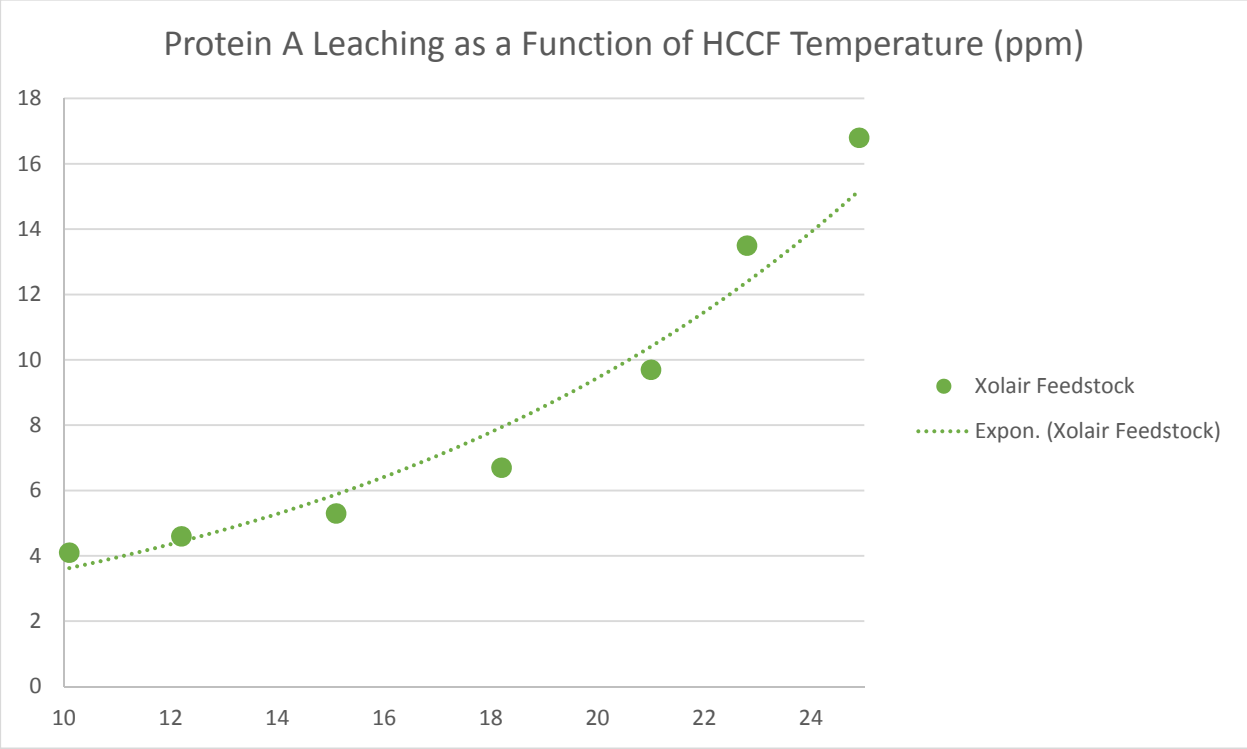
The Fahrner Patent reports a series of experiments designed to evaluate the effect of HCCF temperature on protein A leaching for two different feedstocks of trastuzumab (Herceptin). Cramer ¶¶ 112-13. The results show the extent of protein A leaching is relatively flat within the claimed range of about 10°C to about 18°C, whereas the extent of protein A leaching in the ranges of 18–25°C and 20–25°C tends to increase more sharply per degree relative to the claimed range. Cramer ¶ 115. These data appear below:



Cramer ¶ 113.

These results are not unique to trastuzumab. At Genentech's request, Dr. Dowd repeated the type of study described in the Fahrner Patent for another Genentech antibody, omalizumab (Xolair). Dowd ¶¶ 31-32, 35. His declaration

and accompanying exhibits describe the experiment in detail and its compliance with Rule 42.65. Dowd ¶¶ 35-67; Exs. 2024-2031. The data he generated are reproduced below:



Cramer ¶ 114; *see also* Dowd ¶¶ 62-67. The similarity in the results obtained for the two Herceptin feedstocks and the Xolair feedstock demonstrate that the claimed methods and their benefits are generalizable across the full scope of claims 1 and 5, [redacted]. Cramer ¶¶ 118-121; Dowd ¶¶ 32-35; 68-71.

