

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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HOSPIRA, INC. and PFIZER INC.,

Petitioner,

v.

AMGEN INC.,

Patent Owner.

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IPR2021-00528

Patent 8,273,707 B2

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Before JOHN G. NEW, ZHENYU YANG, and  
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION

Granting Institution of *Inter Partes* Review  
35 U.S.C. § 314(a)

## I. INTRODUCTION

Petitioners Hospira, Inc. and Pfizer Inc. (jointly “Petitioner”) have filed a Petition (Paper 1, “Pet.”) seeking *inter partes* review of claims 1, 2, 4, 8, 10, and 11 of US Patent 8,273,707 B2 (Ex. 1001, the “’707 patent”). Patent Owner Amgen Inc. (“Patent Owner”) timely filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

Under 35 U.S.C. § 314, the Board “may not authorize an *inter partes* review to be instituted unless ... the information presented in the petition ... and any response ... shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Upon consideration of the Petition and Preliminary Response, and the evidence of record, we determine that the evidence presented demonstrates a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of at least one challenged claim of the ’707 patent.

## II. BACKGROUND

### A. *Related Matters*

The ’707 patent has been asserted in pending civil action *Amgen Inc. et al. v. Hospira, Inc. et al.*, No. DDE-1-20-cv-0201-CFC (D. Del.). Pet. 9; Paper 5 at 1.

### B. *The Asserted Grounds of Unpatentability*

Petitioner contends that claims 1, 2, 4, 8, 10, and 11 of the ’707 patent are unpatentable, based upon the following grounds:

Claims Challenged	35 U.S.C. §	References/Basis
1, 2, 4, 8, 10, 11	102(b)	Builder <sup>1</sup>
1, 10	102(b)	Memoli <sup>2</sup>
1, 2, 4, 8, 10, 11	103	Builder, El Rassi <sup>3</sup>
1, 2, 4, 8, 10, 11	103	El Rassi, Pharmacia <sup>4</sup>
1, 2, 4, 8, 10, 11	103	Memoli, Pharmacia

Petitioner also relies upon the Declaration of Dr. Todd Przybycien (the “Przybycien Declaration,” Ex. 1002).

*C. The '707 Patent*

The '707 patent is directed to a process for protein purification using hydrophobic interaction chromatography (“HIC”). Ex. 1001, col. 1, ll. 13–15. Specifically, the '707 patent discloses combinations of salts that are useful for increasing the dynamic capacity of an HIC column compared with the dynamic capacity of the column using separate salts alone. *Id.* at col. 2,

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<sup>1</sup> Builder et al. (US 5,446,024, August 29, 1995) (“Builder”) (Ex. 1003).

<sup>2</sup> V.A. Memoli et al., *Hemoglobin and Serum Albumin: Salt-Mediated Hydrophobic Chromatography*, 66(3) BIOCHEM. AND BIOPHYS. RES. COMMS. (1975) 1011–16 (“Memoli”) (Ex. 1004).

<sup>3</sup> Z. El Rassi et al., *Binary and Ternary Salt Gradients in Hydrophobic-Interaction Chromatography of Proteins*, 499 J. CHROMATOGRAPHY 141–52 (1990) (“El Rassi”) (Ex. 1005).

<sup>4</sup> Amersham Pharmacia Biotech, HYDROPHOBIC INTERACTION CHROMATOGRAPHY: PRINCIPLES AND METHODS (1993) (“Pharmacia”) (Ex. 1006).

ll. 9–12. The Specification of the '707 patent defines the term “dynamic capacity” as meaning: “[T]he maximum amount of protein in solution which can be loaded onto a column without significant breakthrough or leakage of the protein into the solution phase of a column before elution.” *Id.* at cols.

3–4, ll. 64–3. As the Specification explains:

More formally,  $K'$  (capacity factor) = moles of solute in stationary phase divided by moles of solute in mobile phase =  $V_r - V_o / V_o$ , where  $V_r$  is the volume of the retained solute and  $V_o$  is the volume of unretarded solute. Practically, dynamic capacity of a given HIC column is determined by measuring the amount of protein loaded onto the column, and determining the resin load which is mg protein/column Volume (mg/ml-r). The amount of protein leaving the column in the solution phase after the column is loaded (“breakthrough”) but before elution begins can then be measured by collecting fractions during the loading process and first wash with equilibrium buffer. The load at which no significant breakthrough occurs is the dynamic capacity of the protein for those conditions.

*Id.* at col. 4, ll. 3–16.

#### *D. Illustrative Claims*

Independent claim 1 of the '707 patent is representative of the claims at issue and recites:

1. A process for purifying a protein on a hydrophobic interaction chromatography column such that the dynamic capacity of the column is increased for the protein comprising mixing a preparation containing the protein with a combination of a first salt and a second salt, loading the mixture onto a hydrophobic interaction chromatography column, and eluting the protein, wherein the first and second salts are selected from the group consisting of citrate and sulfate, citrate and acetate, and sulfate and acetate, respectively, and wherein the concentration

of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.

Ex. 1001, col. 15, ll. 8–18.

*E. Prosecution History of the '707 Patent*

On June 23, 2010, Patent Owner filed US Application Serial No. 12/822,072 (the “’072 application”) that issued in due course as the ’707 patent. Ex. 1001, 1 at codes (21), (22). The ’707 patent is a division of US Application Serial No. 10/895,581, filed on July 21, 2004, which subsequently issued as US 7,781,395. Petitioner asserts that none of the prior art references asserted in the various Grounds of the Petition were disclosed by Patent Owner, or before the Examiner, during prosecution of the ’072 application. Pet. 61. Consequently, we need not dilate upon the historical details of the prosecution.

### III. ANALYSIS

*A. Claim Construction*

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc.*

*v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is “less significant than the intrinsic record in determining ‘the legally operative meaning of claim language.’” *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

As an initial matter, Petitioner presents a list of claim terms that Petitioner asserts it will contest in the district court litigation as indefinite under the Patent Owner’s proposed construction. Pet. 13–14. However, Petitioner asserts that it will adopt the constructions proposed in the district court by Patent Owner for the purpose of this trial institution decision. *Id.* at 14.

Patent Owner acknowledges that Petitioner agrees to use Patent Owner’s claim constructions for the purposes of this decision to institute. Prelim. Resp. 21. However, Patent Owner argues that the Petition seeks to have the Board assume constructions that Petitioner will directly oppose in the civil litigation, thereby preserving Petitioner’s ability: (1) to argue entirely different constructions in district court; and (2) to argue in district court that certain of the terms and constructions they ask the Board to assume here are indefinite. *Id.* at 18. Patent Owner contends that this approach does not satisfy the requirements of 37 C.F.R. § 42.104(b)(3).<sup>5</sup>

We are not persuaded by Patent Owner’s contentions. As Patent Owner is undoubtedly aware, the unpatentability of contested claims as

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<sup>5</sup> Requiring that “[w]here the claim to be construed contains a means-plus-function or step-plus-function limitation as permitted under 35 U.S.C. 112(f), the construction of the claim must identify the specific portions of the specification that describe the structure, material, or acts corresponding to each claimed function.

being indefinite under 35 U.S.C. § 112(b) is not a ground upon which an *inter partes* review may be instituted. *See* 35 U.S.C. § 311(b) (stating that “[a] petitioner in an *inter partes* review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications”). Whether Petitioner ultimately argues that the proposed claim constructions it seeks to adopt for this proceeding will render the claims indefinite is immaterial insofar as indefiniteness is not an unpatentability ground that can be asserted in an *inter partes* review petition. We can sufficiently understand the scope of the claims to assess the anticipation and obviousness grounds set forth in the Petition. We determine that Petitioner’s willingness to adopt Patent Owner’s proposed constructions for purposes of this proceeding is sufficient to satisfy the requirements of § 42.104(b)(3), as all that rule requires is for the Petition to identify “[h]ow the challenged claim is to be construed.”

Petitioner has done so in this case by identifying the following claim constructions adopted from Patent Owner:

1. The claim term from the preamble of claim 1 reciting “such that the dynamic capacity of the column is increased for the protein” is construed as meaning “such that the dynamic capacity of the hydrophobic interaction chromatography column for the protein that is achieved by using a combination of a first salt and a second salt, at least one at a reduced concentration compared to the concentration of that salt when used alone, is greater than the dynamic capacity of the column for the protein that is achieved by using a single salt at a higher concentration.”<sup>6</sup>

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<sup>6</sup> We are skeptical as to whether the language of the preambles to independent claims 1 and 10 limits the claims. Generally, a preamble is not limiting “where a patentee defines a structurally complete invention in

2. The claim term reciting “mixing a preparation containing the protein with a combination of a first salt and a second salt” is construed to mean “mixing a preparation containing the protein with a combination of a first salt and a second salt.” Patent Owner asserts that this step must be completed before the “loading the mixture” step begins.
3. The claim term reciting “loading the mixture onto a hydrophobic interaction chromatography column” is construed as meaning “causing the protein in the mixture to contact the hydrophobic groups on the matrix.”
4. The claim term reciting “between about 0.1 M and about 1.0 M” is construed as meaning “between approximately 0.1 M and approximately 1.0 M.”<sup>7</sup>

See Pet. 13–14.

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the claim body and uses the preamble only to state a purpose or intended use for the invention.” *Catalina Marketing Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)). In the case of claims 1 and 10, the limitations of the claims, exclusive of the preamble, describe what appears to be a structurally complete invention, whereas the preamble states only the purpose of the invention, i.e., “the dynamic capacity of the column is increased for the protein.” The preamble does not otherwise recite any essential structure or steps of the claimed process or method. In such circumstances, a preamble is generally not limiting. *See id.* We therefore invite further briefing by the parties upon this subject.

<sup>7</sup> We note that the construction of this claim term is identical to that adopted by the district court subsequent to the *Markman* hearing held on June 11, 2021. The court further determined that the limitation was not a functional limitation. *See Amgen*, DDE-1-20-cv-00201, Order, docket no. 74, filed June 16, 2021. No other claims were construed by the court in that order. Hence, Patent Owner’s argument (1) is moot.



Patent Owner argues that Petitioner does not explain why the constructions they present are correct, or even cite any evidence whatsoever supporting their assumed constructions. Prelim. Resp. 18. Patent Owner also argues that Petitioner asks the Board to assume constructions that Petitioner directly opposes in litigation, apparently hoping to preserve their ability (1) to argue entirely different constructions in district court and (2) to argue that certain of the terms and constructions they ask the Board to assume here are indefinite. *Id.* Patent Owner further argues that Petitioners offer no explanation for how the Board could be expected to proceed in applying two of Petitioners' proffered constructions when Petitioners affirmatively assert these render every challenged claim indefinite. *Id.* (citing Pet.13–14).

We fail to see the relevance of Patent Owner's arguments. Petitioner has agreed to adopt Patent Owner's construction of the claims for the purposes of this Decision. Furthermore, Petitioner is precluded from arguing that the claim are indefinite before the Board; indeed the only forum Petitioner can argue that the Patent Owner's claim constructions are indefinite is in the district court. We discern no prejudice against Patent Owner in allowing Petitioner to adopt Patent Owner's claim constructions before the Board (where Petitioner is precluded from arguing indefiniteness), while arguing that that claim construction is indefinite before the district court.

