2018-1933

United States Court of Appeals for the Federal Circuit

GENENTECH, INC.,

Appellant,

– v. –

HOSPIRA, INC.,

Appellee,

UNITED STATES,

Intervenor.

On Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01837

BRIEF FOR APPELLEE

THOMAS J. MELORO
MICHAEL W. JOHNSON
ALEXANDRA F. AWAI
WILLKIE FARR & GALLAGHER LLP
787 Seventh Avenue
New York, New York 10019
(212) 728-8000
tmeloro@willkie.com
mjohnson1@willkie.com
aawai@willkie.com

Counsel for Appellee

CERTIFICATE OF INTEREST

1. The full name of every party represented by us is:

   Hospira, Inc.

2. The name of the Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by us is:

   Hospira, Inc.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of the party represented by us are:

   Pfizer Inc.

4. The names of all law firms and the principals or associates that appeared for the party now represented by us in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

   None.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

   Genentech, Inc. et al. v. Amgen, Inc., No. 17-1407 (D. Del.); *Genentech, Inc. et al. v. Amgen, Inc.*, No. 17-1471 (D. Del.); *Genentech, Inc. et al. v. Pfizer, Inc.*, No. 17-1672 (D. Del.); *Genentech, Inc., et al. v. Sandoz, Inc.*, *et al.*, No. 17-13507 (D.N.J.); *Genentech, Inc. et al. v. Celltrion, Inc., et al.*, No. 18-574 (D.N.J.); *Genentech, Inc. et al. v. Celltrion, Inc., et al.*, No. 18-95 (D. Del.); *Genentech, Inc. et al. v. Celltrion, Inc. et al.*, No. 18-1025 (D. Del.); *Genentech, Inc. et al. v. Celltrion, Inc. et al.*, No. 18-11553 (D.N.J.); *Genentech, Inc. et al. v. Samsung Bioepis Co., Ltd.*, No. 18-1363 (D. Del.).

Dated: November 19, 2018

/s/ Thomas J. Meloro
Thomas J. Meloro

Attorney for Appellee Hospira Inc.

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for appellee Hospira, Inc. ("Hospira") states that (a) no other appeal in or from the same proceeding was previously before this or any other appellate court whether under the same or a similar title; and (b) the title and number of cases known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in this pending appeal are *Genentech, Inc. et al. v. Amgen, Inc.*, No. 17-1407 (D. Del.); *Genentech, Inc. et al. v. Amgen, Inc.*, No. 17-1471 (D. Del.); *Genentech, Inc. et al. v. Pfizer, Inc.*, No. 17-1672 (D. Del.); *Genentech, Inc., et al. v. Sandoz, Inc., et al.*, No. 17-13507 (D.N.J.); *Genentech, Inc. et al. v. Celltrion, Inc., et al.*, No. 18-574 (D.N.J.); *Genentech, Inc. et al. v. Celltrion, Inc., et al.*, No. 18-95 (D. Del.); *Genentech, Inc. et al. v. Celltrion, Inc. et al.*, No. 18-1025 (D. Del.); *Genentech, Inc. et al. v. Celltrion, Inc. et al.*, No. 18-11553 (D.N.J.); *Genentech, Inc. et al. v. Samsung Bioepis Co., Ltd.*, No. 18-1363 (D. Del.).

STATEMENT OF THE ISSUES

Hospira presents the following counterstatement of the issues:

1. Whether the Board correctly found that van Sommeren discloses all of the limitations of claims 1, 2, and 5, and therefore anticipates those claims.

2. Whether the Board correctly found that WO '389 discloses all of the limitations of claims 1 and 5, and therefore anticipates those claims.

3. Whether the Board correctly concluded that claims 1-3 and 5-11 would have been obvious to one of ordinary skill in the art in 2003 based on the teachings of the prior art.

4. Whether the U.S. Patent & Trademark Office's application of *inter partes* review to pre-AIA patents is constitutional.

STATEMENT OF THE CASE

This appeal arises from the United States Patent and Trademark Office Patent Trial and Appeal Board (the "Board") Final Written Decision, entered March 6, 2018, regarding an *inter partes* review ("IPR") petition filed by Hospira challenging claims 1-3 and 5-11 (the "Challenged Claims") of U.S. Patent No. 7,807,799 (the "'799 patent") on eight separate grounds. Independent claim 1 of the '799 patent recites a method of purifying a protein by subjecting a composition to protein A affinity chromatography at a temperature in the range from "about 10ºC to about 18ºC." However, the prior art teaches conducting protein A chromatography at temperatures that overlap with the range of "about 10ºC to about 18ºC," and also provides multiple motivations and means for practicing protein A chromatography at temperatures within the claimed range. Protein A chromatography was, and is, the most commonly used capture step in purification processes for monoclonal antibodies. Put simply, the inventors of the '799 patent did not invent a new way of practicing protein A chromatography.

After receiving and considering the evidence set forth by both parties, the Board found in favor of Hospira on all eight grounds, and properly concluded that the Challenged Claims were unpatentable based on anticipation and/or obviousness. Appx51. The Board correctly found that two prior art references,

van Sommeren[1] and WO '389,[2] both disclose practicing protein A chromatography at the claimed temperature range and thus anticipate claim 1 of the '799 patent. The Board also correctly held that all of the Challenged Claims would have been obvious over van Sommeren or WO '389 alone or in combination with the prior art.

A. Protein A Chromatography

Protein A chromatography is a standard purification technique employed in the processing of therapeutic proteins, especially antibodies. Appx69, Appx408, Appx423. Protein A is a bacterial cell wall protein that has the ability to bind with a specific region common to most antibodies, the C_H2/C_H3 region. Appx423, Appx839. In part because of its ability to specifically bind to the antibody of interest, protein A chromatography has been the most commonly used "capture" or initial step in the purification process for antibodies for decades. Appx894.

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[1] A.P.G. van Sommeren et al., *Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG_1 Antibodies to Protein A Sepharose 4 Fast Flow*, 22 PREPARATIVE BIOCHEMISTRY 135 (1992). Appx555-574.

[2] International Publication No. WO 95/22389 to Shadle et al. Appx508-554.

In protein A chromatography, a composition comprising a mixture of the target antibody and undesired impurities often present in host cell culture fluid ("HCCF"), is placed into the protein A chromatography column. Appx608. The antibody binds to the protein A, which is attached to beads in the chromatography column, while the impurities and HCCF pass through the column. *Id.*, *see also*, Appx985-987, Appx991. Next, the antibody of interest is removed from the column, typically with a low pH wash. Appx608, Appx527-528. The antibody is collected as it is washed from the protein A column, and is typically subjected to further purification steps. Appx608, Appx69.

While protein A chromatography has been a powerful purification tool for antibodies, it was known to have a downside. Appx513. In particular, the protein A that is attached to the chromatography column sometimes "leaches" from the column, and is washed off along with the antibody of interest. *Id.*, Appx427. Thus, further purification steps must be employed to remove the leached protein A (Appx69), and the chromatography column efficiency can degrade upon significant protein A loss (Appx928, Appx931-932).

It was well-known before the priority date of the '799 patent that leaching of protein A was the result of a temperature-dependent chemical reaction called proteolysis. For example, it was understood for decades prior to the '799

patent that proteolytic enzymes in HCCF could cause contamination due to protein A leaching. Appx572-573, Appx578, Appx881-882. The temperature-dependent nature of the proteolysis reaction was known to follow the well-known exponential relationship of the Arrhenius equation. Appx453. Predictably, the amount of protein A leached per milligram of target protein generally decreases with decreasing temperature in an exponential manner as well. *Id*., Appx1466-1470, Appx1584-1585.

Finally, protein A chromatography was also known to work well at a variety of temperatures. Protein A chromatography was known to work at ambient temperatures (18ºC to 25ºC), in cold room settings at temperatures as low as 4ºC, or at temperatures between those two common laboratory settings. Appx933, Appx954-955, Appx958-960.

B. The ’799 Patent

The ’799 patent is directed to methods of purifying proteins by subjecting a composition comprising a target protein to protein A affinity chromatography. Appx53. The alleged contribution of the disclosed methods over the prior art is reducing protein A leaching by lowering the temperature of the composition or by adding protease inhibitors. Appx60, Appx72.

The ’799 patent describes several experiments that tested the amount of protein A leaching at various temperatures. *See* Appx1877, Appx1878-1880. Figures 1 through 3 of the ’799 patent demonstrate the expected exponential relationship between temperature and protein A leaching, which is consistent across the entire measured range of 10°C to 30°C. Appx54-55. The results of the experiments were predictable—the amount of leached protein A increased exponentially with increasing temperature for all antibodies. Appx1877, Appx1894. These results were consistent with the knowledge that protein A leaching was caused by proteolysis. Appx1903. By Genentech’s own admission, the exponential trend is consistent with temperature-activated proteolytic activity. Appx70. In short, the inventors merely conducted experiments that confirmed the existence of the well-known phenomenon of protein A leaching caused by proteolysis, which was known to be a temperature-dependent reaction.