In sum, the contrast between the relatively small changes in leached protein A between about 10°C to about 18°C and the relatively sharper increase in leached protein A as HCCF temperatures rise above about 18°C proves the criticality of the

claimed range. As explained by Dr. Cramer and Dr. Dowd, the POSA engaged in the purification of proteins for therapeutic use would have been concerned with (i) ensuring his downstream purification steps were sufficient to clear any leached protein A and (ii) ensuring consistent results from his chromatography process. *See* Cramer ¶¶ 115-119; Dowd ¶¶ 68-70. The relatively small and steady amount of leaching seen when protein A chromatography is performed at about 10 °C to about 18 °C aligns with both these criteria; the protein A leaching seen at the prior art ranges does not. Cramer ¶¶ 116-18; Dowd ¶ 69. Thus, the POSA would appreciate that there exist "considerable difference[s] between how the method would operate within the claimed range and within the range disclosed in the prior art," *Ineos*, 783 F.3d at 870, and would regard the claimed temperature range as "critical to the operability" of the methods claimed in the Fahrner Patent, *id.* at 871.

III. THE CLAIMED METHODS ARE NOT THE PRODUCT OF "ROUTINE OPTIMIZATION."

Four Grounds in the Petition—Grounds 3, 5, 7, and 8—argue the obviousness of claim 1 (and dependent claims) on the theory that conducting protein A chromatography at reduced temperatures within the claimed range was a matter of "routine optimization." Pet. 37-39, 40-44, 51-53. No reference cited by Hospira exemplifies such allegedly "routine" experimentation—as good evidence

as any of the hindsight-riddled analysis Hospira is proffering. In reality, there was nothing "routine" about inventing the claimed methods.

A. The POSA Would Not Have Been Motivated to Study Temperature as a Matter of Routine Optimization.

1. Neither WO '389 Nor Van Sommeren Present a Problem the POSA Would Have Sought to Solve By Studying Temperature.

As an initial matter, Hospira fails to identify any reason the POSA would have sought to optimize the protein A chromatography processes disclosed in its cited references.

WO '389 presents an efficient multi-step purification process. Ex. 1003 at 15-18. Table 10 reflects that its disclosed method yields a very pure final product. *Id.* at 35; Cramer ¶ 129. And while WO '389 warns of the potential for protein A leaching, it also provides a solution to this leaching problem: downstream purification using hydrophobic interaction chromatography (HIC). The application discloses that SmithKlineBeecham scientists found leached protein A in their eluate at levels at or above 20 ng/mg. By adding HIC as an additional "downstream" step they reduced leached protein A by as much as twenty-fold and well below acceptable levels for therapeutic use. Ex. 1003 at 19-52; Ex. Cramer at ¶¶ 80-83, 129. Of all the prior art the Petition cites, only WO '389 concerns the problem the inventors addressed—leached protein A in the eluate—and it also provides the POSA with a clear solution, Ex. 1003 at 19-52, one that avoids what

Dr. Przybycien described as the expense and inconvenience of chromatography processes conducted at reduced temperatures, Ex. 1002 ¶¶ 34–35.

Dr. Przybycien acknowledged this at his deposition. He agreed that leached protein A "doesn't have to be removed during the protein A process," and that it was "sufficient" to accomplish that "by the end of the process." Ex. 2010 at 72:2-13. And he agreed that WO '389 identifies the problem (leached protein A above acceptable levels) as well as the means to solve it (HIC):

> I would certainly agree that a POSA, person of ordinary skill in the art, would certainly be aware of the potential for leaching and the fact that leaching does occur to greater or lesser extents. And based on the Shadle work [WO '389], HIC would be an option.

Id. at 77:11-16.

In sum, WO '389 presents the POSA with a high yield, high purity process capable of clearing leached protein A. It is for these reasons that Dr. Cramer observes it "would not make sense to the POSA, to consider modifying these processes *further* as part of 'routine optimization.'" Cramer ¶ 129.

Hospira's other principal prior art reference, van Sommeren, likewise provides the POSA no reason to experiment with temperature. As Dr. Cramer explains, the purification methods disclosed in van Sommeren, a 1992 paper, were so outdated by July 2003 that they would not have communicated anything to the POSA about relevant prior art problems to be solved in protein A chromatography.