Furthermore, we find that the Patent Owner's proposed claim constructions, which Petitioner agrees to adopt herein, generally conform to their "given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v.*

*AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Neither party disputes this, at least in this proceeding. We therefore adopt these constructions for the purposes of this Decision.

*B. A Person of Ordinary Skill in the Art*

Petitioner contends that a person of ordinary skill in the field of the '707 patent would have had:

[A]t least a Master's degree and/or Ph.D., and several years of postgraduate training or practical experience in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others, and an appreciation of the various scientific and practical factors that relate to the HIC protein purification process.

Pet. 15 (citing Ex. 1002 ¶ 35). On this record, Patent Owner does not contest this definition and we adopt this definition for the purposes of this Decision.

*C. Discretionary Denial of Institution under 35 U.S.C. § 314(a)*

Patent Owner urges the Board to exercise its discretion under 35 U.S.C. § 314(a) and deny institution of the proposed *inter partes* review. Prelim. Resp. 6.

When deciding whether to exercise our discretion not to institute under § 314(a), the Board must consider whether the nature of co-pending district court litigation on the same patent is such that instituting trial “would be an efficient use of the Board’s resources.” *NHK Spring Co. v. Intrix-Plex*

*Techs., Inc.*, IPR2018-00752, Paper 8 at 19–20 (PTAB Sept. 12, 2018) (precedential)).

Our precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019 (PTAB May 13, 2020) sets forth six non-exclusive factors to be evaluated in deciding “whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding.” Paper 15 at 12–17. In evaluating these factors, the Board is charged with “taking a holistic view of whether efficiency and integrity of the system are best served.” *Fintiv*, Paper 11 at 5–6; *see also Samsung Elecs. Am., Inc. v. Uniloc 2017 LLC*, IPR2020-00117, Paper 11 at 7–11 (PTAB May 28, 2020). The *Fintiv* factors are as follows:

1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
2. proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision;
3. investment in the parallel proceeding by the court and the parties;
4. overlap between issues raised in the petition and in the parallel proceeding;
5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
6. other circumstances that impact the Board’s exercise of discretion, including the merits.

*Fintiv*, Paper 11 at 6. We consider these interrelated factors, as they apply to the facts of the Petition, as follows.

1. *Fintiv* factor 1

*Fintiv* factor 1 evaluates whether the district court, in the parallel proceeding, has granted a stay or whether evidence exists that one may be granted if a proceeding is instituted.

A stay has not been granted in the parallel proceeding,<sup>8</sup> and Patent Owner notes that Petitioner has not indicated that it expects to seek a stay in the event of institution. Prelim. Resp. 7 (citing Pet. 63–64). Patent Owner contends that a stay in the parallel litigation is highly unlikely, because it involves a biosimilar (a type of biologic medical product), which Petitioner is marketing in competition with Patent Owner, making the chance of any stay low to non-existent. Prelim. Resp. 7 (citing Ex. 2003 ¶¶ 31–37 (complaint)). Patent Owner points, *inter alia*, to *Davol, Inc. v. Atrium Med. Corp.*, No. 12-958-GMS, 2013 WL 3013343, at \*4–5 (D. Del. June 17, 2013), in which a stay was denied pending institution of IPR in part because parties were direct competitors and a stay would prejudice patentee.

We decline to speculate about the likelihood of a stay in the district court litigation, and that this factor is neutral.

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<sup>8</sup> A brief stay of twenty-eight days (June 16 through July 14, 2021) was ordered by the district court until a determination could be made whether the Court should entertain summary judgment practice on the issue of noninfringement. *Amgen*, DDE-1-20-cv-00201, Oral Order, filed June 16, 2021. The stay was lifted on July 14, 2021, at which time the court ordered a briefing schedule for a motion for summary judgment. *Id.*, Order, docket no. 76, filed July 14, 2021. We find that this stay has no significant bearing on *Fintiv* factor 1, due to its brevity and the fact that it is unrelated to the institution of *inter partes* review.

2. *Fintiv* factor 2

The second *Fintiv* factor requires us to evaluate whether proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision weighs in favor of denial. Both Petitioner and Patent Owner agree that trial date has been set by the district court for July 11, 2022. Pet. 63; Prelim. Resp. 8. If *inter partes* review is instituted, the Board’s Final Written Decision will be entered on or before August 18, 2022.

Petitioner argues that it is probable that this trial date may be postponed in view of the continuing pandemic crisis. Pet. 63. Petitioner further notes that “[a]n early trial date” is ‘non-dispositive’” and simply means that “the decision whether to institute will likely implicate other factors.” *Id.* (quoting *Fintiv*, Paper 15 at 9).

Patent Owner counters by noting that *Fintiv* states: “If the court’s trial date is earlier than the projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority to deny institution.” Prelim. Resp. 8 (quoting *Fintiv*, Paper 15 at 13) (emphasis omitted). With respect to Petitioner’s assertions regarding the ongoing pandemic, Patent Owner emphasizes that a trial date has been set, and the District of Delaware is “rapidly opening up”: in-person trials (including patent trials) have resumed, and the claim construction hearing in this case was held in person. *Id.* at 9–10 (citing Ex. 2005, 12; Ex. 2002, 21). According to Patent Owner, the Court has not indicated that the trial would be pushed back, but has indicated the opposite, stating that there is “a lot of time” before trial and discovery would only be pushed back “a small amount of time.” *Id.* at 10 (quoting Ex. 2005, 15–16).

We find that the small interval between the trial date and the statutory date for the Board’s Final Written Decision is neutral or weighs only somewhat in favor of denial of institution.

3. *Fintiv* factor 3

With respect to the third *Fintiv* factor, i.e., the amount of investment by the district court and the parties, Petitioner argues that the only substantive investment made by the parties and the Court related to invalidity will have been in preparing and serving invalidity contentions, exchanging claim construction briefing, and conducting a *Markman* hearing (held June 11, 2021). Pet. 64.

Patent Owner argues that it served initial infringement contentions on September 11, 2020, and Petitioner filed initial invalidity contentions on October 27, 2020. Prelim. Resp. 11 (citing Ex. 2002, 16–17). Patent Owner cites, *inter alia*, *TCO AS v. NCS Multistage Inc.*, PGR2020-00077, Paper 16 at 11 (Feb. 18, 2021), as finding that the exchange of infringement and invalidity contentions, filing of claim construction briefing, and conducting a *Markman* hearing constituted substantial investment weighing slightly in favor of denying institution. *Id.* at 9.

Patent Owner further asserts that Petitioner waited over sixteen months after Patent Owner identified the ’707 patent as a patent that could reasonably be asserted against Hospira’s pegfilgrastim product, over thirteen months after Amgen provided Hospira “its detailed statement...describing ‘on a claim by claim basis, the factual and legal basis’ of Amgen’s opinion that certain claims of the ’707 Patent will be infringed,” and five months after Amgen served its Initial Disclosure of Asserted Claims and initial

infringement contentions to file this IPR. Prelim. Resp. 12–13 (citing Ex. 2002, 16; quoting Ex. 2003 ¶¶ 45, 48).

We agree with Patent Owner that the parties and the court have made some investment in the parallel litigation. The parties have exchanged infringement and invalidity contentions, a *Markman* hearing has been held, and a briefing schedule set for motions for summary judgment. *Amgen*, DDE-1-20-cv-00201, Order, docket no. 74 (July 14, 2021). We note, however, that the district court’s *Markman* order only construed one claim term (as its plain and ordinary meaning), and it does not appear that the parties have started discovery. We find this factor be neutral or to only weigh somewhat in favor of denial of institution.

4. *Fintiv* factor four

*Fintiv* factor four requires us to enquire into the degree of overlap between issues raised in the petition and in the parallel proceeding. Petitioner states that, in the district court litigation, it has stipulated that it will not argue the invalidity of the ’707 patent based on any of the prior art grounds identified in this Petition, “or on any other prior-art ground that reasonably could have been raised in an IPR (i.e., any ground that could be raised under 35 U.S.C. §§ 102 or 103 on the basis of prior-art patents or printed publications).” Pet. 64 (quoting Ex. 1027). Petitioner asserts that the stipulation “ensures that an *inter partes* review is a ‘true alternative’ to the district court proceeding” and weighs heavily in favor of institution. *Id.* (quoting *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 19 (PTAB December 1, 2020) (precedential)).

Patent Owner responds that, in the district court litigation, Petitioner has asserted indefiniteness for every challenged claim, and has asserted that two of Patent Owner's litigation constructions are themselves indefinite. Prelim. Resp. 15 (citing Pet. 13–14). Patent Owner contends that Petitioner has not stipulated to forego their indefiniteness arguments in litigation if trial here is instituted. *Id.*

We find this factor to weigh heavily in against denial of institution. Petitioner's stipulation in the district court litigation to forego arguing the invalidity of the '707 patent based on any of the prior art grounds identified either in this Petition, or on any other prior-art ground that reasonably could have been raised in an IPR, mitigates any concerns of duplicative efforts between the district court and the Board, as well as concerns of potentially conflicting decisions. *See Sotera*, Paper 12 at 19 (citing *Sand Revolution II, LLC v. Cont'l Intermodal Group Trucking LLC*, IPR2019-01393, Paper 24 at 12, n.5 (PTAB June 16, 2020) (informative)). Because the grounds for the invalidity contentions before the district court and the Board (indefiniteness *versus* anticipation/obviousness) are different in their legal bases, and given the breadth of Petitioner's stipulation not to pursue any prior art-based invalidity arguments before the district court, we find that this factor militates strongly against denial of institution of trial.

5. Fintiv factor 5

It is undisputed that the parties appearing before the Board in this matter are the same parties to the district court litigation. *See, e.g.*, Prelim.



Resp. 16. We find that this factor weighs somewhat in favor of denial of institution.

6. *Fintiv* factor 6

With respect to other circumstances that impact the Board's exercise of discretion, including the merits, the parties understandably dispute the strength of the Grounds raised in the Petition. Pet. 65; Prelim. Resp. 16. However, we find that, in view of our conclusions below that Petitioner has demonstrated a reasonable likelihood of prevailing by showing that at least one of the challenged claims of the '707 patent is invalid, on this record, the merits of Petitioner's arguments are likely to be stronger.

Furthermore, Patent Owner argues that the fact that Petitioner has asserted claim construction positions in the litigation that are inconsistent with the claim construction being proposed in the Petition amounts to "gamesmanship" that thwarts the Board's purpose in adopting the *Phillips* standard for claim construction.

We find that *Fintiv* factor 6 weighs somewhat against denial of institution of trial. At this stage of the proceeding, Petitioner's arguments on the merits are somewhat stronger than Patent Owner's, as we explain below. We are not persuaded by Patent Owner's objection to Petitioner's agreement to adopt Patent Owner's claim construction for the purposes of deciding whether to institute trial. We fail to see how this prejudices Patent Owner's arguments in this proceeding. Furthermore, Petitioner is statutorily barred from arguing the unpatentability of the '707 patent upon grounds that the claims are indefinite in this forum; only in the district court litigation may Petitioner present such arguments. *See* 35 U.S.C. § 311(b). We

consequently find *Fintiv* factor 6 weighs somewhat against denial of institution.