On July 28, 2003, Genentech filed Provisional Application No. 60/490,500. Appx53. On June 24, 2004, Genentech filed the non-provisional application that issued as U.S. Patent No. 7,485,704 (the “’704 patent”), which is the parent of the ’799 patent. *Id.* Initially, during prosecution of the ’704 patent, Genentech sought claims reciting reducing the temperature of a composition subjected to protein A affinity chromatography in the range from about 3°C to

about 20°C (i.e., about 37°F to about 68°F). Appx667, Appx704. Over the course of the prosecution history, including the examination of the '704 patent and the European counterpart, EP1648940 ("EP '940"), Genentech proposed claims having different scope, at least in part to overcome rejections made by the Examiners. *See, e.g.*, Appx97-98, Appx720-723, Appx739-742, Appx749, Appx762-764, Appx799-800 and Appx833, Appx835-836. Claim 1 of the '799 patent eventually issued as shown:

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

Appx77. Genentech opted not to claim that the temperature was "reduced" to "below room temperature," or that the composition was "chilled," even though specific embodiments described in the specification involve actively reducing the temperature of HCCF. Appx69-71. Instead, Genentech chose to broadly claim temperature in the range of about 10ºC to about 18ºC.

C. The Prior Art and the *Inter Partes* Review Proceeding

On September 16, 2016, Hospira filed an IPR petition challenging claims 1-3 and 5-11 of the '799 patent on eight grounds. Appx78, Appx90-91. As discussed, claim 1 recites purifying a protein by subjecting a composition

containing the protein to protein A chromatography at a temperature in the range from about 10°C to about 18°C. The further limitations of claims 2 and 3 relate to exposing the composition to a protease inhibitor. Dependent claim 5 recites that the protein to be purified is an antibody, and claims 6 through 9 recite further limitations regarding the claimed antibody. Claim 10 depends from claim 1, and recites that the protein is an immunoadhesin. Claim 11 further limits the immunoadhesin of claim 10 to a TNF (tumor necrosis factor) receptor immunoadhesin.

For Grounds 1 and 2, respectively, Hospira demonstrated that claims 1 and 5 were anticipated based on WO '389, and that claims 1, 2, and 5 were anticipated by van Sommeren. Appx112-121. For Grounds 3 and 7, Hospira showed that these claims also would have been obvious over WO '389 alone and van Sommeren alone, respectively, because the claimed temperature range was not critical, and alternatively because a skilled artisan would have been motivated and able to practice protein A chromatography based on teachings in the prior art. Appx121-123, Appx135-137. For Grounds 4-6 and 8, Hospira demonstrated that the Challenged Claims were obvious over WO '389 and van Sommeren, and

further in view of the teachings of Balint,[3] Potier[4] and/or the '526 patent[5]. Appx124-135, Appx137-141.

WO '389 teaches a process for purifying an IgG antibody by sequentially subjecting a cell culture medium containing the antibody to: (1) protein A chromatography, (2) ion exchange chromatography, and (3) hydrophobic interaction chromatography. Appx513. Example 1 reports the results of experiments employing these three purification steps and teaches that "[a]ll steps are carried out at room temperature (18-25°C)." Appx522. WO '389 also recognized that "elution of antibody from such [protein A chromatography] columns can result in leaching of residual Protein A from the support." Appx513.

Van Sommeren reports the results obtained from varying several parameters while conducting protein A chromatography on mouse monoclonal

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[3] J.P. Balint, Jr. & F.R. Jones, *Evidence for Proteolytic Cleavage of Covalently Bound Protein A from a Silica Based Extracorporeal Immunoadsorbent and Lack of Relationship to Treatment Effects*. 16 TRANSFUS. SCI. 85 (1995). Appx578-587.

[4] P. Potier et al., *Temperature-dependent changes in proteolytic activities and protein composition in the psychrotropic bacterium Arthrobacter globiformis S_I55*. 136 J. GEN. MICROBIOL. 283 (1990). Appx592-600.

[5] *Protein Purification by Protein A Chromatography*, U.S. Patent No. 6,127,526 to Gregory S. Blank, issued October 3, 2000. Appx601-610.

IgG_1 antibodies, including temperature, flow rate, and composition of a binding buffer. Appx560. Specifically, van Sommeren studied the effect of temperature during protein A chromatography by comparing processes conducted at "4 °C versus ambient temperature (AT) (20-25°C)." Appx570. Van Sommeren also disclosed that it was already known that temperature could have a significant effect on the protein A binding capacity for certain antibodies. Appx571. Furthermore, van Sommeren teaches that proteolytic activity in starting materials—i.e., the HCCF—and purified fractions resulted in contamination. Appx572-573. As a remedy for this contamination, van Sommeren suggests the addition of pepstatin A, a protease inhibitor. Appx573.

The teachings of Balint and Potier confirm that a person of ordinary skill in the art would have known that protein A leaching is the result of temperature-dependent proteolysis. Balint discloses studies conducted to evaluate potential causes of the release of covalently bound protein A from a silica-based extracorporeal immunoadsorbent matrix—a clinical application of protein A chromatography. Appx578. The authors of Balint concluded that leakage of protein A was due to inherent endogenous proteolytic activity, which cleaved protein fragments from the matrix. Appx582. Potier discloses research regarding temperature-dependent changes in proteolytic activities in the bacterium

Arthrobacter globiformis S_I55. Appx592. These experiments showed that degradation caused by proteolysis increased with temperature and increased faster at higher temperatures. Appx594-595.

The '526 patent is concerned with methods for purifying proteins of interest that comprise a C_H2/C_H3 region, and therefore are amenable to purification by protein A chromatography. Appx602. The '526 patent also discloses specific examples of proteins that may be purified, including humanized anti-HER2 antibody, humanized anti-IgE antibody, chimeric anti-CD20 antibody, and TNF receptor immunoadhesin. Appx608. In addition, the '526 patent discloses that a buffer used to equilibrate the solid phase could include EDTA. *See, e.g.*, Appx603, Appx608. EDTA is known to be effective as a protease inhibitor. Appx448, Appx463.

Genentech declined to file a Preliminary Response, and the Board instituted the IPR trial for each of the eight asserted grounds. In its Response, Genentech only addressed the grounds relating to independent claim 1. Genentech has never argued that the claimed method is patentable because of the type of protein being purified, as recited in claims 5 through 11. *See* Appx174, Appx233-234. Genentech's expert even agreed that the '526 patent teaches the limitations recited in claims 5 through 11. Appx1318, Appx1388-1389. Genentech has also

never claimed that the use of protease inhibitors, as recited in claims 2 and 3, confers patentability on the claimed method. *See* Appx233-234. In fact, Genentech explicitly acknowledged that "Balint already provides the answer—add a cocktail of protease inhibitors." Appx229. Therefore, the patentability of the Challenged Claims rose and fell with the patentability of claim 1.[6]

The Board issued its Final Written Decision on March 6, 2018. Based on the specification and prosecution history of the '799 patent, and after considering the testimony of both parties' experts, the Board adopted Hospira's claim construction of "about 18ºC." Appx11-15. The Board also concluded that both WO '389 and van Sommeren disclosed the temperature of the composition subjected to protein A chromatography. Appx19-21, Appx26-27. The Board recognized that the claimed temperature range was not critical, and that the claimed method did not produce any unexpected results. Appx22-25, Appx28. The Board also found those skilled in the art would have understood that protein A leaching was caused by temperature-dependent proteolysis before the research that led to the '799 patent. Appx32-37. The Board found that the limitations of dependent claims 2, 3 and 5-11 were all taught by the cited references. Appx19,

[6] Genentech also does not argue on appeal that any of the limitations of the dependent claims render those claims patentable.

Appx25, Appx42-44. In addition, the Board found that there was no nexus between any industry praise alleged by Genentech and the claimed invention. Appx39-40.

SUMMARY OF THE ARGUMENT

The only limitation that Genentech argues confers patentability on the Challenged Claims is the temperature range of "about 10ºC to about 18ºC" recited in claim 1. As set forth in Hospira's Petition and Reply, as well as the declarations of Dr. Przybycien, the cited prior art teach temperature ranges overlapping with this claimed range, and also render it obvious.

The Board correctly found that van Sommeren discloses all of the limitations of claims 1, 2, and 5 and therefore anticipates these claims. On appeal, Genentech only argues that the Board's claim construction was wrong. Genentech does not contest any other aspect of the finding that van Sommeren anticipates or renders obvious the Challenged Claims. Genentech originally argued that van Sommeren teaches only the temperature of the room where the protein A chromatography is conducted, but discloses nothing about the temperature of the composition to be purified. *See* Appx27. Genentech has abandoned that argument on appeal, and it is now undisputed that van Sommeren discloses conducting protein A chromatography using a composition at 20-25ºC, which overlaps with

the claimed temperature range to the extent that "about 18ºC" is construed as "18±3ºC." Genentech also does not argue in this appeal that the claimed temperature range is critical to the alleged invention, as it did in the trial below. *See* Appx23-25.