Id. ¶ 130. As Dr. Cramer explains, the POSA seeking to improve on van Sommeren's process "would have started over, using higher-capacity protein A chromatography media that had come to market in the decade since that article was published." *Id.* ¶ 130.

2. The POSA Would Not Have Studied Temperature to Improve Dynamic Binding Capacity.

The Petition also suggests that van Sommeren's disclosed experiments varying temperature (purification in a 4°C cold room and at ambient temperature) might motivate the POSA to purify HCCF chilled within the claimed ranges in order to improve binding capacity. Pet. 51. While binding capacity may well have been a reasonable target for optimization efforts, Hospira's suggestion that the POSA would have studied temperature as part of such efforts is mistaken.

Van Sommeren itself provided the POSA with no reason to experiment with temperature for this purpose. While that publication observed that changes in ionic strength, pH, and type of ion influenced capacity, Ex. 1004 at 16, it dismissed temperature as of only "minor importance if adsorption is performed in a high ionic strength (1.5 M glycine, 3.0M NaCl) buffer pH 8.9," *id.* at 18. This conclusion comports with the data in Table V of van Sommeren, demonstrating that for some antibodies, temperature made no difference, and for others the lower temperature actually decreased capacity. *Id.* at 15. Dr. Cramer thus concludes that "[t]he POSA would have understood . . . that temperature had an unpredictable,

typically relatively minor effect on dynamic binding capacity" and that it "was not an important or reasonable parameter to investigate if the POSA were trying to improve dynamic binding capacity." Cramer ¶¶ 101–02.

Other prior art taught the POSA the same thing. The 2001 Fahrner paper, for example, instructed that binding capacity could be influenced by a host of variables but that "the simplest to control for production and the ones that will have the most significant impact on capacity are the column length, the flow rate, and the chromatography media." Ex. 2006 at 10. While this paper cites van Sommeren, it notably fails to mention temperature as a key consideration. *Id.*; *see also* Cramer ¶ 143. An earlier paper similarly suggested that artisans seeking to optimize capacity should focus on "flow rate and column length, primarily because they are easily varied in bioprocess applications" and listed temperature as a variable to be avoided for fear of its effect on the stability of the protein of interest. Ex. 2007 at 1. These references obliterate Hospira's unsupported allegation that "temperature" was an established "result-effective variable," Pet. 39 (citing no evidence), and the POSA would not have considered it to be one. Cramer ¶ 139. Simply put, Hospira's suggestion that the POSA would have been motivated to chill the HCCF to study binding capacity, Pet. 51, is belied by the art and actual practice. Cramer ¶¶ 141-43.

3. The POSA Would Not Have Studied Temperature to Prevent Antibody Degradation.

Hospira next argues "van Sommeren discloses that contamination due to proteolysis was a known problem," Pet. 52 (citing Ex. 1004 at 18-19). To be clear, this reference to "proteolysis" concerns the proteolysis of the antibody product, not the proteolysis of protein A. The POSA would not have been motivated to experiment with temperature in an effort to avoid degradation of the target antibody by HCCF proteases.

Van Sommeren's Table IV provides measurements of proteolytic activity following protein A chromatography and reveals that, under most buffer conditions tested, the chromatography process itself was sufficient to remove the cathepsin D proteases from the eluate. Ex. 1004 at 13. The paper ultimately concludes by noting that, where proteolytic activity was observed, it could "be inhibited by addition of pepstatin A." *Id.* at 19. Van Sommeren thus would have taught the POSA concerned about proteolytic degradation of the product to simply select an appropriate buffer or, alternatively, employ a protease inhibitor like pepstatin A. Cramer ¶¶ 103-06, 146. In light of these readily available solutions, the POSA would have had no reason to chill the HCCF during protein A chromatography, particularly since van Sommeren discloses proteolytic degradation as a problem encountered "upon storage," not during chromatography itself. Cramer ¶¶ 144-47.

B. Chilling HCCF Was Not a Matter of Routine Optimization.

Even if the POSA had some motivation to experiment with temperature, the POSA would not have viewed temperature as a simple variable to adjust and thus not a subject of "routine experimentation." The Petition suggests otherwise, referring (without citation) to "the ease with which temperature can be varied," Pet. 39, but that just is not true.