7. Summary

We take “a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review” when considering the six *Fintiv* factors. *Fintiv*, Paper 11 at 6. As we have explained, Petitioner has stipulated not to argue any of the strong prior-art based allegations of unpatentability in the district court litigation. *See* Ex. 1027, 2. Reserving those arguments for the Petition, significantly reduces needlessly duplicative proceedings, as well as concerns of potentially conflicting decisions, despite the unlikelihood of a stay in the litigation, the earlier trial date, and the investment in the litigation by the same parties. *See* Ex. 1027, 2. This is consistent with the reasoning in our precedential opinion in *Sotera*, in which we found that such a broad stipulation by Petitioner ensures that an *inter partes* review is a “true alternative” to the district court proceeding. *Sotera*, Paper 12 at 19; *see also Sand Revolution*, Paper 24 at 12, n.5.

As such, we are not persuaded that the interests of the efficiency and integrity of the system would be best served by invoking our authority under 35 U.S.C. § 314(a) to deny institution. For these reasons we decline to exercise our discretion to deny institution under § 314(a).

*D. Ground IV: Alleged Obviousness of Claims 1, 2, 4, 8, 10, and 11 over El Rassi and Pharmacia*

1. Overview of El Rassi

El Rassi was published in 1990 and on this record is prior art to the '707 patent. Ex. 1005, 141 (Abstr.). The El Rassi reference is entitled *Binary and Ternary Salt Gradients in Hydrophobic-Interaction Chromatography of Proteins*, and was published in the Journal of Chromatography. *Id.* El Rassi teaches that “[h]ydrophobic-interaction chromatography of mixtures of acidic and basic proteins having a wide range of molecular weights and hydrophobic character was carried out by using binary and ternary salt gradients.” *Id.* Specifically, El Rassi teaches that “[a]t constant eluent surface tension, gradient elution with two or three aqueous salt solutions was found to be superior to single-salt gradients in modulating hydrophobic-interaction chromatography retention and electivity. The effect was attributed to the competitive salt-specific binding to the protein molecule and/or the stationary phase surface.” *Id.*

Table II of El Rassi shows the adjusted retention volumes of protein on the HIC columns volumes (i.e., the maximum amount of protein that can be retained on the column), measured with single-salt or binary-salt gradients. The maximum amount of protein capable of being retained on the column corresponds to the dynamic capacity of the column as defined *supra*. Retention. Table II of El Rassi is reproduced below:

Protein	Gradient									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Cytochrome <i>c</i>	0.30	0.85	0.70	1.40	2.13	5.71	0.40	0.77	0.53	1.93
Ribonuclease A	5.77	5.59	7.50	9.50	12.62	12.64	6.93	7.85	9.02	9.98
$\beta$ -Lactoglobulin A	10.98	13.27	13.80	13.70	15.07	15.48	11.36	13.22	13.98	14.55
Lysozyme	12.66	22.10	17.13	24.27	19.05	26.95	17.13	23.96	18.60	24.96
Ovalbumin	13.28	14.72	14.18	13.70	16.97	16.69	14.39	14.63	17.00	15.98
$\alpha$ -Chymotrypsinogen A	20.14	24.63	21.60	25.40	23.26	26.20	21.10	23.70	23.69	25.37
Fetuin	19.97	22.89	22.12	22.60	23.25	24.97	21.60	22.65	24.43	24.02

With respect to Table II, El Rassi teaches that:

As expected, binary salt gradients of decreasing concentrations of both ammonium sulfate and sodium citrate in the eluent, from 1.0 to 0M and from 0.69 to 0M, respectively, yielded an elution pattern significantly different from that obtained by using either ammonium sulfate or sodium citrate gradients while maintaining the surface tension of the eluents constant (compare gradient IX with gradients I and V in Table II).

Ex. 1005, 144. Of particular relevance are the data presented in columns I, V, and IX. The salt gradient in the eluent of column I of Table II is an ammonium sulfate gradient from 2.0 [M] to 0 M. *Id.* That of column V is a sodium citrate gradient from 1.38 [M] to 0 M. *Id.* The gradient in column IX is a two-salt combination of ammonium sulfate and sodium citrate from 1.0 M to 0 M and from 0.69 M to 0 M, respectively. *Id.* El Rassi concludes that: “Gradient elution with two or three salts is more efficient than single-salt gradients in modulating HIC selectivity.” *Id.* at 151.

## 2. Overview of Pharmacia

The Pharmacia reference, entitled *Hydrophobic Interaction Chromatography: Principles and Methods*, was published by Amersham Pharmacia Biotech AB in 2000 and on this record is prior art to the '707 patent. Ex. 1006, 2.

Pharmacia is a user's guide to principles and methods of using HIC, and teaches that, “[p]rotein binding to HIC adsorbents is promoted by moderately high concentrations of anti-chaotropic salts, which also have a stabilizing influence on protein structure. Elution is achieved by a linear or stepwise decrease in the concentration of salt in the adsorption buffer.” Ex. 1006, 12.

Relevantly, Pharmacia teaches that “[i]n general, the adsorption process is often more selective than the desorption process and it is therefore important to optimize the starting ‘binding’ buffer conditions with respect to critical parameters such as pH, type of salt, concentration of salt and temperature.” Ex. 1006, 42. Consequently, teaches Pharmacia:

If the protein of interest binds weakly to the column, an alternative approach is to choose the starting buffer conditions which will result in the maximum binding of a large proportion of the contaminating proteins but allowing the protein of interest to pass through unretarded. An extension of this strategy is to increase the salt concentration in the unbound fraction to such an extent that the protein of interest binds to the same column in a second run while most of the impurities pass through the column unretarded.

*Id.*

Pharmacia also relevantly teaches that:

In this mode, the entire bed volume is utilized for sample binding and the prime consideration when optimizing for highest possible productivity is to find the highest possible sample load over the shortest possible sample application time with acceptable loss in yield. In this situation, more emphasis should be given to the binding strength of the compound of interest than to selectivity during sample application. This means that the salt concentration during sample application should not be too low since this will have a negative effect on dynamic binding capacity.

Ex. 1006, 49.

3. Obviousness of claims 1, 2, 4, 8, 10, 11 over El Rassi and Pharmacia

*a. independent claims 1 and 10*

Petitioner argues claims 1 and 10 together, using claim 1 as the example. Petitioner designates the elements of claim 1 as follows:

- [a] A process for purifying a protein on a hydrophobic interaction chromatography column such that the dynamic capacity of the column is increased for the protein comprising
- [b] mixing a preparation containing the protein with a combination of a first salt and a second salt,
- [c] loading the mixture onto a hydrophobic interaction chromatography column, and
- [d] eluting the protein,
- [e] wherein the first and second salts are selected from the group consisting of citrate and sulfate, citrate and acetate, and sulfate and acetate, respectively, and
- [f] wherein the concentration of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.

Pet. 29.

Petitioner argues that El Rassi expressly teaches employing a two-salt combination of “ammonium sulfate and sodium citrate gradients from 1.0M to 0M and from 0.69M to 0M, respectively” (limitations [e] and [f]) to purify seven proteins in an HIC analysis. Pet. 46 (citing Ex. 1005, 144) (emphasis omitted). Patent Owner argues that, because El Rassi teaches that the proteins were eluted from the HIC column (limitation [d]), a person of

ordinary skill in the art would have understood that the protein in the load solution contacted the hydrophobic groups on (and was retained on) the matrix (limitation [c]) prior to elution, as required by Patent Owner's proposed construction of the "loading" claim phrase. *Id.*

Petitioner also argues that a person of ordinary skill in the art would have understood that increasing protein retention by an HIC column, as taught by El Rassi, corresponds to increasing the dynamic capacity of the HIC column for the protein, as recited by limitation [a] of claim 1. Pet. 40. Specifically, Petitioner argues that El Rassi teaches increased protein retention by an HIC column in a two-salt combination of sulfate and citrate (the same combination as in the '707 patent claims), compared to a higher concentration of at least one of those salts alone. *Id.* (citing Ex. 1005, 144–45; Ex. 1002 ¶¶ 82–89).

Petitioner points to El Rassi's demonstration, in Table II, that all seven proteins tested exhibited increased retention in the binary salt mixture of "ammonium sulfate and sodium citrate gradients from 1.0M to 0M and from 0.69M to 0M, respectively," when compared to the retention rates observed with higher concentrations of at least one of the salts (ammonium sulfate) alone. Pet. 41 (citing Ex. 1005, 144, Table II, columns I, IX).

Petitioner also points to Figure 1 of El Rassi as demonstrating that, when compared to higher concentrations of ammonium sulfate or sodium citrate alone (2.0 to 0M and 1.38 to 0M, respectively), the greatest overall retention for all proteins was observed with a combination of ammonium sulfate and sodium citrate from 0.375 to 0M and from 1.125 to 0M, respectively. Pet. 42. Petitioner cites the Przybycien Declaration as explaining, with respect to El Rassi's Figure 1, that each of the successive

peaks in plot C (corresponding to the different proteins in Table II) are shifted to the right, compared to the same peaks in plots A and B. *Id.* at 43. Dr. Przybycien opines that this indicates that retention increased for each protein using the combination of ammonium sulfate and sodium citrate at lower concentration compared to the retention observed when using at least one of those salts alone. *Id.* (citing Ex. 1002 ¶¶ 157–62).

Petitioner also points to subsequent prior art publications<sup>9,10</sup> that describe El Rassi as teaching the benefits of employing “two or three aqueous salt solutions” to purify proteins in HIC columns, which “was found to be superior to single salt gradient in modulating HIC retention” due to the “competitive salt-specific binding to the protein molecule and/or the stationary phase.” Pet. 43 (quoting Ex. 1009, 93; Ex. 1010, 113; also citing Ex. 1011, 353R, 363R (in a paper<sup>11</sup> focused on “significant” and “important developments in the chemistry of the separation process,” explaining that El Rassi discovered that “[b]inary and ternary salt gradients . . . modulate retention” in HIC columns, “presumably through competitive salt-binding interactions with proteins and/or stationary phase”); Ex. 1012, 147; Ex.

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<sup>9</sup> Z. El Rassi, *Reversed-Phase and Hydrophobic Interaction Chromatography of Carbohydrates and Glycoconjugates*, in *Carbohydrate Analysis by Modern Chromatography and Electrophoresis*, in JOURNAL OF CHROMATOGRAPHY LIBRARY (Vol. 66) (2002) (Ex. 1009).

<sup>10</sup> Z. El Rassi, *Recent Progress in Reversed-Phase and Hydrophobic Interaction Chromatography of Carbohydrate Species*, 720 J. CHROMATOGRAPHY A 93–118 (1996) (Ex. 1010).

<sup>11</sup> J.G. Dorsey et al., *Liquid Chromatography: Theory and Methodology*, 64 ANAL. CHEM. 353R–389R (1992) (Ex. 1011).