The Board's finding of anticipation in view of van Sommeren is based on substantial evidence, and should be affirmed because the Board properly construed the term "about 18 º C" to mean "18±3ºC." This construction is supported by the specification, the prosecution history, and the manner in which a person of ordinary skill in the art would understand such a term. The specification itself suggests a meaning of the term that encompasses "±3ºC." Appx70-71. There is no evidence that requires a narrower construction. Genentech argues that the Board's construction is too broad because it would mean that the claims encompass temperatures that are "room temperature," while a preferred embodiment of the '799 patent is directed to using protein A chromatography at temperatures that are "below room temperature." Appellant Brief ("Br.") at 27. However, the Board properly declined to read "below room temperature" into the claims. *See* Appx12.

The Board's finding that WO '389 anticipates claims 1 and 5 should also be affirmed. The temperature range disclosed in WO '389, i.e., 18-25ºC,

overlaps with the claimed temperature range regardless of the construction of "about 18ºC." However, while Genentech has dropped its argument made below that van Sommeren discloses only the temperature of the room, Genentech continues to argue that WO '389 discloses only the temperature of the room, but nothing else. Br. at 20. The Board rejected Genentech's argument, and found that WO '389 anticipates for two distinct reasons, both of which are well-supported by the evidence.

First, WO '389 teaches that protein A chromatography is conducted at "room temperature (18-25°C)." Appx522. The Board heard both parties' evidence on this point and correctly found that this temperature range applies to all components used in that purification process, including the composition intended for purification. Appx20. In particular, the Board credited Dr. Przybycien's explanation of how a person of ordinary skill in the art would understand the teachings of WO '389. Appx20-21. This factual finding of the Board is well-supported, and should not be disturbed.

Second, as an alternative reason why the WO '389 anticipates claims 1 and 5, the Board inferred that the HCCF described in WO '389 would equilibrate to room temperature during the purification process. Appx21-22. Genentech argues that the Board's holding of anticipation based on WO '389 should be

reversed because it relies on this inference. Br. at 20. In fact, the Board's holding of anticipation is based on a thorough analysis of WO '389 and the relevant expert testimony, in addition to the Board's logical inference, which it was permitted to make. The Board's alternative finding of anticipation in view of WO '389 is likewise based on substantial evidence, and should also be affirmed.

With regard to obviousness, the Board properly found that the claims would have been obvious based on Grounds 3 to 8 as set forth in Hospira's IPR petition. Genentech attempts to collapse the obviousness inquiry for Grounds 3 through 8 into two questions: 1) whether a person of ordinary skill in the art would routinely optimize temperature to reduce proteolysis, and 2) whether a skilled artisan would routinely optimize temperature to improve the binding capacity of protein A. Br. at 39. However, the Board also found that the prior art taught temperature ranges overlapping with the claimed range, and that Genentech had failed to rebut the presumption of obviousness with evidence of criticality. Appx39-40. Although Genentech no longer argues that the claimed temperature range is critical, it has completely disregarded this additional reason that the Board found the claims obvious. The Board's determination of obviousness should be affirmed on this basis alone.

Furthermore, the Board also properly concluded that the claimed method would have been obvious because temperature is a result-effective variable that affects both the proteolysis that causes protein A leaching, and the binding capacity of protein A. Appx38-39, Appx46-47. Genentech suggests that varying the temperature at the industrial scale of protein purification would have been so difficult that no person of ordinary skill in the art would have attempted it. Br. at 40-42. However, based on evidence in the prior art, and expert testimony, the Board recognized that modifying the temperature for conducting protein A chromatography would have been well within the purview of a skilled artisan. Appx39. In addition, the Board correctly found that Genentech had failed to establish any nexus between industry praise and the claimed invention. *See* Appx40. The Board's factual findings relating to Grounds 3 through 8 are based on substantial evidence, and its legal conclusions are supported by the case law. The Board's findings on obviousness should be affirmed.

Lastly, application of IPR to patents granted before the enactment of the America Invents Act does not violate the Takings Clause of the Fifth Amendment. Genentech has not pointed to any precedent that supports its argument that subjecting a patent to an IPR proceeding interferes with reasonable investment-backed expectations. As with other types of post-grant review, such as

inter partes reexamination, which IPR replaced, and *ex parte* reexamination, which this Court held previously to be constitutional, IPR does not affect the remedies available to holders of valid patents against infringers. Rather, IPR involves the reconsideration of the government's decision to grant a public franchise based on the statute governing patent validity. This Court should hold that the application of IPR to pre-AIA patents is constitutional, because it implements overriding public purposes in a rational way.

STANDARD OF REVIEW

The court reviews the Board's conclusions of law *de novo*, and its findings of fact for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1315-16 (Fed. Cir. 2000). Substantial evidence is something less than the weight of the evidence, but more than "a mere scintilla" of evidence. *Id.* at 1312 (Fed. Cir. 2000) (quoting *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 305 (1938)). Substantial evidence means "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Id.*

Anticipation under 35 U.S.C. § 102 is a question of fact, while obviousness under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015). This Court reviews the Board's factual findings relating to

those inquiries for substantial evidence. *See Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1356 (Fed. Cir. 2018) ("If two inconsistent conclusions may reasonably be drawn from the evidence in record, [the PTAB]'s decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence." (internal citations omitted)).

Claim construction is also a question of law with underlying questions of fact. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015). Accordingly, this Court reviews the Board's claim constructions *de novo* and its underpinning factual determinations involving extrinsic evidence for substantial evidence. *Wasica Fin. GmbH v. Cont'l Automotive Sys., Inc.*, 853 F.3d 1272, 1278 (Fed. Cir. 2017).

This Court reviews constitutional challenges to the patent laws *de novo*. *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1287 (Fed. Cir. 2015).

ARGUMENT

I. Van Sommeren Anticipates Claims 1, 2, and 5

Anticipation of a patent claim requires that a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *In*

re Cruciferous Sprout Litig., 301 F.3d 1343, 1349 (Fed. Cir. 2002). Where the patent claims a range, it is anticipated by prior art disclosing a single point within the range. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985). And, where the prior art discloses an overlapping range, it anticipates unless there is evidence establishing that the claimed range is "critical to the operability of the claimed invention." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015); *see also ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012).

Van Sommeren discloses each and every limitation of claims 1, 2, and 5. Van Sommeren discloses a method that uses protein A chromatography to purify an antibody having a C_H2/C_H3 region as provided in claims 1 and 5. Appx119, Appx560. Van Sommeren also discloses conducting protein A chromatography on antibodies at 4°C and at 20°C to 25°C. Appx119-120, Appx569-570. The higher range of temperatures disclosed in van Sommeren, 20°C to 25°C, overlaps with the claimed range of about 10°C to about 18°C because "about 18°C" should be construed to mean "18±3°C." Appx120.

Genentech does not contest that under the Board's construction, van Sommeren anticipates claims 1, 2, and 5. Br. at 32-33. Genentech's only argument on appeal against anticipation by van Sommeren is that "about 18ºC"

should not be construed to mean "18±3ºC."[7] As discussed below, "18±3ºC" is the proper construction, and indeed the only construction supported by the intrinsic evidence. Thus, this Court should affirm the Board's determination that claims 1, 2, and 5 are invalid as anticipated by van Sommeren.

A. The Board's Construction of "About 18ºC" to Encompass "18±3ºC" Is Correct

In an IPR proceeding, the Board should give claims their broadest reasonable construction consistent with the specification. *Cuozzo Speed Technologies, LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). Here, the Board considered the intrinsic evidence, weighed the expert testimony concerning how a skilled artisan would understand the phrase "about 18ºC," and determined that the phrase encompasses "18±3ºC." That construction is the broadest reasonable interpretation, and should be affirmed.

1. *The Specification Supports the Construction of "18±3ºC"*

The specification demonstrates that, as the patentee, Genentech considered "±3°C" to reflect typical temperature fluctuations during protein A chromatography. While it is true that there is no explicit definition of the term

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[7] The Board also declined to construe the claims as requiring active cooling of the composition to the claimed range (Appx16), and Genentech does not argue this point on appeal.

"about" in the specification, the specification demonstrates that ±3°C is a normal fluctuation for temperatures in these types of processes. For example, the specification states that "[f]ive harvests were recovered through the protein A step. The HCCF was collected and held at 15±3°C. for the duration of loading." Appx70, *see also* Appx71.