1. Dr. Cramer explains that, at the time of invention, bioprocess engineers typically would use automated equipment like the ÄKTA Explorer to perform chromatography research. Cramer ¶¶ 40-44, 138–39. These machines allowed scientists to "vary certain chromatography parameters at lab scale and study the results." *Id.* ¶ 40. Engineers could, for example, study with relative ease each of the "result-effective variables" of "flow rate, column length, and media." *Id.* ¶ 139 (citing Ex. 2006 at 10); *see also id.* ¶¶ 42-43.

Temperature, however, was not a parameter that could be studied with these machines. Dr. Przybycien, whose laboratory has an ÄKTA EXPLORER, acknowledges that it does not allow for temperature controlled experiments.

> Q. Does the machine itself provide a means to adjust that condition, the temperature of the cell culture fluid that is being processed through the column?
>
> A. No.

> Q. And there is not a control to control the temperature of the column either on the machine, is there?
>
> A. Not on the machine, no.

Ex. 2010 at 131:21-132:5. A scientist who wished to measure the effects of varying temperature could not simply turn a knob or flip a switch;[11] rather, she would be forced to develop her own system of temperature adjustment. Cramer ¶ 44. The lab-scale experiments disclosed in the Fahrner Patent are illustrative. The inventors were forced to control temperature "by immersing the column and the 5 ml stainless steel upstream line in a water bath controlled to the desired temperature of the run." Ex. 1001 at 20:37–39. "The inlet line acted as a heat exchanger cooling or heating the HCCF prior to entering the protein A column, similar to the effect of chilling the HCCF in a tank at manufacturing scale." Ex. 1001 at 20:39–42.

[11] Nor could the POSA realistically make use of a "cold room." As Dr. Cramer explains, because these rooms are usually small and invariably used for other purposes, including storage of materials for other experiments, it is not feasible to conduct temperature-adjusted chromatography experiments there other than testing at 4°C. *Id.* ¶ 45.

Certainly if it were routine optimization to experiment with temperature changes, one would expect standard laboratory equipment to make such experimentation possible.

2. Even if temperature-controlled experiments were easy to conduct, and they were not, the challenge of implementing such changes on an industrial scale would have discouraged the POSA. Dr. Cramer and Dr. Przybycien both agree that the POSA would be investigating refinements in full-scale chromatography for commercial manufacturers—any methods found to reduce protein A leaching had to be scalable to a commercial/industrial operation. Cramer ¶¶ 46-47; Ex. 2010 at 142:14-25. But the costs of chilling large volumes of cell culture fluid are substantial, and large volumes are precisely what are involved in industrial protein A chromatography. The full-scale control study disclosed in the Fahrner Patent, for example, involved *12,000 liters* of HCCF. *See, e.g.*, Ex. 1001 at 21:4.

Implementing the claimed methods at such scale requires significant energy expenditures to chill such volumes. Cramer ¶¶ 134-36. It also requires specialized and expensive equipment. *Id.* ¶ 137. As Dr. Przybycien himself acknowledges, simply reducing the temperature of the room or facility in which the chromatography occurs would have its own drawbacks, as it would create an "uncomfortable" and "inconvenient" environment for laboratory personnel. Ex. 1002 ¶ 35 ("[S]killed artisans may have chosen not to use reduced temperatures,

because it requires additional lab equipment such as jacketed columns, or raises operating costs, or may simply be uncomfortable or inconvenient to laboratory personnel.").

* * *

In light of all this, Hospira's failure to cite a single prior art reference disclosing any experiments within the claimed range is not surprising. The only experiments cited regarding temperature's effect on protein A chromatography, van Sommeren, occurred at the two temperatures already available to the POSA—room temperature and the standard laboratory "cold room," the two "easily accessible disparate temperatures" available to researchers, even today according to Dr. Przybycien. Ex. 2010 at 147:9-148:10, 151:3-18. Were temperature such an easy variable to control and adjust, it is inexplicable that the van Sommeren authors when experimenting with the effect of temperature on binding capacity would have limited themselves to just two data points—"ambient temperature" and the 4°C "cold room"—rather than exploring a range. That they did not strongly suggests they could not. Cramer ¶ 92.