1013, 71; Ex. 1002 ¶ 164) (emphasis omitted). Petitioner contends that a person of ordinary skill in the art would also have expected that El Rassi's disclosure of increased protein retention in a dual salt combination of citrate and sulfate would correlate with increased dynamic binding capacity. *Id.* at 44 (citing Ex. 1002 ¶¶ 165–66).

Petitioner acknowledges that El Rassi does not expressly disclose limitation [b] of claim 1 (mixing a preparation containing the protein with two salts), before limitation [c] (loading the mixture onto an HIC column). Nevertheless, Petitioner argues, a person of ordinary skill in the art would have been motivated to mix the protein with El Rassi's two-salt combination prior to loading the protein onto the HIC. Pet. 49. According to Petitioner's declarant, Dr. Przybycien, it was common practice in the prior art to load proteins in water, rather than in salt mixtures, when purifying proteins on an HIC column at an analytical scale (i.e. lab-scale). *Id.* (citing Ex. 1002 ¶ 17). Dr. Przybycien states that in such processes as those described in El Rassi, the salts promote binding to the HIC column by mixing with the protein once the protein is loaded, because the salts are equilibrated directly on the column. *Id.* (citing Ex. 1002 ¶¶ 59–63; Ex. 1005, 141). Dr. Przybycien notes that, when purifying proteins at a preparative (or industrial) scale, however, it was routine to load the protein in a salt solution. *Id.* at 49–50 (citing Ex. 1002 ¶¶ 59–63).

Petitioner points to Pharmacia as disclosing the difference between HIC purification techniques at the analytical and preparative scales. Pet. 50. Petitioner asserts that Pharmacia discloses that, at preparative scales, it would have first been necessary to load the protein with a sufficient amount of salt, rather than simply load the protein in water onto a column

equilibrated with salt, in order to promote protein binding to the column without causing the protein to elute. *Id.* (citing, e.g., Ex. 1006, 42, 49, 61).

Petitioner therefore contends that a person of ordinary skill in the art would have known that, to use El Rassi's two-salt combinations with larger sample loads, it would have been necessary to mix the protein in a salt solution prior to loading; otherwise, the protein would not adequately bind to the column. *Id.* (citing Ex. 1002 ¶¶ 59–63, 191–200; also citing, e.g., Ex. 1015, 24–26 (disclosing loading protein in water in the analytical samples (Figs. 4–8), but in a buffered solution in the preparative samples (Figs. 9–10)). Consequently, Petitioner argues, a skilled artisan would have known to mix the protein with ammonium sulfate and sodium citrate, between about 0.1M and about 1.0M, before loading the preparation onto the HIC column so as to enable the protein to bind to the column. *Id.* (citing Ex. 1002 ¶¶ 186, 194).

Petitioner further argues that it was known in the prior art that obtaining increased protein retention to the HIC column correlates with obtaining increased dynamic capacity of the HIC column for the protein. Pet. 51–52 (citing Ex. 1022, 930; Ex. 1002 ¶¶ 202–10). By way of example, Petitioner points to C. Machold et al., *Hydrophobic Interaction Chromatography of Proteins: I. Comparison of Selectivity*, 972 J. CHROMATOGRAPHY A 3–19 (2002) (“Machold,” Ex. 1008). Petitioner states that Machold describes the capacity factor, or retention, of seven proteins on fifteen HIC columns over a range of ammonium sulfate concentrations, and discloses that retention increased for each protein with increasing salt concentration in the salting-out range. Pet. 52 (citing Ex. 1008, 9–11, Fig. 2; also citing Ex. 1002 ¶¶ 48, 206). Petitioner further points to a subsequent

paper by the same research group, R. Hahn et al., *Hydrophobic Interaction Chromatography of Proteins II. Binding Capacity, Recovery and Mass Transfer Properties*, 970 J. CHROMATOGRAPHY B 99–114 (2003) (“Hahn,” Ex. 1007), which teaches that the dynamic binding capacities in the same study also increased with increasing salt concentration in the salting-out range. *Id.* at 52–53 (citing Ex. 1007, 105–07, Figs. 2–3; also citing Ex. 1002 ¶¶ 48, 205).

Petitioner asserts that the data disclosed by Machold and Hahn demonstrate that, as protein retention increases, dynamic binding capacity also increases. Pet. 53 (citing Ex. 1007, 105–07, Figs. 2–3; Ex. 1008, 9–11, Fig. 2; Ex. 1002 ¶¶ 48, 205–07). Dr. Przybycien reasons that when protein binds more strongly to the HIC column, the likelihood that more protein can be loaded onto the column and bind without significant breakthrough is increased. Ex. 1002 ¶¶ 45, 204; *see also* Pet. 53. Dr. Przybycien also declares that additional prior art confirms the correlation between increased retention and increased dynamic binding capacity. Ex. 1002 ¶¶ 48, 206; *see also* Pet. 53. Therefore, according to Petitioner, a person of ordinary skill in the art would have reasonably expected that El Rassi’s disclosure of increased protein retention to the salt mixture would correlate with obtaining element [a], i.e., increased dynamic binding capacity of the HIC column for the protein. *Id.* (citing Ex. 1002 ¶¶ 202–10).

*b. claims 2 and 11*

Claims 2 and 11 depend from claims 1 and 10, respectively, and recite “wherein the pH of the mixture loaded onto the column is between about pH 5 and about pH 7.” Ex. 1001, col 15, ll. 19–21. Petitioner argues that the

seven proteins in El Rassi's analytical scale experiment were purified at pH 6.5, within this claimed range. Pet. 53 (citing Ex. 1005, 144–45, Table II, Fig. 1).

Petitioner additionally argues that a skilled artisan would have been motivated to mix a protein with El Rassi's combination of 1.0 M ammonium sulfate and 0.69 M sodium citrate and to maintain the same pH range for the load solution prior to loading the mixture onto an HIC column. Pet. 54 (citing Ex. 1002 ¶¶ 211–14). Petitioner points to Pharmacia's teaching that "pH is an important separation parameter in the optimization of hydrophobic interaction chromatography" and that "an increase in pH weakens hydrophobic interactions," whereas "a decrease in pH results in an apparent increase in hydrophobic interactions." *Id.* (Ex. 1006, 18). Petitioner additionally notes that Pharmacia further discloses loading a sample onto an HIC column at pH 7.0 in a screening condition protocol and states that "usually a lowering of the pH leads to increased binding of proteins." *Id.* (citing Ex. 1006, 34–35; Ex. 1002 ¶ 94).

*c. claim 4*

Claim 4, which depends from claim 1, recites, "wherein the first and second salts are selected from the group consisting of sodium, potassium and ammonium salts." Ex. 1001, col. 15, ll. 24–26. Petitioner argues that El Rassi discloses that the first and second salts are sodium citrate and ammonium sulfate, which meets the requirement of this limitation. Pet. 54 (citing Ex. 1005, 144–45, Table II, Gradient IX, Fig. 1(C)).

*d. claim 8*

Claim 8 depends from claim 1, and recites, in relevant part, “formulating the protein.” Ex. 1001, col. 16, ll. 5–6. Petitioner argues that El Rassi discloses that “[h]ydrophobic-interaction chromatography (HIC) with rigid, microparticulate stationary phases is increasingly used for the analysis and purification of proteins.” Pet. 55 (quoting Ex. 1005, 141). Petitioner notes that El Rassi further discloses purifying the following seven proteins: cytochrome c, ribonuclease A,  $\beta$ -lactoglobulin A, lysozyme, ovalbumin,  $\alpha$ -chymotrypsinogen A, and fetuin. *Id.* (citing Ex. 1005, 144, Table II).

Petitioner argues that a person of ordinary skill in the art would have been motivated to scale-up the El Rassi process for use at a preparative or industrial scale in order to purify proteins efficiently, as argued above with respect to claims 1 and 10. Pet. 55. Petitioner contends that it would have been routine for a skilled artisan to formulate the protein following HIC and any subsequent polishing purification. *Id.* (citing Ex. 1002 ¶¶ 217–20). Petitioner points to Pharmacia’s disclosure that HIC “is an ideal separation method” used “[w]ith the rise of the modern biotechnology industry and its requirement for highly purified pharmaceutical proteins, and that HIC processes can provide “economy, capacity and resultant product quality.” *Id.* (quoting Ex. 1006, 5) (alteration in original).

4. Patent Owner’s Preliminary Response

*a. claims 1 and 10*

Patent Owner responds that Petitioner asserts that El Rassi explicitly discloses limitations [d]-[f], and that, with respect to limitation [a], a person

of ordinary skill in the art would have understood increasing protein retention “correlates” with increasing dynamic capacity. Prelim. Resp. 52 (citing Pet. 46). Patent Owner contends that Petitioner’s “correlation” argument regarding limitation [a] fails because Petitioner makes no express obviousness or inherency argument regarding this limitation, and also points to no explicit disclosure in the cited references. *Id.* at 51.

Patent Owner further asserts that, with respect to limitations [b] and [c], Petitioner contends that a “[Person of ordinary skill in the art] would have been motivated to mix the protein with El Rassi 1990’s two-salt combination.” Prelim. Resp. 53 (quoting Pet. 46) (emphasis omitted). Patent Owner contends that it is unclear how Petitioner uses Pharmacia, and whether, why or how a person of ordinary skill in the art would have been motivated to modify El Rassi using Pharmacia. *Id.*

Furthermore, Patent Owner argues, the claims require that the two salts be at a concentration between 0.1M and 1.0M. Prelim. Resp. 51. Patent Owner contends that Petitioner again fails to identify any disclosure by the cited references of increasing dynamic binding capacity using two salts added to a protein preparation before loading the protein on a column, as required by the limitations reciting “such that the dynamic capacity of the column is increased for the protein” and “increasing the dynamic capacity of a [HIC] column for a protein.” *Id.* at 50–51.

Patent Owner points out that the two salts in El Rassi that Petitioner identifies, *viz.*, ammonium sulfate and sodium citrate, are used as the eluent in a concentration gradient. Prelim. Resp. 53. Patent Owner contends that Petitioner does not explain why a person of ordinary skill in the art would have chosen a fixed concentration within the claimed concentration range.

*Id.* Nor, Patent Owner argues with respect to a reasonable expectation of success, does Petitioner explain how the selection of a concentration within the claimed range would influence results when converting an eluent with a salt concentration gradient to a load buffer with fixed salt concentrations.

*Id.* (citing *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00358, Paper 9 at 9 (PTAB July 2, 2015); *Linear Tech. Corp. v. In-Depth Test LLC*, IPR2015-00421, Paper 15 at 17 (PTAB July 21, 2015)).