This understanding of the meaning of "about" is also consistent with how a person of ordinary skill in the art would understand the term. Dr. Przybycien explained that a skilled artisan would have considered ±3ºC to be a normal temperature fluctuation in the context of protein A chromatography. Appx450. In view of this evidence, a person of ordinary skill in the art would conclude that "about 18ºC" encompasses "18±3°C." Appx938-941. The Board's fact-finding aligned with Dr. Przybycien's testimony (Appx11-14), and the little weight accorded to Genentech's arguments (Appx14-15) is entitled to deference. *See Cephalon, Inc. v. Abraxis Bioscience, LLC*, 618 F. App'x 663, 665 (Fed. Cir. 2015).

According to Genentech, the results of the experiments where the temperature was held at 15±3°C do not inform the proper construction of "about 18°C." Br. at 29-30. Genentech also asserts that the variation of ±3°C is only appropriate where it results in temperatures that are entirely within the claimed

range of "about 10°C to about 18°C." *Id*. at 16. However, the meaning of the term "about" is context dependent. *See Atlas IP, LLC v. Medtronic, Inc.*, 809 F.3d 599, 605 (Fed. Cir. 2015) (observing that this Court gives "words of a claim their ordinary meaning in the context of the claim and the whole patent document . . ."). In the specification, "about" captures an acceptable temperature fluctuation associated with controlling temperature. Appx450. Nothing in the specification requires a narrower construction. As such, the Board properly found that the construction of "about 18°C" encompasses "18±3°C."

2. *The Prosecution History Supports the Construction of "18±3°C"*

During prosecution of the applications for the '704 patent and EP '940, Genentech implicitly acknowledged that "about" means at least ±2°C but less than ±4°C. As discussed above, the original claims recited a temperature range of "from about 3°C to about 20°C." Appx704. The claims were rejected by the Examiner as anticipated by Horenstein,[8] which disclosed performing protein A chromatography at about 22°C. Appx716. Genentech acquiesced to the Examiner's rejections, eventually amending the claims to recite "about 18°C" in

[8] Horenstein et al., *Design and scaleup of downstream processing of monoclonal antibodies for cancer therapy: from research to clinical proof of principle*, 275 JOURNAL OF IMMUNOLOGICAL METHODS, 99 (2003).

order to obtain allowance. Appx740. Thus, Genentech interpreted the term "about 20°C" to encompass 22°C, while the term "about 18°C" apparently excluded 22°C. This interpretation is consistent with construing "about" to mean "±3°C," as suggested by the specification. Appx450, Appx451.

Genentech contends that the amendments made during prosecution are irrelevant to claim construction because they were "made without prejudice or disclaimer." Appx198. The Board did not "disregard" those statements, as Genentech suggests. Rather, the Board accorded Genentech's statements little weight because Genentech *did* acquiesce by narrowing the claimed temperature range, and never again pursued a broader temperature range. Appx15, Appx743; *see Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1097-98 (Fed. Cir. 2013). The Board found that a broad construction of "about 18ºC" was reasonable, based on the pattern of amendments during prosecution for the '704 patent and EP '940. Appx14.

In its appeal, for the first time, Genentech argues that "about" cannot be ±3ºC because otherwise conducting protein A chromatography at "about 22ºC" as taught by Horenstein would overlap with "about 18ºC." Br. at 31-32. However, it is apparent that during prosecution, Genentech believed that it could distinguish the claims from the prior art by amending the claims to recite "about 18ºC" rather

than "about 20ºC," regardless of any overlap. Arguing that the claimed method (as amended) was patentably distinct from the method taught by Horenstein, Genentech stated that "it would not appear that 'about 18ºC' could *include 22ºC*." Appx789 (emphasis added). Therefore, Genentech's view during prosecution of "about" as claimed was consistent with at least ±2ºC, but less than ±4ºC. The Board took into account evidence that could justify or detract from its factual determinations, and drew the reasonable conclusion that "about 18ºC" means "18±3ºC." *See In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000).

B. The Board Properly Rejected Genentech's Claim Construction

Genentech's proposed construction of "about 18ºC" as "approximately 18ºC" (*see* Appx195-196) does nothing to advance the invalidity analysis. Perhaps recognizing this deficiency, Genentech also argues that "about 18ºC" should mean "18±1ºC." Br. at 27. Genentech does not cite to any portion of the intrinsic evidence to support this narrow construction. Rather, Genentech argues that "'approximately 10ºC to approximately 18ºC' cannot be reasonably construed to add ±3 to each end of the claimed range." *Id.*

According to Genentech, "the Specification makes it clear that 'about 20ºC' means 'below room temperature'." *Id*. Genentech asserts that one embodiment, where the method is practiced at "below room temperature," sheds

light on the meaning of the claim term. However, the "below room temperature" standard is far from illuminating, and renders Genentech's position internally inconsistent. As observed by the Board:

> . . . if "about" means "no[t] more than ±1 ºC," the upper limit of "about 20ºC" is 21ºC—which Patent Owner equates with room temperature. Thus, contrary to its position that claim 1 requires the method to be conducted at below room temperature, Patent Owner's construction would require 21 ºC to be both room temperature *and* below room temperature.

Appx13 (emphasis in original).

The root of this inconsistency is that Genentech seeks to import limitations into the claims, not only from the specification, but also from the "consensus definition of room temperature." Br. at 30. Genentech points to extrinsic evidence that "'[r]oom temperature' is commonly understood to span 21ºC to 25ºC, i.e., 69-77ºF." *Id.* at 27. However, there is no consensus when it comes to the meaning of room temperature. According to WO '389 and van Sommeren, temperatures as low as 18ºC or 20ºC would also be "room temperature." Appx522, Appx570. During the prosecution of EP '940, a third party offered Observations noting that the European Pharmacopoeia defined room temperature as between 15ºC and 25ºC. Appx1165-1166. Most importantly, none

of this extrinsic evidence is helpful for construing the claims because the claims do not recite "room temperature."

Genentech also argues that the Board concluded that the phrase "preferred embodiment" rendered this portion of the specification "irrelevant" to claim construction. Br. at 29. This is not the case. The Board considered the specification as a whole and, following long-established case law, the Board declined to read a "below room temperature" limitation into claims. Appx12; *see SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004). The Board weighed Hospira's evidence against Genentech's inconsistent statements, and articulated the broadest reasonable construction for the disputed term. Therefore, the Board's claim construction of "about 18 ºC" to mean "18±3ºC," should be affirmed.

As stated above, Genentech's only argument for reversing the Board's finding that van Sommeren anticipates claims 1, 2 and 5 is that Board's construction of "about 18 ºC" to mean "18±3ºC" is wrong. Because the Board's construction is correct, and Genentech has not advanced any other arguments, the Board's finding of anticipation in view of van Sommeren should be affirmed.

II. WO '389 Anticipates Claims 1 and 5

The Board also properly found that WO '389 discloses all of the limitations of claims 1 and 5, and therefore anticipates these claims. Genentech's claim construction argument is inapplicable to the finding of anticipation by WO '389. Therefore, Genentech attempts to attack the Board's fact-finding with regard to the teachings of WO '389 by arguing that the Board made an improper inference. Br. at 34. Genentech's argument is misplaced for several reasons.

WO '389 teaches conducting protein A chromatography at 18-25ºC as part of a process for purifying antibodies. Appx522. Genentech and its expert, Dr. Cramer, argue that the teaching that the purification steps are performed at a temperature of 18-25ºC applies *only* to the temperature of the laboratory, and *not* the temperature of the composition subject to protein A chromatography. Appx1352. Hospira provided substantial evidence to support the conclusion that WO '389 uses the term, "room temperature (18-25ºC)," to describe the temperature for conducting protein A chromatography, and all of the components involved in that process, including the composition to be purified. Appx946-947; *see* Appx1551-1553.

The Board found that WO '389 anticipates for two distinct reasons. First, the Board determined what the teachings of WO '389 would mean to the

skilled artisan by weighing the testimony of Dr. Cramer and Dr. Przybycien. The Board credited the testimony of Dr. Przybycien, and found that WO '389 discloses all limitations of claims 1 and 5 of the '799 patent. Appx19-21. The Board's fact-finding here is entitled to deference. *See In re Gartside*, 203 F.3d at 1312.

Second, the Board inferred that during protein A chromatography as described in WO '389, the composition being purified would equilibrate with room temperature (18-25ºC). Appx21-22. For this additional reason, the Board also found that WO '389 discloses all elements of claims 1 and 5. The Board's reasoning was based on substantial evidence (*see* Appx946-947), and should be affirmed. Genentech's arguments concerning the Board's inference only apply to this second reason for finding that WO '389 anticipates claims 1 and 5.