Dr. Przybycien had no coherent answer when asked to explain the absence of other, intermediate temperature points in the van Sommeren experiments. Ex. 2010 at 147:9-151:18. Nor did he find, after more than half a day searching for anything of "remote relevance," any reference disclosing protein A

chromatography conducted at a temperature in between 4°C and room temperature. *See id.* at 15:12-22, 54:7-10, 172:4-176:19. It is odd, to put it mildly, that the vast library of protein A publications does not include a single article as of the priority date that discloses optimization of HCCF temperature were it true, as Hospira and its expert argue, that it was so routine to adjust.

IV. THE RELATIONSHIP BETWEEN PROTEIN A LEACHING, TEMPERATURE, AND PROTEOLYTIC ACTIVITY WAS NOT OBVIOUS.

In Grounds 4 and 6, Hospira argues that the POSA in July 2003 would have known proteolytic activity was causing protein A leaching. Pet. 40-44, 49-50. For this proposition, Hospira and Dr. Przybycien rely on a single reference—Balint (Exhibit 1005). Hospira nowhere establishes that Balint is actually analogous prior art, and it is not. It cannot form the basis for an obviousness challenge.

Even if it could, the claimed methods would still not have been obvious because the art already provided to the POSA multiple, easier ways to reduce protein A leaching besides chilling the HCCF.

A. Balint Is Not Analogous Prior Art.

Hospira's burden to prove obviousness includes establishing that Balint is analogous prior art. *See, e.g.*, *Schott Gemtron Corp. v. SSW Holding Co., Inc.*, IPR2014-00367, Paper 62 at 28 (May 26, 2015) ("Petitioner bears the burden of showing by a preponderance of evidence that the asserted prior art references are

analogous art and otherwise combinable."). Neither the Petition nor Dr. Przybycien attempts to do that. Nor could they.

Published in 1995 in a medical journal called *Transfusion Science*, Balint reported on clinical testing of an immunoadsorbent column marketed as a medical device called "PROSORBA." Cramer ¶ 150. Containing protein A immobilized on silica, the device was akin to an oil filter on an automobile, extracting unwanted antibodies from a patient's blood as it was removed and then returning it to the body by way of intravenous tubing. *Id.*; Ex. 1005 at 4-5.

It is easy to see why the Petition forgoes any attempt to prove Balint is analogous prior art.

First of all, Balint is not "from the same field of endeavor" as the claimed invention. *In re Clay*, 966 F.2d 656, 658-59 (Fed. Cir. 1992). Balint discloses that its experiments concerned the "field of apheresis," Ex. 1005 at 4—a discipline so far removed from the field of protein purification that Dr. Przybycien was not comfortable even describing what it was. "I'm not a medical practitioner, so I can't comment knowledgeably on that treatment process." Ex. 2010 at 156:23-157:10. It is "not [his] field." *Id.* at 157:9-10. "Again, the application is outside of my field." *Id.* at 158:2-8.

Balint appeared in a journal, *Transfusion Science*, where neither Dr. Przybycien nor (to his knowledge) any protein purification expert has ever

published. Ex. 2010 at 161:5-162:11. Indeed, before Hospira's counsel supplied him with a copy of Balint, Dr. Przybycien had never even heard of *Transfusion Science*. *Id.* at 161:22-24. Dr. Cramer's experience is similar. Cramer ¶¶ 151-58. As Dr. Cramer explains, he analyzed the article in Web of Science and concluded that Balint had never been cited by any publication outside of its field of treating blood disorders until Genentech did so when it published research following-up on the Fahrner Patent's studies. *Id.* ¶¶ 153-58; Dowd ¶ 30. Were Balint actually pertinent to the problems faced by the bioprocessing field, one of the publications read regularly by those in the field—*e.g.*, the Journal of Chromatography A, the Journal of Chromatography B, Separation Science and Technology, *see* Ex. 2010 at 33:5-15—would have published before the priority date at least one article citing it. On the contrary, the only reason it was eventually cited in such a journal (and the reason it formed part of the file history and could be provided by Hospira to Dr. Przybycien) is that Genentech scientists (including some of the named inventors) made the creative connection between the fields. Cramer ¶¶ 155-58; Ex. 2019 at 7.