Patent Owner further argues that, whereas Petitioner presents El Rassi as the primary reference and Pharmacia as the secondary reference in establishing motivation to combine, Petitioner in fact argues that Pharmacia would have motivated a skilled artisan to scale up El Rassi. Prelim. Resp. 53–54 (citing Pet. 51). Patent Owner states that it is therefore not clear as to what purpose Pharmacia serves in the purported combination. *Id.* at 54. Rather, Patent Owner contends that the only motivation Petitioner argues involving El Rassi and Pharmacia is conclusory and insufficient: “In view of El Rassi 1990 ... and Pharmacia, a POSA accordingly would have been motivated to practice limitations [b]-[f] to improve HIC efficiency.” *Id.* (quoting Pet. 51). Patent Owner contends that such conclusory assertions cannot meet Petitioner’s burden. *Id.* (citing, *inter alia*, *In re Magnum Oil Tools, Int’l., Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016)).

Patent Owner contends that Petitioner’s arguments with respect to this ground thus leaves Patent Owner and the Board to guess at what aspects of which references are relied on for which combinations, fail to sufficiently identify or explain any motivations to combine, and fail to address the separate and distinct requirement of a reasonable expectation of success. Prelim. Resp. 54–55 (citing, *inter alia*, *InVue Sec. Prods. v. Mobile Tech*,

*Inc.*, PGR2019-00019, Paper 7 at 8–9 (PTAB May 29, 2019)). Patent Owner thus argues that Petitioner has failed to meet both its burden and its statutory obligations under 35 U.S.C. § 312(a)(3) with respect to Ground 4.

*b. claims 2 and 11*

Patent Owner argues further that, with respect to dependent claims 2 and 11, Petitioner’s reliance on Pharmacia is similarly confusing and inadequate. Prelim. Resp. 55. Patent Owner notes that Petitioner states that El Rassi teaches the additional pH limitation of these claims. *Id.* (citing Pet. 53). However, Patent Owner points out, Petitioner then discusses Pharmacia, before arguing that a person of ordinary skill in the art would have been motivated to mix the protein with a combination of two salts at pH 6.5. *Id.* at 55–56 (citing Pet. 54). Patent Owner contends that this is inconsistent with Petitioner’s argument that El Rassi alone already teaches the same thing. *Id.* at 56 (citing Pet. 53; also citing *Taiwan Semiconductor Mfg. Co. v. Godo Kaisha IP Bridge I*, IPR2016-01442, Paper 7 at 20 (PTAB Jan. 27, 2017)).

*c. claim 8*

Patent Owner contends that Petitioner’s arguments with respect to claim 8 are similarly flawed. Prelim. Resp. 56. According to Patent Owner, Petitioner again refers to Pharmacia, but does not explain whether or how Pharmacia would have been used to modify El Rassi. *Id.* (citing Pet. 55). Patent Owner also argues that Petitioner fails to identify which protein in El Rassi would have been formulated or why one would have been motivated to formulate that protein. *Id.* Patent Owner contends that, although



Petitioner states that formulating the protein would have been obvious, it fails to address whether it would have been obvious, routine, or beneficial to formulate any particular protein from El Rassi. *Id.* (citing Pet. 55).

5. Analysis

*a. independent claims 1 and 10*

We conclude that, with respect to Petitioner’s Ground IV, Petitioner has established a reasonable likelihood of prevailing at trial. We agree with Petitioner that El Rassi teaches the limitations of independent claims 1 and 10<sup>12</sup>, with the exception of limitation [b], which recites, “mixing a preparation containing the protein with a combination of a first salt and a second salt.” Ex. 1001, col. 15, ll. 11–12, col. 16, ll. 11–12.

Specifically, El Rassi describes how “[h]ydrophobic-interaction chromatography of mixtures of acidic and basic proteins having a wide range of molecular weights and hydrophobic character was carried out by using binary and ternary salt gradients.” Ex. 1005, Abstr. El Rassi discloses that “[a]t constant eluent surface tension, gradient elution with two or three aqueous salt solutions was found to be superior to single-salt gradients in modulating hydrophobic-interaction chromatography retention and selectivity.” *Id.*

Specifically, El Rassi teaches:

As expected, binary salt gradients of decreasing concentrations of both ammonium sulfate and sodium citrate in the eluent, from 1.0 to 0M and from 0.69 to 0M, respectively, yielded an elution pattern significantly different from that obtained by using either

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<sup>12</sup> *But see* n.5, *supra* (regarding whether the preamble is limiting).

ammonium sulfate or sodium citrate gradients while maintaining the surface tension of the eluents constant.

Ex. 1005, 144–45 (internal citation omitted). Table II of El Rassi, and especially a comparison of columns I (ammonium sulfate gradient, 2.0M–0M) and V (sodium citrate 1.38M–0M) with column IX (combined ammonium sulfate and sodium citrate gradients, 1.0M to 0M, 0.69M to 0M, respectively) directly supports this disclosure. *Id.* at Table II.

El Rassi further discloses:

As seen in Fig. 1C, with the binary salt gradient, the seven proteins were retained to an extent closer to that obtained by using a sodium citrate gradient than an ammonium sulfate gradient. However, the elute pairs ribonuclease A and  $\beta$ -lactoglobulin A, ovalbumin and  $\beta$ -lactoglobulin A, and fetuin and  $\alpha$ -cbymotrypsinogen A are better resolved with the binary salt gradient than with single-salt gradients at virtually equal eluent surface tension.

Ex. 1005, 145–46.

Petitioner also cites evidence from the prior art that supports Petitioner's contention that a person of ordinary skill in the art would have understood that increased protein retention in the HIC column correlates with increased dynamic capacity. The latter term is defined in the '707 patent as "[T]he maximum amount of protein in solution which can be loaded onto a column without significant breakthrough or leakage of the protein into the solution phase of a column before elution." Ex. 1001, cols. 3–4, ll. 64–3. Petitioner contends that it was well understood in the prior art that there was a direct correlation between increased protein retention and

increased dynamic capacity. *See* Ex. 1008, 9–11, Fig. 2; Ex. 1007, 105–07, Figs. 2–3). We find this argument to be persuasive.<sup>13</sup>

With respect to limitations [c]–[f] of claims 1 and 10 of the ’707 patent, we find that Petitioner is likely to be able to demonstrate at trial that El Rassi teaches these limitations. Specifically, limitations [c] and [d] recite: “loading the mixture onto a hydrophobic interaction chromatography column” and “eluting the protein.” El Rassi teaches loading the protein onto the HIC column (“[the proteins] were chromatographed by using 30-min linear gradient elution of one, two, or three salts at room temperature and a flow rate of 1.0 ml/min”). Ex. 1005, 143. El Rassi also teaches eluting the protein with a binary salt solution [limitation d]. *Id.*

Limitation [e] of claims 1 and 10 recites “wherein the first and second salts are selected from the group consisting of *citrate and sulfate*, citrate and acetate, and sulfate and acetate, respectively.” Ex. 1001, col. 15 ll. 14–16, col. 16 ll. 14–16 (emphasis added). El Rassi expressly teaches eluting the HIC column with a binary salt gradient consisting of ammonium sulfate and sodium citrate. *See* Ex. 1005, 144, Table II (col. IX, legend)).

Limitation [f] recites “wherein the concentration of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.” Ex. 1001, col. 15 ll. 16–18, col. 16 ll. 16–18. El Rassi teaches that the concentration gradients employed in column IX of Table II were ammonium sulfate from 1.0 to 0M and sodium citrate from 1.0 to 0M and from 0.69 to 0M. Ex. 1005, Table II (legend). These respective concentration gradients entirely, or very considerably, overlap the range recited in claims 1 and 20.

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<sup>13</sup> *But see* n.5, *supra* (regarding whether the preamble is limiting).

*See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that “[i]n cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness”).

Petitioner relies upon Pharmacia as teaching that it would have been obvious to combine the protein and salts together before loading the resulting mixture into the HIC columns. *See* Pet. 50. Pharmacia teaches that:

If HIC, on the other hand, is used as an initial product capture step where the major concern is to remove critical contaminants and reduce volume, selectivity during desorption is not a prime issue.

After having washed out the non-bound substances, the compound of interest is eluted with a single-step procedure.

In this mode, the entire bed volume is utilized for sample binding and the prime consideration when optimizing for highest possible productivity is to find the highest possible sample load over the shortest possible sample application time with acceptable loss in yield. *In this situation, more emphasis should be given to the binding strength of the compound of interest than to selectivity during sample application. This means that the salt concentration during sample application should not be too low since this will have a negative effect on dynamic binding capacity.* Note also that less hydrophobic contaminating substances will not have any dramatic effect on the binding capacity for the compound of interest since they will be displaced by the latter.

Ex. 1006, 49 (emphasis added); *see also* 42, 61.

Petitioner’s declarant, Dr. Przybycien, opines that “[i]t was common in the prior art, at both preparative and analytical scales, to use two-salt

mixtures—and salts that were each within a concentration range of 0.1 M to 1.0 M—for loading the protein onto the HIC column.” Ex. 1002 ¶ 63 (citing Ex. 1003, col. 35, ll. 30–35; Ex. 1004, 1012–13; Ex. 1015, 25–26, Figs. 9–10; Ex. 1016, 5). Specifically, Dr. Przybycien attests that:

A POSA would have known that optimizing the salt concentration in the solution loaded onto the HIC column is particularly important at the preparative or industrial scale. As compared to HIC purification at an analytical or lab scale, larger volumes of load solutions must contain a sufficient amount of salt consistent with the salt concentrations present in the column equilibration solution. Ex. 1006 at 44; *id.* at 61 (“[S]ample volume becomes important when the salt concentration in the sample is lower than in the buffer used for equilibration.”). The point is to limit the possible dilution of the high-salt concentration mobile phase in which the column has been equilibrated when a large volume of material to be purified is loaded onto an HIC column.

Ex. 1002 ¶ 59. Dr. Przybycien concludes that:

In view of a POSA’s general knowledge and as taught by Pharmacia, a POSA would have known that in order to use El Rassi 1990’s two-salt combinations with larger sample loads (i.e. at the preparative or process scale), it would have been necessary to mix the protein in a salt solution prior to loading, otherwise the protein would not adequately bind to the column and would prematurely begin to elute. E.g., *id.* at 49.

In particular, in view of Pharmacia, a POSA would have been motivated to match the HIC load with the salts applied to the HIC column for equilibration in order to avoid diluting the equilibration solution. *See, e.g., id.* at 61. Accordingly, a POSA would have been motivated to mix a protein with a combination of 1.0 M ammonium sulfate and 0.69 M sodium citrate (limitation [b]) prior to “loading the mixture onto a [HIC] column” (limitation [c]) such that the salt concentration of the

HIC load would match the equilibration solution on the column.  
See *id.*; EX1005 at 144, Table II; *see also id.* at 145, Fig. 1.

*Id.* at ¶¶ 198–99.

Patent Owner argues that Petitioner’s arguments with respect to the Pharmacia reference are “not clear as to what purpose Pharmacia serves in the purported combination,” and that “the only motivation Petitioner argues involving El Rassi and Pharmacia is conclusory and thus insufficient.” *See* Prelim. Resp. 54. We disagree because, as we have explained *supra*, Petitioner points specifically to various teachings of Pharmacia that teach that it would have been obvious, particularly when scaling up HIC chromatography, to combine salts with the protein, as recited in limitation [b] of claim 1. Patent Owner makes no argument that this teaching is not present in Pharmacia. Furthermore, Petitioner has presented additional evidence concerning the state of the art at the time of invention to support this contention. *See, e.g.*, Exs. 1003, 1004, 1015.