A. A Skilled Artisan Would Understand that Conducting Protein A Chromatography at 18-25ºC Means the Composition Is at 18-25ºC

The purification process taught by WO '389 includes a step using protein A affinity chromatography, which is "carried out at room temperature (18-25°C)." Appx522. The disclosed range of 18°C to 25°C overlaps with the claimed range of about 10°C to about 18°C regardless of the construction of the term "about." Genentech suggests that WO '389 merely informs the skilled artisan what the temperature of the laboratory was, and that the temperature of the composition

being purified can only be established through inherency. Br. at 34-35. However, Hospira has never argued that the temperature of the composition disclosed in WO '389 is inherently or inevitably at room temperature, and the Board did not find anticipation on that basis. The proper question is what WO '389's teaching of conducting protein A chromatography at "18-25ºC" would mean to a skilled artisan. "[R]oom temperature (18-25°C)" is not idle commentary on the laboratory, it is the term WO '389 uses to describe the conditions for practicing protein A chromatography.

As Dr. Przybycien explained, WO '389 sets forth a clear protocol for practicing protein A chromatography at ambient temperature. Appx946. A skilled artisan would have understood this teaching to mean that all of the materials employed as part of this step, including the HCCF, were at this temperature based on generally known laboratory practices. Appx1556. In the field of antibody purification, absent contrary language, a skilled artisan would understand that experiments are being conducted at ambient temperature with all materials equilibrated, in order to obtain robust scientific data. For example, multiple peer-reviewed publications cited by Genentech also do not specify the temperature of the HCCF. *See, e.g.*, Appx1075-1076. It is noteworthy that when WO '389 described processes requiring a fluid to be at a temperature other than room

temperature, WO '389 specifically stated the temperature of that fluid. Appx523-524 ("The resulting solution is filtered . . . and held in sterile containers at 4ºC, or frozen and held at -70ºC."). However, as the Board observed, it would have been redundant to specifically call out the temperature of the HCCF during protein A chromatography in light of the blanket teaching to carry out all steps at room temperature (18-25°C). Appx20.

Instead of reading WO '389 through the eyes of a skilled artisan, Genentech asks this Court to imagine an unlikely scenario in which warm HCCF is rushed from the bioreactor and loaded onto the equilibrated chromatography column.[9] As Dr. Przybycien explained, no reasonable person of ordinary skill in the art would conduct the purification in this way, and then report having performed the step at 18-25ºC. Appx947. Using HCCF that was much warmer than the chromatography column would raise the temperature of the whole system, making it impossible to conduct all steps at room temperature. Appx946-947.

Genentech argues that Dr. Przybycien's explanation of WO '389 is not substantial evidence because he allegedly offered contradictory testimony

[9] When Dr. Cramer was asked during his deposition (Appx1053-1056) whether he was aware of any commercial process where warm, filtered HCCF went immediately to the protein A column, he answered, "I'm not aware of that, but I can imagine it happening." Appx1075.

during his deposition. Br. at 38. However, Dr. Przybycien's deposition testimony does not contradict the analysis provided in his declarations, which was adopted by the Board. Genentech's counsel asked Dr. Przybycien to speculate as to whether the cell culture fluid used by the inventors of WO '389 could have been warm from a bioreactor immediately prior to purification (Appx1554-1557), despite WO '389's explicit teaching to carry out all steps at 18-25ºC (Appx522). He attacked inherency by asking Dr. Przybycien if it was "not inevitable" that the composition would be at room temperature. Appx1555. Genentech's straw man argument against inherency assumes that the ill-advised, hypothetical practice of utilizing warm HCCF is interchangeable with the generally accepted laboratory practice of using equilibrated components to conduct protein A chromatography. *See* Appx2284-2285, Appx2296. Dr. Przybycien provided his practical interpretation of WO '389's teachings, based on his expert knowledge of protein A chromatography. Appx2296-2297. He explained that a reasonable person of ordinary skill in the art would understand that the HCCF described in WO '389 would come to room temperature, and be in equilibrium with its surroundings. Appx1555-1556.

The Board analyzed the teachings of WO '389 as well as the testimony of Drs. Cramer and Przybycien. In doing so, the Board took into

account evidence that could justify or detract from its factual determinations, and drew a reasonable conclusion. *See In re Gartside*, 203 F.3d at 1312. The Board found that WO '389 teaches every limitation of claims 1 and 5, including conducting "protein A affinity chromatography at a temperature in the range of about 10ºC. to about 18ºC." As discussed above, this temperature range is not critical, and Genentech does not argue that it is. Therefore, the Board's finding of anticipation based on WO '389 is supported by substantial evidence, and should be affirmed.

B. Alternatively, the Composition Would Reach the Claimed Temperature Range During Purification

As an alternate ground for finding that WO '389 anticipates claims 1 and 5, the Board also considered what would happen within the chromatography column during protein A chromatography if "warm" HCCF were placed on the column as Genentech posits. The Board construed "'subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 ºC to about 18 ºC' (claim 1) as referring to the temperature of the composition prior to *and/or during* protein A affinity chromatography." Appx16. The Board then inferred that the composition subjected to protein A chromatography would be at 18-25ºC *during* the purification process, based on its reasonable understanding

of the method disclosed in WO '389. Appx21-22. This additional reason for finding that WO '389 anticipates is also supported by substantial evidence.

The Board observed that at least the apparatus and column buffers used to carry out the protein A chromatography are within the temperature range of 18-25ºC because WO '389 discloses that "[a]ll steps are carried out at room temperature (18-25ºC)." Appx22, Appx522. Genentech has never contended that the apparatus used for the protein A chromatography was not at 18-25ºC. *See* Appx1555. Genentech's position is that it would be possible, in theory, to load warm HCCF onto the room temperature column, despite the teaching to carry out all steps at room temperature. Br. at 34. However, even if the HCCF were warmer than room temperature before being loaded onto the chromatography column, utilizing a room temperature column and room temperature buffers would cause the HCCF to equilibrate during the process, just as the Board explained. Appx22. In fact, Dr. Przybycien stated during his deposition that it would be reasonable to assume that HCCF would come to equilibrium with its surroundings at least by the time it is handled in the column. Appx1556.

Genentech does not provide any reason why the Board's logical inference could be wrong. Instead, Genentech suggests that the fact finder is foreclosed from making any inferences. Br. at 33-34. Relying on *Nidec Motor*

Corp. v. Zhongshan Broad Ocean Motor Co., Genentech asserts that the Board cannot base its anticipation determination on "improperly assum[ing] disclosure of a claim element." 851 F.3d 1270, 1274 (Fed. Cir. 2017). But here there is no missing element. WO '389 teaches purifying a composition by conducting protein A chromatography at 18-25ºC, and claim 1 recites, "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10 ºC to about 18 ºC."[10]

The fact finder need not remain blind to the implicit teachings that would be evident to a person of ordinary skill in the art. "Anticipation is established when 'one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference.'" *CRFD Res., Inc. v. Matal*, 876 F.3d 1330, 1338 (Fed. Cir. 2017) (quoting *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3 1186, 1192-93 (Fed. Cir. 2003)); *see also In re Preda*, 401 F.2d 825, 826 (C.C.P.A. 1968) ("[I]n considering the disclosure of a reference, it is proper to take into account not only the specific teachings of the reference but also the inferences

[10] During the prosecution of EP '940, Genentech narrowed the claims "to refer to an upper temperature limit of 15ºC" in an effort to overcome the teachings of WO '389. Appx806-807.

which one skilled in the art would reasonably be expected to draw therefrom.”). Therefore, the Board’s ruling is not based on any misapplication of law. Its finding of anticipation should be affirmed because WO ’389 discloses every limitation of claims 1 and 5 of the ’799 patent.

III. The Board Properly Found that Claims 1 to 3 and 5 to 11 Would Have Been Obvious Based on the Teachings of the Prior Art

The Board properly found that claims 1 and 5 also would have been obvious over WO ’389 alone (Ground 3) and claims 1, 2 and 5 would have been obvious over van Sommeren alone (Ground 7) because the claimed temperature range is not critical, and alternatively because a skilled artisan would have been motivated and able to practice protein A chromatography at the claimed temperature range based on teachings in the prior art. The Board also concluded that the Challenged Claims would have been obvious over WO ’389 or van Sommeren, in view of the teachings of Balint, Potier and/or the ’526 patent, as set forth in Grounds 4-6 and 8.

Genentech’s Brief only addresses Grounds 3 and 7, and does not challenge the Board’s separate findings regarding Grounds 4-6 and 8. However, Genentech’s characterization of the Board’s holdings with regard to obviousness over WO ’389 alone and van Sommeren alone omits key findings. When viewed

in the proper light, the Board's fact-finding and legal conclusions on obviousness are well-supported and should be affirmed.