Nor is Balint "reasonably pertinent to the particular problem with which the inventor is involved," the other part of the test for satisfying the analogous prior art requirement. *In re Clay*, 966 F.2d at 659-60. "A reference is reasonably pertinent if it, as a result of its subject matter, logically would have commended itself to an inventor's attention in considering his problem." *K-TEC, Inc. v. Vita-Mix Corp.*,

696 F.3d 1364, 1375 (Fed. Cir. 2012). "If it is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it." *Id.*

First of all, Balint used a silica-based protein A matrix. Ex. 1005 at 4; Cramer ¶¶ 159-60. That would be unthinkable in the field of bioprocessing because, everyone agrees, a silica-based matrix would be destroyed by the harsh (very basic) washing conditions used to regenerate protein A columns. Ex. 2010 at 158:9-160:24; Cramer ¶ 160. As Dr. Przybycien conceded, "silica was not commonly used and still really isn't commonly used as a media for protein separations." Ex. 2010 at 61:14-62:4. In a 2003 survey of fifteen marketed protein A resins for antibody purification, not one of them used a silica matrix. Cramer ¶ 160; Ex. 2014 at 3. Balint, on the other hand, could use a silica-based column because, as a medical device, it would be used only once and then discarded. Ex. 2010 at 159:5–160:2.

The POSA would have disregarded Balint as not pertinent for a second reason as well. As Dr. Przybycien acknowledged, human blood is a complex biological system loaded with proteases, *id.* at 162:14-163:3, and the one or ones responsible for the leaching in Balint are not identified. HCCF is a much different substance. Cramer ¶¶ 161-64. The host cells used in antibody manufacturing are selected for yield; if they produced proteases that destroyed antibodies, they would

not be selected. *Id.* ¶ 163. Even after the priority date, there was "little information available on the extracellular proteases expressed by [CHO cells]." Cramer ¶ 164. There would have been no reason for the POSA to think that what happened when blood was poured on a silica-based column would have any pertinence to what would happen when HCCF was poured on a protein A column made of different material. *Id*. ¶ 165.

That Balint is *not* analogous art is reinforced by what *was* taught by art that plainly *does* belong in the field. For example, Füglistaller (Exhibit 2033) is an early comparative study of the degree to which different columns leach protein A. Cramer ¶¶ 172-175. With the benefit of hindsight and the Fahrner patent, this study is plainly flawed because its experiments used antibodies *already purified by other means*—that is, free of proteases. Cramer ¶ 173. Such experiments would have made no sense were it known, as Hospira suggests, that leaching was caused by proteolysis. And there would be no value in citing such research if the tests purposefully excluded the contaminant in the composition that was (according to Hospira) known to cause this problem. Yet despite this flaw, this study continued to be cited in review chapters and publications about protein A chromatography, right up to the priority date and for years after Balint. Cramer ¶ 175.

Likewise, in 2005, one of the named inventors, Dr. Laverdiere, was selected from a field of competitors to present the research described in the Fahrner Patent

in an oral presentation at the National Meeting of the American Chemical Society. Cramer ¶¶ 176-78. Dr. Cramer was involved in selecting the research for presentation and explains how this prestigious, competitive forum is not the place "for the presentation of 'obvious' results or the product of 'routine' development work." *Id.* ¶¶ 178-79. If it were correct that Balint was analogous art that would have been recognizably pertinent to the POSA (an issue as to which Hospira has presented no evidence), it would have made no sense for the American Chemical Society to honor Dr. Laverdiere and her colleagues by asking her to present this research about leaching.

Accordingly, because Balint is not analogous art, it cannot be used as a basis to allege that the claims instituted on Grounds 4 and 6 would have been obvious.

B. Potier Adds Nothing.

Grounds 4 and 6 cite Ex. 1006, Potier, for the unremarkable proposition that the POSA would have known that proteolytic activity increases with temperature. Pet. 42. The only thing remarkable about Potier is how it ended up in the Petition at all. When Dr. Przybycien conducted his literature search over "five, six hours," having already concluded that he believed the patent was invalid and looking for any reference with "remote relevance" to substantiate the conclusion he had already reached, this is the only reference he found worthy—a report on experiments with bacterial enzymes and having nothing whatsoever to do with

protein purification generally or the problem of protein A leaching in particular. Ex. 2010 at 14:24-15:22. Were the invention as obvious as he contends, it is surprising to say the least Dr. Przybycien's extensive review of the literature yielded in effect a dry hole. That Hospira relies upon this reference demonstrates only that its arguments are hopelessly hindsight driven.