Patent Owner next argues that Petitioner does not explain why a person of ordinary skill in the art would have chosen a fixed concentration within the claimed concentration range. Prelim. Resp. 53. Furthermore, Patent Owner argues that Petitioner fails to explain how the selection of a concentration within the claimed range would influence results when converting an eluent with a salt concentration gradient to a load buffer with fixed salt concentrations. *Id.* Nevertheless, El Rassi teaches using salt concentration gradients that fall within the claimed ranges. *See* Ex. 1005, 144, Table II. Furthermore, the teachings of Pharmacia cited by the Petitioner provide guidance to a person of ordinary skill in the art regarding salt concentrations in a loading mixture. *See, e.g.*, Ex. 1006, 49, 61.

In summary, we conclude, with respect to independent claims 1 and 10, that Petitioner has established a reasonable likelihood of prevailing at trial, and that Patent Owner's arguments do not overcome Petitioner's arguments.

*b. the dependent claims*

With respect to dependent claims 2 and 11, we agree with Petitioner that both El Rassi and Pharmacia expressly teach ranges of pH that fall within the ranges recited in the claims. *See* Ex. 1005, 144–45, Table II, Fig. 1, Ex. 1006, 34–35. Pharmacia further teaches that a skilled artisan would have understood how pH affects the results of HIC chromatography. *See* Ex. 1006, 18. Patent Owner's argument that Petitioner's reliance upon both El Rassi and Pharmacia is inconsistent does not overcome the fact that both references teach using pHs within the claimed range, and that Pharmacia teaches that a person of ordinary skill would have understood the effects of pH in the claimed process. We conclude that Petitioner has established a reasonable likelihood of prevailing at trial with respect to claims 2 and 11.

With respect to claim 4 of the '707 patent, Petitioner points to El Rassi, which expressly teaches that, in one embodiment, the first and second salts are sodium citrate and ammonium sulfate, which satisfies the requirement of the claim. Pet. 54 (citing Ex. 1005, 144–45, Table II, Gradient IX, Fig. 1(C)). We agree, and Patent Owner does not contest Petitioner's arguments on this claim. We consequently conclude that Petitioner has established a reasonable likelihood of prevailing at trial with respect to claim 4.

Finally, with respect to claim 8, Petitioner contends that El Rassi discloses that “[h]ydrophobic-interaction chromatography (HIC) with rigid, microparticulate stationary phases is increasingly used for the analysis and purification of proteins.” Pet. 55 (quoting Ex. 1005, 141). Petitioner also points to Pharmacia, which teaches that HIC “is an ideal separation method” used “[w]ith the rise of the modern biotechnology industry and its requirement for highly purified pharmaceutical proteins,” and that HIC processes can provide “economy, capacity and resultant product quality.” *Id.* (quoting Ex. 1006, 5).

Patent Owner responds that Petitioner does not explain whether or how Pharmacia would have been used to modify El Rassi, or identify which protein in El Rassi would have been formulated or why one would have been motivated to formulate that protein. *See* Prelim. Resp. 56. We disagree, and find that Petitioner has pointed out with sufficient particularity why a person of ordinary skill in the art would have wanted to formulate an isolated protein using the HIC chromatography method described in the references, *viz.*, to provide “economy, capacity and resultant product quality” in protein products intended for use in the modern biotechnology industry. *Id.* (citing 1006, 5). We therefore conclude that Petitioner has established a reasonable likelihood of success at trial, and that Patent Owner’s arguments fail to overcome those set forth by Petitioner.

## 6. Summary

Having determined that Petitioner has established a reasonable likelihood of success at establishing at trial that claims 1, 2, 4, 8, and 11 are unpatentable under 35 U.S.C. § 103 as being obvious over El Rassi and



Pharmacia (Ground IV of the Petition), we consequently institute trial on all Grounds and all claims set forth in the Petition. *See SAS Institute, Inc. v. Iancu*, 138 S.Ct. 1348, 1354–55 (2018) (holding that, when *inter partes* review is instituted, the Board shall issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner). We add below our comments on the remaining grounds for guidance to the parties.

*E. Ground I: Alleged Anticipation of Claims 1, 2, 4, 8, 10, and 11 over Builder*

1. Overview of Builder

Builder issued on August 29, 1995 and on this record is prior art to the '707 patent. Ex. 1003. Builder is directed to a process for purifying IGF-1 from variants of IGF-1. *Id.* at Abstr. Specifically, Builder teaches that a mixture containing IGF-1 and its variants is loaded onto a reversed-phase liquid chromatography column and the IGF-1 is eluted from the column with a buffer at a pH of about 6–8. *Id.* Builder further teaches that this process can be preceded by a hydrophobic interaction chromatography step. *Id.*

2. Anticipation of claims 1, 2, 4, 8, 10, and 11 over Builder

Petitioner points to claims 14, 17, and 18 of Builder as disclosing elements [b] through [d] of claim 1 of the '707 patent. Pet. 32. Claim 14 of Builder recites, in relevant part:

14. A process for purifying IGF-I comprising:

(a) loading a buffer containing IGF-I [a protein] at a pH of about 3–8 onto a hydrophobic interaction chromatography column;

- (b) washing the column with a buffer at a pH of about 3–8;
- (c) eluting the IGF-I with a buffer at a pH of about 3–8;

....

Ex. 1003. Claim 17 of Builder recites: “The process of claim 14 wherein the buffers for steps (a)–(c) are a citrate or ammonium buffer or both at pH about 6–8.” *Id.* Claim 18 recites: “The process of claim 17 wherein the buffers for steps (a)–(c) are 0.1–1 mM [sic] ammonium sulfate or ammonium citrate.” *Id.*

Petitioner asserts that to “load[ ] a buffer” containing protein, ammonium sulfate (a first salt), and ammonium citrate (a second salt) onto an HIC column as recited in claims 14, 17, and 18 of Builder, the protein and dual-salt solution must be mixed prior to loading. Pet. 33 (citing Ex. 1002 ¶¶ 115–20). Therefore, argues Petitioner, Builder claims a process that requires mixing a combination of a first salt (ammonium sulfate) and a second salt (ammonium citrate) with protein [IGF-I] prior to loading the mixture onto an HIC column and eluting the protein. *Id.*

With respect to elements [e] and [f], Petitioner argues that dependent claim 18 of Builder limits the two-salt loading buffer of the claim 17 process (i.e., the buffer including “both” a citrate and ammonium salt) to “ammonium sulfate” and “ammonium citrate,” each with a concentration between 0.1M and 1M. Pet. 34 (citing Ex. 1003, claim 18).

Patent Owner responds that Petitioner’s theory that Builder anticipates the challenged claims of the ’707 patent depends on the assertion that Builder teaches adding two salts—ammonium sulfate and ammonium citrate—to a preparation containing the protein. Prelim. Resp. 23. However, Patent Owner argues, the only disclosure of Builder that Petitioner

points to as disclosing two salts, as required by the '707 patent, are Builder's claims 14, 17, and 18. *Id.* (citing Pet. 29–34). Patent Owner asserts that Petitioner's reading of those claims is contrary to their plain meaning. *Id.*

Patent Owner contends that Builder's claim 17 states that the buffers used in Builder's purification process "are a citrate or ammonium buffer or both." Prelim. Resp. 23 (citing Ex. 1003, col. 41, ll. 6–7). Patent Owner alleges that Petitioner reads Builder claim 17 as disclosing a buffer with a citrate salt or a buffer with an ammonium salt or a combination of a first buffer with a citrate salt and a second buffer with a second (and different) ammonium salt. *Id.* (citing Pet. 30, 33). But, Patent Owner argues, citrate and ammonium can form a single salt, as reflected in claim 18, which lists "ammonium citrate." *Id.* at 23–24 (citing Ex. 1003). Nor, Patent Owner asserts, does Petitioner explain why Builder claim 17's reference to "a citrate or ammonium buffer or both" should be read as a citrate buffer or an ammonium buffer, or two buffers with two different salts where one salt uses citrate and the other ammonium, rather than as a citrate buffer or an ammonium buffer or a citrate ammonium buffer. *Id.*

Patent Owner argues that interpreting Builder claim 17 as disclosing a buffer with a citrate salt, an ammonium salt, or an ammonium citrate salt is further supported by Builder's claim 14. Prelim. Resp. 24. Claim 14 steps (a)–(c) recite "loading a buffer containing IGF-1," "washing the column with a buffer" and "eluting the IGF-1 with a buffer," respectively. *Id.* (citing Ex. 1003, col. 40, ll. 55–61). In other words, Patent Owner contends, claim 14 refers to a single buffer used for loading the protein, whereas Petitioner interprets the Builder claims as disclosing the use of multiple buffers for the loading step (a) of claim 14 (i.e., as disclosing not the loading of "a buffer"

but instead the loading of the combination of two different buffers including a citrate buffer and an ammonium buffer). *Id.* at 24–25 (citing Pet. 30, 33). Patent Owner argues that Petitioner asserts Builder claim 17 “recites that the buffers for step 14(a) [alone] are ‘a citrate or ammonium buffer or both.’” *Id.* at 25 (citing Pet. 33). Patent Owner further argues that Petitioner asserts Builder claim 18 “recites that the buffers for step 14(a) are ‘ammonium sulfate’ and ‘ammonium citrate.’” *Id.* (citing Pet. 33). But claim 14, from which claim 17 depends, is clear that a single buffer, not two buffers, is used in step 14(a). *Id.*

Patent Owner also points to the Specification of Builder, which repeatedly discloses only a single buffer (with a single salt) being added to the protein before loading onto the column. Prelim. Resp. 25 (citing, e.g., Ex. 1003, col. 17, ll. 62–66). Similarly, Patent Owner contends, the reference to plural buffers in claims 17 and 18 refers to the fact that a different buffer can be used for each of steps 14(a), (b), and (c). *Id.* Indeed, each of steps (a) through (c) in claim 14 refers to “a buffer,” indicating a single buffer is used for each step individually, but that the same buffer need not be used for each different step. *Id.* According to Patent Owner, interpreting Builder’s claim 17 as teaching a buffer with a citrate salt, or an ammonium salt, or an ammonium citrate salt is also supported by the plain language of Builder’s claim 18, which specifies that each buffer in steps (a)–(c) is either “ammonium sulfate or ammonium citrate” (not both). *Id.* (citing Ex. 1003, col. 42, ll. 1–2).

With respect to Petitioner’s argument that Builder claim 18 teaches using ammonium sulfate and ammonium citrate together in combination (*see* Pet. 31), Patent Owner contends that the plain language of the claim

discloses using either ammonium sulfate or citrate, not both. Prelim. Resp. 26. Patent Owner argues that Petitioner’s interpretation of the claim language is inconsistent with the Specification, which also treats ammonium sulfate and ammonium citrate as salts of two separate buffers. *Id.* (citing, e.g., Ex. 1003, col 17, ll. 62–66, col. 34, ll. 35–39).