Here, the Board found that the prior art teaches temperature ranges that overlap with a claimed range. Appx21, Appx28. Therefore, that claimed range is obvious unless the patentee can show that it is critical to practicing the invention. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015). The Board also found that Genentech failed to show criticality in the claimed range (Appx24), and Genentech does not challenge this on appeal. Genentech's brief does not address the fact that its failure to show criticality renders claims 1, 2 and 5 obvious over WO '389 and van Sommeren.

Furthermore, the prior art also provides at least two additional motivations for modifying the teachings of WO '389 and van Sommeren with regard to the temperature for conducting protein A chromatography. First, protein A leaching was known to be caused by temperature-dependent proteolysis. Appx578. Second, the binding capacity of protein A was known to be temperature-dependent. Appx571. Thus, a person of ordinary skill in the art would have been motivated and able to vary the temperature at which protein A chromatography was conducted in order to obtain the advantages of reduced

protein A leaching and/or improved binding capacity with a reasonable expectation of success. Appx460-461, Appx470-471.

A. The Claimed Methods Would Have Been Obvious at the Time of the Alleged Invention Because the Claimed Temperature Range is Not Critical

WO '389 and van Sommeren both teach conducting protein A chromatography at temperature ranges that overlap with the claimed range as described above. In cases involving overlapping ranges, courts have consistently held that even a slight overlap in range establishes a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). "[T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious . . . ." *Id.* at 1330. Recently, in *E.I. DuPont de Nemours v. Synvina C.V.*, this Court reiterated the established principle that overlapping ranges create a presumption of obviousness, and concluded that the same framework governing overlapping ranges in district court adjudications and PTO examinations controls in IPR proceedings. 904 F.3d 996, 1008 (Fed. Cir. 2018).

A patentee may attempt to rebut this presumption by demonstrating that practicing the process at the claimed range produces unexpected results, and is therefore "critical." *Id.* at 1006. The claimed temperature range of about 10°C to

about 18°C is not critical to the invention (*see* Appx452-454, Appx953-960), and Genentech no longer argues that it is. Protein A chromatography performed at temperatures in the claimed range, and in the prior art ranges, leads to low levels of protein A leaching. Appx253, Appx955-957. This leaching follows a smooth exponential function across temperatures in the claimed range and in the prior art ranges. Appx954, Appx957-960.

The patentee may also rebut the presumption of obviousness by showing that the prior art taught away from the claimed range, or that the parameter in question was not recognized as "result-effective." *Id.* However, where the general conditions of a claim are disclosed in the art, "it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (citing *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)). "[The] overlap itself provides sufficient motivation to optimize the ranges." *Id.*

In this case, a skilled artisan would have been motivated to find additional optimal or workable ranges based on the known operability of protein A chromatography at 18-25°C (WO '389), and 20-25°C (van Sommeren). The normal desire of scientists to improve upon what is already known provides the motivation to determine optimal ranges. *Id.* Moreover, discovering an optimum

value of a result-effective variable is ordinarily within the skill of the art. *Id.* Where the prior art recognizes that a variable affects the relevant property or result, "then the variable is result-effective." *DuPont*, 904 F.3d at 1009. Based on substantial evidence, the Board found that temperature is a result-effective variable because it can affect temperature-dependent proteolysis, as well as protein A binding capacity. Appx38.

Furthermore, a skilled artisan could have practiced protein A chromatography in the range of about 10ºC to about 18ºC with a reasonable expectation of success. Rather than arguing that the prior art teaches away from conducting protein A chromatography at the claimed range, Genentech states that researchers never attempted the process at intermediate temperatures. Br. at 11-12. According to Genentech, this alleged silence in the prior art proved that modifying the temperature used for conducting protein A chromatography would not have been routine. *Id.* at 12. The Board rejected Genentech's argument that the named inventors had developed a new system for temperature adjustment. Appx39. The Board credited Dr. Przybycien, and concluded that modifying temperature would have been routine because it was well known to regulate chromatography column temperature using only conventional equipment that was available before the filing date of the '799 patent. Appx39.

The burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results or criticality, or other pertinent objective indicia of non-obviousness. *DuPont*, 904 F.3d at 1008. Genentech failed to show that temperature is not a result-effective variable, failed to prove criticality, and never attempted to show that the prior art teaches away from the claimed range. Therefore, the Board's finding of obviousness based on either of WO '389 or van Sommeren alone should be affirmed.

B. A Skilled Artisan Would Have Been Motivated to Vary Temperature Based on the Prior Art

As noted above, WO '389 and van Sommeren both teach conducting protein A chromatography at temperatures that overlap with the claimed range of about 10ºC to about 18ºC. Even if these teachings did not establish a prima facie case for obviousness, persons of ordinary skill in the art would have been motivated to and able to carry out protein A chromatography at about 10ºC to about 18ºC based on disclosures from the prior art. The claimed temperature need not be explicitly taught in the prior art, so long as temperature can be optimized using only routine experimentation. *See Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 729 (Fed. Cir. 2017).

WO '389 discloses that proteins may be purified by a protocol including the step of protein A chromatography, "such protocol being modified if necessary by routine, non-inventive adjustments that do not entail undue experimentation." Appx514. Furthermore, proteolytic degradation and leaching of protein A were known problems. Appx521-522. The Board found that a person of ordinary skill in the art would have known, based on the available general knowledge, that reactions such as proteolysis are temperature dependent, and that decreasing the temperature would decrease proteolysis. Appx24, Appx35-36; *see also* Appx453, Appx227. Genentech does not challenge this finding on appeal. In addition, Balint teaches that protein A leakage following affinity chromatography "is due to inherent endogenous proteolytic activity which cleaves protein fragments from the matrix. . . ." Appx578. Proteolysis is widely known to be activated by temperature—a fact conceded by Genentech. Appx227, Appx594-595.

Van Sommeren also teaches at least two motivations for reducing the temperature at which protein A chromatography is conducted. First, van Sommeren discloses that conducting protein A chromatography at the lower temperature of 4°C improves the binding of certain antibodies with protein A. Appx571. A skilled artisan would have appreciated that lowering the temperature

of the process below ambient temperature could enhance its performance, and would have been motivated to determine an optimal range using routine experimentation. Appx470. Second, van Sommeren discloses that contamination due to proteolysis was a known problem. Appx572-573. It would have been obvious for a person of ordinary skill in the art to try temperatures within the claimed range for applications, whether at lab or commercial scale, in order to see if lower temperatures could affect contamination caused by proteolysis. Appx470. Accordingly, the Board properly concluded that "exploring the temperature dependence of protein A leaching is not more than routine experimentation." Appx39.

Furthermore, a person of ordinary skill in the art would have been motivated to use an intermediate temperature for protein A chromatography. Appx461. Because the temperature dependence of protein A leaching is exponential, there are diminishing returns for reducing temperature at colder temperatures. Reducing the temperature below 10°C, to the range of 3° to 10°C, may not provide a significant benefit relative to the cost. As Dr. Przybycien opined, a person of ordinary skill in the art would have balanced the costs and effort of reducing the temperature below about 10°C against the minute changes in protein A leaching observed at such low temperatures. *Id.* The Board found, after

considering the record as a whole, that practicing protein A chromatography "in the claimed intermediate temperature range would have been an obvious design choice that balances the cost and effort of using reduced temperatures against the benefit of reducing proteolysis. . . ." Appx30.

C. Genentech's Attempts to Negate the Motivations Taught by the Prior Art Are Unavailing

None of the evidence presented by Genentech weighs against the concrete teachings, suggestions and motivations summarized above. Genentech argues that it would not have been obvious to practice protein A chromatography as disclosed by WO '389 because protein A leaching "matters *only* in the industrial production of therapeutic antibodies," and modulating temperature at the industrial scale would have been too difficult. Br. at 41. Genentech also contends that while van Sommeren suggested modifying temperature to improve binding capacity in 1992, by the time of the alleged invention in 2003, the person of ordinary skill in the art would no longer have been motivated by those earlier findings. *Id.* at 46-47. According to Genentech, "a 'routine' development process is one that has been performed dozens of times." *Id.* at 50. Genentech's arguments lack factual support and are insufficient to overcome the teachings of the prior art.

1. *The Board's Conclusion that a Skilled Artisan Would Have Routinely Optimized Temperature to Reduce Proteolysis Is Supported by Substantial Evidence*

Genentech claims that the Board's ultimate conclusion of obviousness rests on an improper combination of findings made at two different scales. Br. at 41. Genentech reasons that it is unnecessary to remove leached protein A for non-clinical uses, and therefore protein A contamination is only relevant for commercial-scale processes. *Id.* Genentech then contends that it was not easy to control temperature at commercial scale. *Id.* at 42. Both of Genentech's contentions are factually inaccurate and legally irrelevant.