C. Chilling the HCCF Was Not An Obvious Solution.

Even were Balint analogous art and even if the POSA would have understood from it that proteases can cause protein A leaching in columns used for bioprocessing, the POSA would not have developed the claimed methods because the art already provided multiple solutions to this problem.

1. As of 2003, the art did not consider leached protein A to be a problem. Cramer ¶ 185. As the Fahrner review emphasized, throughput, not purity, was the concern for engineers designing protein A processes. Cramer ¶¶ 25-26. The processes downstream of protein A chromatography were understood to be able to clear leached protein A, Cramer ¶¶ 185-86, and indeed the primary reference in Ground 4 (Ex. 1003, WO '389) touts that its disclosed the use of hydrophobic interaction chromatography for exactly that purpose. Ex. 1003 at 6. The data presented in WO '389 would have taught the POSA that its processes did not suffer from a leaching problem, no matter what might be the cause of leaching. Cramer ¶¶ 80-83, 185-86. The notion that the POSA would disregard these

express teachings of this reference and begin modifying the process disclosed in WO ’389 is simply not credible.

2. If, somehow, the POSA remained concerning about protein A leaching despite the presence of downstream steps to address it, Balint already provides the answer—add a cocktail of protease inhibitors. Cramer ¶¶ 187-189. Once again, the notion that the POSA would take what the Balint reference teaches about a problem (leaching) but disregard what the Balint reference teaches about a solution (inhibitors) is unsupportable. *Id.* ¶¶187-88. Similarly, to the extent that Hospira contends that the fourth piece of its four-reference obviousness ground (Exhibit 1007, Ground 6) would have taught the POSA that a preservative like EDTA would usefully inhibit proteases, then Exhibit 1007 would have taught the POSA toward the same solution as Balint—solve leaching by the addition of protease inhibitors. Again, there is no reason for the POSA to take the non-routine step of modifying the temperature of the HCCF in order to address a problem already solved by at least one of the references cited in Hospira’s grounds.

V. OBJECTIVE INDICIA CONFIRM THE NONOBVIOUSNESS OF THE CLAIMED INVENTIONS

Hospira’s obviousness analyses—its invocation of “routine optimization” and three- and four-reference combinations—is ripe for infection by hindsight analysis. Despite the abundance of scientific literature on protein purification as of the priority date, the Petition cites no reference disclosing the chilling of harvested

cell culture fluid to the claimed range, let alone hinting that temperature reduction was a solution to protein A leaching. Hospira's expert, though an accomplished scientist, was not active in protein A chromatography research until well after the priority date. Ex. 2010 at 44:18-45:7. He nevertheless concluded that the Fahrner Patent was invalid immediately after reading it, only then reviewing the references from the file history and searching for hours—in vain—for anything more pertinent.

In these circumstances, "objective indicia of non-obviousness play an important role as a guard against the statutory proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012) (objective evidence "inoculate[] the obviousness analysis against hindsight"). Objective indicia, by placing the invention "in the proper temporal and technical perspective," *Mintz*, 679 F.3d at 1378, can be "the most probative and cogent evidence in the record," *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *see also Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) ("[o]bjective indicia of nonobviousness play a critical role in the obviousness analysis"). In this case, evidence exists that powerfully rebuts Hospira's arguments in Grounds 3 through 8 that the claimed methods would have been obvious.

A. The Claimed Methods Produce Unexpected Results.

Evidence of an invention's unexpected properties is a well-recognized objective indicium of nonobviousness. *See, e.g., Leo Pharm.*, 726 F.3d at 1358. As explained above (Section II.C), performing protein A chromatography on HCCF chilled to about 10°C to about 18°C produces unexpected results relative to the prior art process using HCCF at room temperature. Specifically, "the extent of protein A leaching is relatively flat within the claimed range of about 10 °C to about 18 °C, whereas the extent of protein A leaching [at room temperature] tends to increase more sharply per degree relative to the claimed range." Cramer ¶ 192. As Dr. Cramer explains, this property would have been surprising to the POSA, who would not have had "any expectation concerning the relative 'flatness' or 'sharpness' of the protein A leaching/temperature curve." *Id.* ¶ 193. It would also have represented a meaningful improvement over the prior art, providing the POSA with a method to reduce levels of protein A leaching and keep those levels comparatively more stable, ensuring a more consistent process. *Id.* ¶ 115-22.