As an initial matter, we make no comment or finding at this stage of the proceeding concerning whether Builder discloses “such that the dynamic capacity of the column is increased for the protein” in view of our comment in footnote 5 of this Decision as to whether the respective preambles are limiting upon claims 1 and 10.

Turning to the remaining limitations of independent claims 1 and 10, we find that the principle argument in this Ground relies upon the textual interpretation of claims 14, 17, and 18 and, particularly, whether claim 17 recites two separate salt buffers or just a single one. We find that the issue is a close one, but one which, based upon the arguments presented *supra*, slightly favors Patent Owner. This is not least because the single Example (Example IV) in the Specification of Builder that discloses using HIC, uses only a single salt (*see* Ex. 1003, col. 34, ll. 35–45), and also because the language of claim 17 is ambiguous as to whether a single salt (i.e., ammonium citrate), or two salts are mixed with the protein. We invite the parties to further develop the record with respect to this Ground at trial.

*F. Ground II: Alleged Anticipation of Claims 1 and 10 over Memoli*

1. Overview of Memoli

Memoli was published in 1975 and on this record is indisputably prior art to the ’707 patent. Ex. 1004. Memoli discloses the binding of pure

human serum albumin and pure human hemoglobin to L-phenylalanine sepharose and aniline sepharose columns of differing hydrophobicity, for various concentrations of ammonium sulfate salts. *Id.* at Abstr.

Specifically, Memoli discloses combining the proteins with Tris-acetate buffer and ammonium sulfate, the latter at a known concentration. *Id.* at 1012. Memoli discloses that:

At a high ammonium sulfate concentration the protein peak occurs at a later position in the elution profile than the peak in the next lower ammonium sulfate concentration indicating an increase in the relative retention of protein on the column at the higher concentration. It can also be readily seen that the bulk of protein is also eluted much later from the column and in a greater volume of buffer as the ammonium sulfate concentration used increases.

*Id.* at 1013.

## 2. *Anticipation of claims 1 and 10 over Memoli*

Petitioner argues that Memoli discloses mixing proteins with a two-salt combination of ammonium sulfate and Tris-acetate at concentrations of 0.2 M – 0.8M and 0.1 M, respectively, for loading the proteins onto an HIC columns. Pet. 37 (citing Ex. 1002 ¶ 140). Petitioner contends that Memoli discloses that these two-salt combinations increased retention of the protein by the HIC column. *Id.* at 38 (citing Ex. 1004, 1013–15, Figs. 1–2; Ex. 1002 ¶ 140), Petitioner points to the testimony of its declarant, Dr. Przybycien, who explains that person of ordinary skill in the art would understand that increasing protein retention to the HIC column correlates with increasing the dynamic capacity of the HIC column for the protein. *Id.* (citing Ex. 1002 ¶¶ 39, 43–49).

Petitioner asserts that Memoli discloses limitation [b] of claims 1 and 10, “mixing a preparation containing the protein with a combination of a first salt and a second salt.” Pet. 39. Specifically, Petitioner points to Memoli’s disclosure of mixing two different protein samples (containing serum albumin and hemoglobin) with Tris-acetate and ammonium sulfate salts prior to loading this mixture onto the HIC column. *Id.* (citing Ex. 1004, 1012; Ex. 1002 ¶¶ 142–43).

Petitioner contends that Memoli also discloses limitations [c] and [d], “loading the mixture onto a hydrophobic interaction chromatography column” and “eluting the protein.” Pet. 39. Petitioner argues that Memoli discloses that “[e]ach sample at a known ammonium sulfate concentration was applied to either L-phenylal[a]nine Sepharose or aniline Sepharose [i.e., HIC] columns previously equilibrated with the same concentration of buffered ammonium sulfate, which was then employed for each elution.” *Id.* at 39–40 (quoting Ex. 1004, 1012).

With respect to limitations [e] and [f], Petitioner argues that Memoli discloses that the first and second salts are ammonium sulfate and Tris-acetate. Pet. 39 (citing Ex. 1004, 1012–13, Fig. 1). Petitioner contends that Memoli discloses combinations with 0.1M Tris-acetate together with 0.2–0.8M ammonium sulfate, both of which fall within the claimed concentration range. *Id.* (citing Ex. 1004, 1013–14, Figs. 1–2; Ex. 1002 ¶¶ 146–49).

Patent Owner responds that Memoli discloses an experiment involving loading already “pure” protein (serum albumin or hemoglobin) to a column to assess binding at various salt concentrations. Prelim. Resp. 34 (citing Ex. 1004, 1011, 1015). Patent Owner asserts that Petitioner fails to

explain how running a pure protein through a column amounts to “purification.” *Id.* (citing Pet. 37).

Patent Owner also argues that Petitioner’s argument fails because Petitioner “mix[es] and match[es]” the various embodiments disclosed by Memoli, and because did not establish that Memoli discloses an HIC column. Prelim. Resp. 35. According to Patent Owner, Petitioner asserts that Memoli discloses an HIC column, but does not identify the specific corresponding disclosure in Memoli. *Id.* (citing Pet. 37).

Patent Owner argues that Petitioner also fails to demonstrate that Memoli discloses the limitation “such that the dynamic capacity of the column is increased for the protein,” as required by both independent claims 1 and 10. Prelim. Resp. 36 (citing Pet. 37–40).

Again, we do not comment at this stage upon whether the prior art references teach the requirements set forth in the preambles to claims 1 and 10. *See* n.5, *supra*. We agree with Petitioner that Memoli appears to disclose the remaining limitations of claims 1 and 10, and therefore has established a reasonable likelihood of prevailing at trial. Patent Owner’s arguments that Petitioner has “mixed and matched” embodiments does not overcome Petitioner’s arguments for the simple reason that Patent Owner fails to point out with particularity precisely how Petitioner has done this, but makes only a general, unsupported allegation. With respect to Patent Owner’s argument that Memoli fails to disclose an “HIC column,” the Memoli reference is entitled *Hemoglobin & Serum Albumin: Salt-Mediated Hydrophobic Chromatography*, expressly teaches the use of columns that are hydrophobic, and that the columns are used in a manner consistent with the ’707 patent’s teaching of HIC. *See* Ex. 1004, 1011, 1012, 1015.



We invite the parties to further develop the record with respect to this Ground at trial.

*G. Ground III: Alleged Obviousness of Claims 1, 2, 4, 8, 10, and 11 over Builder and El Rassi*

We have explained *supra* why we agree with Petitioner that El Rassi teaches limitations [c] through [f] of claims 1 and 10, but does not teach limitation [b], “mixing a preparation containing the protein with a combination of a first salt and a second salt.” Builder teaches that:

A solution of IGF-I obtained from the S SEPHAROSE™ agarose purification steps of Examples I and II in 0.2M citrate, pH 6, was adjusted to pH 3.0 with phosphoric acid. The solution was then conditioned by the addition of 3.5M ammonium sulfate to a final concentration of 0.4M. This solution was then applied to a column of phenyl Toyopeard 650M equilibrated in 0.4M ammonium sulfate, 50 mM acetate, pH 3.0.

Ex. 1003, col. 35, ll. 30–38. Builder consequently teaches mixing salt with protein prior to loading the mixed solution to the HIC column. Although it is unclear from the language of claim 17 of Builder whether a single or a two salt buffer is added to the protein in question, El Rassi expressly teaches using two salts as an eluent. *See* Ex. 1005, 144, Table II.

At this stage of the proceeding, and for the reasons we have explained *supra* with respect to the teachings of Builder and El Rassi, we agree with Petitioner that a person of ordinary skill would have found it obvious to combine the teachings of Builder and El Rassi to arrive at the claimed invention. We acknowledge that there exists uncertainty as to whether Builder teaches one or two salts combined with the protein, but Builder

teaches not only HIC chromatography generally, but also expressly teaches adding salt to the protein prior to loading the HIC column with the mixture, *See* Builder claims 14, 17. thereby satisfying the requirement of limitation [b] of claims 1 and 10, which is not taught by El Rassi.

With respect to the dependent limitations, we repeat our findings *supra* that El Rassi teaches the claimed pH range and the salts recited in claims 2 and 11, and claim 4, respectively. With respect to claim 8, Builder expressly teaches “formulating the protein”:

After the IGF-I is eluted from the column, it is suitably formulated into a pharmaceutical composition as follows.... Generally, the formulations are prepared by contacting the IGF-I uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

Ex. 1003, cols. 18–19, ll. 60–18.

We invite the parties to further develop the record with respect to this Ground at trial.

*G. Ground V: Alleged Obviousness of Claims 1, 2, 4, 8, 10, and 11 over Memoli and Pharmacia*

1. Independent claims 1 and 11

Petitioner repeats the argument that Memoli anticipates claims 1 and 10 of the '707 patent. Pet. 55. Petitioner argues that the claims would have also been obvious to a person of ordinary skill in the art over the combined

teachings of Memoli and Pharmacia. *Id.* Specifically, Petitioner contends that a skilled artisan would have reasonably expected that obtaining increased retention of protein to an HIC column correlates with improved dynamic capacity of the HIC column. *Id.* at 56 (citing Ex. 1002 ¶¶ 39, 43–49). Petitioner therefore argues that claims 1 and 10 of the '707 patent would have been obvious to a person of ordinary skill in the art in view of Memoli's express disclosure of limitations [b]–[f] and a skilled artisan's general knowledge of the correlation between increased protein retention on an HIC column and increased dynamic binding capacity of the HIC column for a protein (limitation [a]). *Id.* (citing Ex. 1002 ¶¶ 223–24).

Patent Owner responds that Petitioner's arguments fail to address any of the alleged defects of Memoli presented by Patent Owner in Ground II and, specifically, that the requisite increase in dynamic binding capacity is not expressly taught by Memoli. Prelim. Resp. 56.

Patent Owner also repeats the argument presented with respect to Ground IV, i.e., that Petitioner does not explain how, if at all, Pharmacia is to be used in the Ground 5 combination. Prelim. Resp. 57 (citing Pet. 56). Patent Owner again contends that Petitioner's obviousness theory is not sufficiently clear, and argues that *inter partes* review should not be instituted.

Furthermore, argues Patent Owner, Petitioner does not identify any motivation to combine, nor does Petitioner explain how or why Memoli would have been modified or why there would have been a reasonable expectation of success for any such modification. Prelim. Resp. 57.

2. Dependent claims

With respect to the dependent claims 2 and 11, Petitioner argues that Memoli discloses mixing proteins with a two-salt combination buffered to a pH of 8.0 and running the columns at a constant pH of 7.4. Pet. 57 (citing Ex. 1002 ¶ 226; Ex. 1004, 1011–12).