First, reducing contamination for clinical applications is not the only reason a person of ordinary skill in the art would have for reducing protein A leaching. Protein A leaching degrades chromatography columns, reducing the usable capacity and life span of a valuable resource. *See, e.g.*, Appx903-904, Appx932. Therefore, even in non-clinical settings, it would be desirable to reduce protein A leaching. Additionally, not all clinical applications are on the industrial scale. There are smaller scale, or academic applications for protein A chromatography that would also benefit from reduced protein A leaching. For example, WO '389 and Balint describe research conducted at the pilot or

laboratory scale, and both explicitly name protein A as an undesirable impurity. Appx513, Appx578.

Second, the Board's finding that controlling temperature would have been "easy," is not limited to laboratory-scale experiments. As an initial matter, the Board observed that this argument is irrelevant because the claims are not limited to commercial-scale applications. Appx20. Additionally, it would have been routine before 2003 for a skilled artisan in the field of protein purification to control or vary the temperature of compositions intended for purification, at both laboratory and industrial scales. Genentech suggests that temperature control was not routine because chilling large volumes of liquid was, "anything but easy," "challenging" (Br. at 42), "inconvenient," and "requires specialized and expensive equipment" (Appx220). However, techniques that require expense, time, and effort to carry out may nevertheless be routine to one of ordinary skill in the art. *See Velander v. Garner*, 348 F.3d 1359, 1378 (Fed. Cir. 2003) (noting with approval the Board's observation that there was a reasonable expectation of success for a process that was "expensive, technically challenging and laborious"). It is routine optimization where the steps implemented would have been within the capabilities of one skilled in the art. *Merck Sharp & Dohme*, 874 F.3d at 731.

Both experts agreed that conventional means for varying temperature would have been available for those skilled in the art before the time of the alleged invention. Citing to Dr. Przybycien's second declaration, the Board observed that it was "well known to regulate chromatography column temperature by using refrigerated HCCF and chromatography buffers, and/or conducting the procedure in jacket-cooled chromatography columns, refrigerated spaces, or temperature-controlled water baths." Appx39; *see also*, Appx977. During his deposition, Dr. Cramer admitted that the devices used to control the HCCF temperature in the laboratory scale and pilot scale experiments discussed in the '799 patent were standard, commercially available laboratory equipment in 2003. Appx1080. He also conceded that the '799 patent does not even explain how temperature was controlled for the full-scale batches. Appx1081.

"[A] patent need not teach, and preferably omits, what is well known in the art." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Unsurprisingly, the '799 patent provides only a minimal disclosure of chilling HCCF at lab and pilot scales, and does not describe any means for chilling HCCF at the commercial scale, except to note that the HCCF is chilled to 15±3ºC in an "HCCF tank." Appx71. The Board's determination that it

would have been routine to explore the temperature dependence of protein A leaching is therefore supported by substantial evidence, and should be affirmed.

2. *The Board's Conclusion that a POSA Would Have Routinely Optimized Temperature to Improve Binding Capacity Is Supported by Substantial Evidence*

According to Genentech, the Board's conclusion of obviousness based on van Sommeren was legally erroneous for failing to consider the obviousness of the claimed methods "at the time the invention was made." Br. at 46. In other words, Genentech argues that van Sommeren is too old to be proper prior art, because intervening references such as Fahrner 1999[11] and Fahrner 2001[12] discouraged persons of ordinary skill in the art from varying temperature. *Id.* at 47.

First, van Sommeren is just one example of published research that placed the concept of temperature-dependent binding in the public domain. Intervening prior art cannot remove this teaching from the knowledge available to

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[11] Fahrner et al., *The optimal flow rate and column length for maximum production rate of protein A affinity chromatography*, 21 BIOPROCESS ENGINEERING 287–292 (1999). Appx1312.

[12] Fahrner et al., *Industrial Purification of Pharmaceutical Antibodies: Development, Operation, and Validation of Chromatography Process*, 18 BIOTECHNOLOGY AND GENETIC ENGINEERING REVIEWS 301–327 (2001). Appx1285.

those skilled in the art, and consequently there is no such thing as prior art that is "too early." In addition, there is no evidence that skilled artisans in the field have never varied temperature in order to affect binding since the publication of van Sommeren. This is mere speculation on Genentech's part.

Second, Genentech has mischaracterized the teachings of Fahrner 1999 and Fahrner 2001. Far from supplanting the teachings of van Sommeren, these references both cite to van Sommeren, and specifically reference "column temperature" as one of several variables that affect binding capacity. Appx1294, Appx1312, Appx1316. The Board also noted that Fahrner 2001 teaches that binding capacity is affected by column temperature. Appx38. The fact that these publications mention column temperature, but also focus on other parameters, is not a teaching away from motivations relating to temperature. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Obviousness may be based on any motivation or suggestion found in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). The Fahrner references affirmatively teach that temperature is a result-effective variable for protein A chromatography, and demonstrate that van Sommeren continued to be regarded as a relevant authority in the field for many years after its publication.

Based on the substantial evidence summarized above, the Board correctly concluded that 1) there was no evidence supporting Genentech's claim that the claimed temperature range achieves unexpected results or is critical, and 2) exploring the temperature dependence of protein A leaching is not more than routine experimentation. Appx40, Appx45-47. Accordingly, claims 1, 2, and 5 would have been obvious in view of van Sommeren alone, and claims 1 and 5 would have been obvious in view of WO '389 alone. As noted above, Genentech has not appealed the Board's findings with regard to the teachings of Balint, Potier or the '526 patent. Genentech has also not argued at any time that any limitation disclosed in the dependent claims renders them patentable. Therefore, claims 1-3 and 5-11 are also unpatentable as obvious for the same reasons discussed above, and in greater detail in the Board's Decision and Hospira's Reply.

D. Genentech Failed to Establish a Nexus Between Any Objective Indicia of Non-Obviousness and the Claims

Analysis of secondary considerations may assist a court in avoiding hindsight bias. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). However, a showing of secondary considerations must be commensurate to the showing of obviousness—a weak showing of secondary considerations cannot overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co.*,

616 F.3d 1231, 1246 (Fed. Cir. 2010). In addition, the patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the claim. *In re Kao*, 639 F.3d 1057, 1068, 1072 (Fed. Cir. 2011) (finding that the only element not expressly disclosed in the prior art was an inherent property, and concluding that evidence of secondary considerations did not outweigh the strong showing of obviousness).

As discussed above, Genentech no longer contends that performing protein A chromatography as claimed produces any unexpected results. With regard to the alternative indicium of industry praise, Genentech has only identified a single meeting at which Genentech's researchers presented their work. Br. at 51. Based on this, Genentech asserts that the fact that the research embodied by the '799 patent was selected "as worthy of the time of the other attendees at the conference" is powerful objective evidence of non-obviousness. *Id.* However, Genentech does not provide the necessary context for evaluating the import of the inventors' presentation. The Board correctly found that there is no evidence that there was any industry praise, and there is no evidence that any industry praise was received because of the claimed invention. Appx40.

According to Genentech, Dr. Cramer explained that the process of being selected "to present at ACS is competitive." Br. at 51. This mischaracterizes Dr. Cramer's declaration testimony. In fact, Dr. Cramer praised this meeting as "prestigious" and stated that presenters were selected, but he never stated that the process for selecting presenters was competitive. Appx1392. Dr. Przybycien's unrebutted testimony is that "it was commonplace for 90% to 95% of the submitted reports to be selected for presentation at such conferences." Appx982. In addition, Genentech did not provide evidence showing how the inventors' research was received by the attendees, or how it has been relied upon and praised since, outside of Genentech. Appx982. Genentech also failed to prove that there was any nexus between the presentation and the *claimed* invention. Indeed, the presentation may have been selected because it was by a major manufacturer, or because of the drug at issue, and not due to the data regarding the claimed temperature range of "about 10ºC to about 18ºC." Appx983. The Board's decision to accord little weight to Genentech's evidence of secondary considerations is therefore supported by substantial evidence.

The objective indicia alleged by Genentech are insufficient to disprove the strong case of prima facie obviousness discussed in Sections III.A-III.C above. Accordingly, claims 1 to 3 and 5 to 11 of the '799 patent are obvious

under Grounds 3 through 8, and the Board's conclusions relating to obviousness should be affirmed.

IV. Conducting *Inter Partes* Review of Pre-AIA Patents Is Constitutional

Genentech's argument that "[t]he retroactive application of inter partes review to a patent issued before that procedure existed is unconstitutional, a taking without just compensation and a denial of due process" (Br. at 53) is baseless. As an initial matter, the application of IPR to patents issued pre-AIA is not a retroactive application of the law because it does not attach new legal consequences to pre-AIA conduct. *See Landgraf v. USI Film Prods*., 511 U.S. 244, 269-70 (1994) ("the court must ask whether the new provision attaches new legal consequences to events completed before its enactment"). Rather, the Board "considers the same statutory requirements that the PTO considered when granting the patent." *Oil States Energy Serv., LLC v. Greene's Energy Grp., LLC*, 138 S. Ct. 1365, 1374 (2018). Furthermore, in enacting IPR, Congress merely allocated jurisdiction to the USPTO and prescribed the procedure governing the USPTO's reconsideration of patents. *See Landgraf*, 511 U.S. at 275 ("Because rules of procedure regulate secondary rather than primary conduct, the fact that a new procedural rule was instituted after the conduct giving rise to the suit does not make application of the rule at trial retroactive.").