B. The Inventors' Work Was Recognized By Their Peers.

The inventors publicly disclosed these unexpected results at the 2005 National Meeting of the Division of Biochemical Technology of the American Chemical Society, a prestigious annual event attended by many of the leading scientists in the field. Cramer ¶¶ 176-79, 181, 194; Dowd ¶¶ 27-30; Ex. 2012.

From among the abstracts submitted, the organizers selected a handful for oral presentation to the entire group. Cramer ¶¶ 177-78; Ex. 2021. One of the named inventors, Dr. Laverdiere, was among this group of invited presenters. Her presentation—*Working in a Sauna: The Effect of Temperature on Protein A Leaching*—reported that "Controlling the temperature of HCCF during protein A chromatography load can reduce/control the protein A leaching," and that the "same exponential trend was seen for all products tested." Ex. 2012 at 34.

Dr. Cramer happened to be one of the organizers for this annual meeting. Cramer ¶ 177. As he explains in his declaration, "[g]iving an oral presentation at BIOT is a prestigious event," reflecting the opinion of leaders in the field "that the research is worthy of the time of the other attendees at the conference." *Id.* ¶ 178. "Put another way, my colleagues and I attend symposia like the BIOT division of the American Chemical Society to learn about cutting edge developments in our field. It is not a forum for the presentation of 'obvious' results or the product of 'routine' development work." *Id.* ¶ 179.

Recognition by one's peers is important and powerful objective evidence of nonobviousness. "Industry participants, especially competitors, are not likely to praise an obvious advance over the known art." *WPIB*, 829 F.3d at 1334; *see also Apple Inc. v. Samsung Electronics Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc) (same). "Industry praise" is a "real world indicator[] of whether the

combination would have been obvious to the skilled artisan" that can "'tip the scales of patentability' or 'dislodge the determination that [the] claim [is] obvious.'" *Id*. at 1058. In this instance, objective evidence of how the inventors' research was treated at the time is completely at odds with Dr. Przybycien's opinion that this research reflected "routine" work that would have been obvious to the POSA.

CONCLUSION

For the foregoing reasons, Hospira's Petition should be denied and the patentability of the instituted claims confirmed. In particular:

Ground 1: Claims 1 and 5 are not anticipated because WO '389 does not disclose the temperature of the HCCF being purified, does not disclose a temperature point within the claimed range, and because the claimed range is critical to the invention. *See supra* §§ II.A, II.C.

Ground 2: Van Sommeren does not anticipate Claims 1, 2, or 5 because it does not disclose the temperature of the HCCF being purified, does not disclose a temperature within the claimed range; and because the claimed range is critical to the invention. *See supra* §§ II.B, II.C.

Ground 3: WO '389 does not render obvious claims 1 and 5 because the POSA would not have developed the claimed methods through routine experimentation. *See supra* §§ III, V.

Ground 4: WO'389, in view of Balint and Potier, does not render obvious claims 1-3 and 5 for the reasons already stated and because Balint is not analogous art and the POSA would not have developed the claimed methods based upon it. *See supra* §§ III, IV, V.

Ground 5: WO '389, in view of the '526 patent, does not render obvious claims 2, 3, and 6-11 because the POSA would not have through routine experimentation developed from them the claimed methods. *See supra* §§ III, V.

Ground 6: WO '389, in view of Balint, Potier, and the '526 patent, does not render obvious claims 2, 3, and 6-11 for the reasons stated above. *See supra* §§ III, IV, V.

Ground 7: Van Sommeren does not render obvious claims 1, 2 and 5 because the POSA would not have developed from it the claimed methods through routine experimentation. *See supra* §§ III, V.

Ground 8: Van Sommeren, in view of the'526 patent, does not render obvious claims 3 and 6-11 for the same reasons stated for Grounds 5 and 7. *See supra* §§ III, V.

Date: June 28, 2017

Respectfully submitted,

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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 12,489 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 foregoing *Patent Owner Response* and all Exhibits and other documents filed together with this *Patent Owner Response* was served on June 28, 2017 by filing these documents through the E2E System as well as delivering a copy via electronic mail on the following attorneys of record for the Petitioner:

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