Petitioner argues that Pharmacia emphasizes the importance of pH in HIC, teaching that “pH is an important separation parameter in the optimization of hydrophobic interaction chromatography.” Pet. 57 (quoting Ex. 1006, 18). According to Petitioner, Pharmacia teaches that, generally, retention behavior of proteins changes “more drastically at pH values above 8.5 and/or below 5 than in the range of pH 5–8.5.” *Id.* (quoting Ex. 1006, 18). Petitioner contends that, given these teachings of Pharmacia, a person of ordinary skill in the art would have expected a protein to exhibit similar retention behavior within a pH range of 5–8.5. *Id.* (citing Ex. 1006, 18–19). Petitioner points to Pharmacia’s disclosure of data showing the effects of pH on retention of various proteins, including human serum albumin (the same protein analyzed in Memoli), confirms that the retention profile for human serum albumin is similar in the range of pH 5 to pH 8.5. *Id.* (citing Ex. 1006, 18). Petitioner asserts that it would therefore have been obvious to a skilled artisan to buffer the mixture loaded onto the column to a pH between 5 and 8.5, which overlaps with the claimed range. *Id.* at 58 (citing Ex. 1006 at 34–35).

With respect to claim 4, Petitioner argues that Memoli discloses employing a two-salt combination of Tris-acetate and ammonium sulfate. Pet. 58 (citing Ex. 1004, 1012). Petitioner contends that it would have been obvious to a person of ordinary skill in the art to substitute Tris-acetate with

a sodium, potassium, or ammonium salt in view of the teachings of Pharmacia and the general knowledge of the prior art. *Id.* (citing Ex. 1002 ¶¶ 231–35).

In support of this contention, Petitioner points to Pharmacia’s teaching that “[t]he effects of salts in HIC can be accounted for by reference to the Hofmeister series,” which is primarily based on the salt’s anion (i.e., acetate, citrate, sulfate), rather than the corresponding cation (i.e., sodium, potassium, or ammonium). Pet. 59 (citing Ex. 1006, 18). Petitioner asserts that a person of ordinary skill in the art would have understood that similar results could be obtained by substituting Tris-acetate with another acetate. *Id.* (citing Ex. 1002 ¶¶ 234–35). Because Memoli does not teach that Tris-acetate is preferred over other acetates, Petitioner argues that it would have been routine (and preferred) to use a sodium, potassium, or ammonium salt in lieu of Tris as the buffer cation. *Id.* (citing Ex. 1002 ¶¶ 230–35).

With respect to claim 8, Petitioner contends that, in view of Memoli’s teaching of increased retention using its two-salt combination within the claimed ranges, a person of ordinary skill in the art would have been motivated to practice the methods taught by Memoli to formulate a protein for pharmaceutical use as a biologic. Pet. 59 (citing Ex. 1002 ¶¶ 236–39).

In support of this contention, Petitioner also points to Pharmacia, which teaches that HIC “is an ideal separation method” used “[w]ith the rise of the modern biotechnology industry and its requirement for highly purified pharmaceutical proteins.” *Id.* (citing Ex. 1006, 5) (explaining HIC processes can provide “economy, capacity and resultant product quality”). Petitioner also notes that Pharmacia further discloses strategies for “preparative, large

scale applications” intended for “a pharmaceutical or a diagnostic for commercial application.” *Id.* at 59–60 (citing Ex. 1006, 87–89).

Patent Owner responds that, with respect to claims 2 and 11, Petitioner never explains why, or even contends that, a person of ordinary skill in the art would have modified Memoli’s 8.0 pH to be within the pH 5–7 range required by claims 2 and 11. Prelim. Resp. 58 (citing Pet. 57–58).

Patent Owner argues that Petitioner’s arguments with respect to claim 4 are inconsistent. Prelim. Resp. 59. On one hand, Patent Owner asserts, Petitioner argues the effects of salts in HIC are accounted for primarily based on the salt’s anion (e.g., acetate) rather than its cation (e.g., Tris, sodium, potassium, or ammonium). *Id.* (citing Pet. 59). On the other hand, Patent Owner argues, Petitioner argues that the salt’s cation matters, and that sodium, potassium, and ammonium salts were preferred salts for HIC purification. *Id.* (citing Pet. 59). Patent Owner questions why sodium, potassium, and ammonium salts (which have specified cations but not specified anions) would have been preferred if the anion of the salt is what matters for HIC. *Id.* Patent Owner also notes that Petitioner does not explain why its assertion of achieving only “similar results” with either Tris or one of the claimed salts would have motivated a POSA to actually make that substitution. *Id.*

Patent Owner points to the Declaration of Dr. Przybycien as stating that Pharmacia discloses that the most efficient salts for HIC are normally ammonium sulfate and sodium sulfate. Prelim. Resp. 59 (citing Ex. 1002 ¶ 234). However, Patent Owner notes, Petitioner argues that a person of ordinary skill in the art would have been motivated to substitute a sodium acetate, potassium acetate, or ammonium acetate salt (and not ammonium

sulfate or sodium sulfate) for Tris-acetate, as taught by Memoli. *Id.* (citing Pet. 59). Patent Owner also argues that Petitioner fails to address how the interaction of Memoli’s alleged “two-salt combination” might have influenced any decision to change the Tris-acetate in Memoli. *Id.* at 60 (citing Pet. 58).

With respect to claim 8, Patent Owner argues that Petitioner again refers to Pharmacia, but fails to explain how it would have been used to modify Memoli. Prelim. Resp. 60 (citing Pet. 59–60). Patent Owner also argues that Petitioner fails to explain why one would have been motivated to formulate the purified protein taught by Memoli (or which protein in Memoli would have been formulated). *Id.* Patent Owner further argues that Petitioner also fails to explain what the benefits of formulating that particular protein would have been or how it would have been formulated. *Id.*

### C. Comments

We conclude that Petitioner has established a reasonable likelihood of prevailing at trial. We have explained in Section III.F why we conclude that Petitioner has established a reasonable likelihood that Memoli anticipates claims 1 and 10 of the ’707 patent, and we incorporate that analysis by reference here. Furthermore, we have explained why we find that Patent Owner’s arguments with respect to Petitioner’s reliance on Pharmacia are not persuasive: we find that Petitioner has pointed with particularity to the teachings of Pharmacia and explained the reasons for which Petitioner relies upon those teachings.

With respect to claims 2 and 11, Petitioner explains that a person of skill in the art, understanding the teachings of Pharmacia, would have understood that a pH range of 5–8.5 would be optimal, and that it would have been obvious to a person of ordinary skill in the art to use a pH within that range. Where a skilled artisan merely pursues “known options” from a “finite number of identified, predictable solutions,” obviousness under § 103 arises. *KSR Int’l. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). For similar reasons, we agree with Petitioner that a person of ordinary skill in the art would have found it obvious to substitute sodium acetate for the Tris-acetate taught by Memoli, particularly since Memoli also teaches ammonium sulfate with a citrate buffer. *See* Ex. 1004, 1012–13.

With respect to claim 8, we agree with Petitioner that Pharmacia expressly contemplates scaling up the HIC process for purifying proteins used “[w]ith the rise of the modern biotechnology industry and its requirement for highly purified pharmaceutical proteins,” and that such a requirement suggests formulation of the protein into a pharmaceutical product. Ex. 1006, 5.

We therefore conclude that Petitioner has established a reasonable likelihood of prevailing at trial upon Ground V.

#### *H. Secondary Considerations of Nonobviousness*

Finally, Patent Owner argues that, during prosecution of the ’707 application, the then-applicant presented evidence of secondary indicia of non-obviousness in the form of cost savings achieved by increasing the dynamic binding capacity through use of various two-salt combinations, as claimed in the ’707 patent. Prelim. Resp. 60 (citing Ex. 1024, 45–46).



Patent Owner argues that Petitioner has failed to address cost savings, and failed to explain why the method of the '707 patent would not have been adopted earlier if, as Petitioner asserts, it was known, given the significant cost savings achieved by the method claimed in the '707. *Id.* at 60–61 (citing Pet. 60–63; Ex. 1024, 67–70).

With respect to any alleged unexpected results, Patent Owner asserts that Petitioner argues that El Rassi taught one of the salt combinations that gives rise to increased binding and that therefore, achieving increased dynamic binding capacity of an HIC column was not an unexpected result. Prelim. Resp. 61 (citing Pet. 61). However, Patent Owner argues, Petitioner does not explain why El Rassi's salt combinations, which are not added to the protein preparation before loading the solution onto to the column as required by the claims, would have had any bearing on the expected impact of the claimed salt pairs on dynamic binding capacity, or how El Rassi would have resulted in cost savings as compared to the '707 claims. *Id.* (citing Pet. 51–52).

We do not find Patent Owner's arguments, as they are developed at this stage of the proceeding, sufficiently persuasive to overcome the likelihood established by Petitioner of prevailing at trial.

As the sole evidence of cost savings, the then-Applicant relied upon paragraph 4 of the Declaration of Ms. Anna Senczuk (Ex. 1024, 67–70). In the relevant portion of paragraph 4, Ms. Senczuk calculates the estimated cost efficiency of using a two-salt buffer, and declares that: "Use of this particular combination of salts greatly improves the cost-effectiveness of commercial manufacturing by reducing the amount of cycles required for each harvest and reducing the processing time for each harvest." Ex. 1024,

69. Nevertheless, the prior art, particularly El Rassi, had previously demonstrated the use of two-salt buffers, and we find that such an increased cost efficiency as described by Ms. Senczuk would have naturally flowed from such use. *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (“It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable”).

With respect to Patent Owner’s assertion of unexpected results, Patent Owner asserts that, “Petitioner did not explain why El Rassi’s salt combinations, which are not added to the protein preparation before loading the solution onto to the column as required by the claims, would have had any bearing on the expected impact of the claimed salt pairs on dynamic binding capacity.” *See* Prelim. Resp. 61. However, in asserting unexpected results as a defense against obviousness, the burden of persuasion is on Patent Owner to demonstrate that the results are unexpected compared to closest the prior art (in this instance, Patent Owner asserts, El Rassi). *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Patent Owner points to no evidence of record showing that the claimed method of the ’707 patent produced unexpected results compared to El Rassi. A mere assertion of unexpected results, without supporting evidence, is insufficient to overcome Petitioner’s showing that it is likely to prevail at trial. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (holding that “[i]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements . . . [do] not suffice.” (citation omitted)).

We consequently conclude that Petitioner has demonstrated a reasonable likelihood of prevailing at trial with respect to Grounds II, III, IV, and V, and we consequently institute *inter partes* review in this case.

#### IV. CONCLUSION

For the reasons we have explained, we conclude that Petitioner has made a sufficiently persuasive showing that the cited prior art references disclose, teach, or suggest the elements of at least one of claims 1, 2, 4, 8, 10, and 11 of the '707 patent. We further conclude that Petitioner has articulated sufficient reasoning as to why, where applicable, a person of ordinary skill would have been motivated to combine these teachings with a reasonable expectation of success. Petitioner has thus established a reasonable likelihood of prevailing with respect to at least one of claims 1, 2, 4, 8, 10, and 11 over the prior art or combinations of prior art set forth in the asserted Grounds I–V. 35 U.S.C. § 314. Furthermore, and for the reasons we have explained, we decline to exercise our discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review.

#### V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), that an *inter partes* review of claims 1, 2, 4, 8, 10, and 11 of the '707 patent is instituted with respect to all Grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), that the *inter partes* review of the '707 patent shall commence on

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the entry date of this Order, and notice is hereby given of the institution of trial.

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