Even if IPR were a retroactive application of the law, it would not constitute a taking without just compensation or a denial of due process. The application of IPR to pre-AIA issued patents serves "a rational legislative purpose." *See Pension Ben. Guar. Corp. v. R.A. Gray & Co*., 467 U.S. 717, 730 (1984). For example, "inter partes review protects 'the public's paramount interest in seeing that patent monopolies are kept within their legitimate scope.'" *Oil States*, 138 S. Ct. at 1374 (quoting *Cuozzo Speed Technologies, LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016)). This Court has explained that "Congress sought to 'provid[e] a more efficient system for challenging patents that should not have issued' and to 'establish a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs.'"[13] *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1290-91 (2015) (quoting H.R. REP. NO. 112-98, pt. 1, at 39–40 (2011)). Thus, Congress authorized *inter partes* review of pre-AIA patents in order to "correct mistakes"

[13] Genentech sought these benefits when it availed itself of the IPR process in order to challenge the validity of a patent in *OSI Pharmaceuticals & Genentech, Inc. v. Arch Development Corp. & Dana-Farber Cancer Institute, Inc.* (Case IPR2016-01034). And in the pending appeal before this Court, Genentech is relying on the government's briefing in support of the constitutionality of IPR. *Arch Development Corp. et al. v. OSI Pharmaceuticals, LLC*, No. 18-1485, D.I. 57 at 11 n.1 ("petitioners defer to the government's response to ARCH's constitutional challenges").

and to "give comprehensive effect to a new law Congress considered salutary." *Landgraf*, 511 U.S. at 268. Indeed, Genentech has not even attempted to meet its burden of establishing that Congress acted in an arbitrary and irrational way in enacting the IPR statute. *See Pension*, 467 U.S. at 729.

Genentech argues that the termination of its patent rights based on "retroactive" legislation interfered with its investment-backed expectations. Br. at 55. Specifically, Genentech suggests that it disclosed a discovery that it might otherwise have kept secret because its "settled expectations at the time did not include being subject to the subsequently enacted inter partes review process."[14] *Id*. Genentech's argument fails because all patent owners who have applied for a patent since 1981, when *ex parte* reexamination was enacted, did so with the understanding that issued patents are subject to administrative review and cancellation by the USPTO. And, since *ex parte* reexamination was applied to previously issued patents, patent owners were aware that administrative review proceedings could be applied to patents that issued before their enactment. IPR

[14] Genentech's reliance on *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) is misplaced because there the Court addressed changes to the doctrine of equivalents and prosecution history estoppel in the Federal Circuit's opinion—i.e., changes to the laws of patentability. As explained, IPR allows for the review of a patent grant under the same laws of patentability.

differs from previously existing administrative proceedings only procedurally; the proceedings are alike in terms of the character of the governmental action, and their intended economic impact.[15]

Further, IPR does not result in the taking of constitutionally protected property rights because no such rights exist in an erroneously granted patent. It is a "bedrock requirement that the existence of a valid property interest is necessary in all takings claims." *Wyatt v. United States*, 271 F.3d 1090, 1097 (Fed. Cir. 2001); *see also*, *e.g.*, *Love Terminal Partners, LP v. United States*, 889 F.3d 1331, 1339 (Fed. Cir. 2018). Here, Genentech has not explained what valid property interest a patent owner has in an invalid patent that would result in an unconstitutional taking. Indeed, because IPR merely involves the reconsideration of the government's decision to grant a public franchise under the same patentability laws applied to the original grant, it is not an unconstitutional taking any more than the refusal of the Patent Office to grant a patent is in the first instance.[16] *See*, *e.g.*, *Oil States*, 138 S. Ct. at 1374 (2018) ("Inter partes review

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[15] To the extent that IPR is more litigation-like than previous administrative procedures, as Genentech appears to argue, that aspect of IPR does not interfere with patent owners' reasonable or investment-backed expectations because patents have always been subject to invalidation in federal court litigation.

[16] Genentech's reliance on *Fla. Prepaid Postsecondary Educ. Expense Bd. v. Coll. Sav. Bank,* 527 U.S. 627 (1999), *Richmond Screw Anchor Co. v. United*

involves the same basic matter as the grant of a patent. It is a 'second look at an earlier . . . grant,' and it involves the same interests as the original grant. That inter partes review occurs after the patent has issued does not make a difference here.") (internal citations omitted).

Moreover, this Court's rationale in *Patlex Corp. v. Mossinghoff* underlying its rejection of a Fifth Amendment challenge to *ex parte* reexamination applies equally to IPR. 758 F.2d 594, 603 (Fed. Cir. 1985) (rehearing of constitutional challenges denied). In *Patlex*, the Court concluded that the overriding public purposes Congress articulated in enacting *ex parte* reexamination with retrospective effect were entitled to great weight, and that Congress did not act in an arbitrary or irrational way to achieve its desired purposes. *Id*. And, in *Joy Tech., Inc. v. Manbeck*, this Court again rejected Fifth Amendment challenges to *ex parte* reexamination on the basis that *Patlex* was controlling. 959 F.2d 226, 229 (Fed. Cir. 1992), *cert. denied*, 506 U.S. 829 (1992). Although Genentech asserts that this Court's opinion in *Patlex* does not foreclose its argument in this

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States, 275 U.S. 331 (1928), and *Horne v. Dep't of Agric.*, 135 S. Ct. 2419 (2015) is misplaced because *Fla. Prepaid* and *Richmond Screw* involved the possible taking of infringement causes of action arising out of *valid* patents and *Horne* did not involve the taking of any patent rights. Thus, none of those cases are instructive here.

case, it fails to identify any material differences between *ex parte* reexamination at issue in *Patlex* and IPR that warrant a different outcome here. Br. at 56. In fact, a finding of constitutionality is even more appropriate for IPR considering that administrative procedures for reexamining patents had existed for decades when IPR was enacted, whereas no administrative proceedings existed when *ex parte* reexamination was created. In addition, Genentech's statement that "Oil States explicitly recognized and left open this issue" (*id.* at 56) is misplaced. The majority in *Oil States* pointed out that the appellant had not challenged the retroactive application of IPR or raised a due process challenge, but this does not suggest that this Court's rationale in *Patlex* does not also apply to IPR.

For these reasons, this Court should reject Genentech's argument that application of IPR to pre-AIA issued patents is a taking without just compensation and a denial of due process.

CONCLUSION

Hospira respectfully submits that the Board's Final Written Decision holding that claims 1-3 and 5-11 are unpatentable should be affirmed.

Dated: November 19, 2018 Respectfully submitted,

/s/ Thomas J. Meloro

Thomas J. Meloro
Michael W. Johnson
Alexandra F. Awai
Willkie Farr & Gallagher LLP
787 Seventh Avenue
New York, NY 10019-6099
Telephone: (212) 728-8000
Facsimile: (212) 728-8111

Attorneys for Appellee Hospira, Inc.

CERTIFICATE OF SERVICE

I certify that on this 19th day of November 2018, I caused the foregoing Brief of Appellee Hospira, Inc. to be electronically filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the Court's CM/ECF system. The following counsel of record were served electronically via the Court's CM/ECF system and by electronic mail:

Paul B. Gaffney
Thomas S. Fletcher
Jonathan S. Sidhu
Eden Schiffmann
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005

Attorneys for Appellant

Katherine T. Allen
Scott R. McIntosh
U.S. Department of Justice
950 Pennsylvania Ave., NW
Washington, DC 20530

Farheena Y. Rasheed
Joseph Matal
Thomas W. Krause
Office of the Solicitor, U.S. Patent and Trademark Office
Mail Stop 8, P.O. Box 1450
Alexandria, VA 22313-1450

Attorneys for Intervenor

Dated: November 19, 2018 /s/ Thomas J. Meloro

Thomas J. Meloro
Willkie Farr & Gallagher LLP
787 Seventh Avenue
New York, New York 10019-6099
Telephone: (212) 728-8000
Facsimile: (212) 728-8111

Attorney for Appellee Hospira, Inc.

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). This brief contains 12,178 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

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Dated: November 19, 2018 /s/ Thomas J. Meloro

Thomas J. Meloro
Willkie Farr & Gallagher LLP
787 Seventh Avenue
New York, New York 10019-6099
Telephone: (212) 728-8000
Facsimile: (212) 728-8111

Attorney for Appellee Hospira, Inc.