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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and FRESENIUS KABI SWISSBIOSIM GmbH,
Petitioner,

v.

AMGEN INC.,
Patent Owner.

IPR2019-01183
Patent 9,643,997 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH ("Petitioner") filed a Petition (Paper 3, "Pet.") to institute an *inter partes* review of claims 9, 10, 13–21, and 23–30 of U.S. Patent No. 9,643,997 B2 ("the '997 patent"). Amgen Inc. ("Patent Owner") timely filed a Preliminary Response (Paper 7, "Prelim. Resp.").

We have authority under 35 U.S.C. § 314 to determine whether to institute an *inter partes* review. The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted unless "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." The Supreme Court has held that the Board, in a decision to institute under 35 U.S.C. § 314(b), may not institute review on less than all claims challenged in the petition. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Moreover, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial) ("USPTO Guidance"); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has demonstrated a reasonable

likelihood of success in proving that at least one claim of the '997 patent is unpatentable. Accordingly, we institute an *inter partes* review of all challenged claims (9, 10, 13–21, and 23–30) of the '997 patent, based on the grounds raised in the Petition.

II. BACKGROUND

A. *Related Proceedings*

The parties identify the following district-court litigations as related matters under 37 C.F.R. § 42.8(b)(2): *Amgen Inc. v. Kashiv Biosciences, LLC*, No. 2:18-cv-03347 (D.N.J.); *Amgen Inc. v. Mylan Inc.*, No. 2:17-cv-01235 (W.D. Pa.); *Amgen Inc. v. Hospira Inc.*, No. 1:18-cv-01064 (D. Del.); and *Sandoz Inc. v. Amgen Inc.*, No. 3:19-cv-00977 (N.D. Cal.). Pet. 4; Paper 5, 2.

The '997 patent was the subject of an *inter partes* review designated IPR2019-00797, which was filed by Petitioner Kashiv BioSciences, LLC ("Kashiv"). Pet. 4; Paper 5, 2. The '997 patent is related to U.S. Patent No. 8,940,878, which was the subject of an *inter partes* review designated IPR2019-00791, also filed by Kashiv. Paper 5, 3. Both proceedings terminated on December 6, 2019, due to settlement. *See Kashiv BioSciences, LLC v. Amgen Inc.*, IPR2019-00791, Paper 22 at 3 (PTAB Dec. 6, 2019); *Kashiv BioSciences, LLC v. Amgen Inc.*, IPR2019-00797, Paper 23 at 3 (PTAB Dec. 6, 2019).

U.S. Patent Application No. 15/476,691 claims priority to the '997 patent and is pending. Pet. 4; Paper 5, 3.

B. *The '997 patent (Ex. 1001)*

The '997 patent, titled "Capture Purification Processes for Proteins Expressed in a Non-Mammalian System," relates to methods for purifying

proteins of interest expressed in non-mammalian expression systems. Ex. 1001, code (54). The '997 patent states that the proteins of interest are commonly expressed in non-mammalian expression systems in non-native, limited-solubility forms, such as inclusion bodies. *Id.* at 1:21–55. Because they are in non-native form, these proteins must undergo "refolding" into native form—which typically occurs in a refold mixture or solution. *Id.* at 1:41–46.

"Commonly, a refold solution contains a denaturant (e.g., urea or other chaotrope, organic solvent or strong detergent), an aggregation suppressor (e.g., a mild detergent, arginine or low concentrations of PEG), a protein stabilizer (e.g., glycerol, sucrose or other osmolyte, salts) and/or a redox component (e.g., cysteine, cystine, cystamine, cysteamine, glutathione)." *Id.* at 4:45–51. The '997 patent states that, although "beneficial for refolding proteins, these components can inhibit purification" of the expressed proteins. *Id.* at 4:52–54. Thus, in the prior art, "it was believed that after a protein has been refolded[,] it was necessary to dilute or remove the components of the refold mixture in a wash step" before purification. *Id.* at 1:46–52. "This dilution step can consume time and resources which, when working at a manufacturing scale of thousands of liters of culture, can be costly." *Id.* at 1:52–55.

According to the '997 patent, the disclosed methods allow for the "direct capture" of proteins of interest from the refold mixture. *Id.* at 1:16–17. The '997 patent states that "the advantages of the present invention over typical processes include the elimination of the need to dilute the protein out of a refold solution prior to capturing it on a separation matrix." *Id.* at 3:54–57. "In one embodiment of the disclosed method, purification is achieved

by directly applying a protein of interest, which is present in a refold mixture, to a separation matrix." *Id.* at 4:58–60.

C. *Illustrative Claim*

Of the challenged claims, only claim 9 is independent. *See* Ex. 1001, 22:36–55. Claims 10, 13–21, and 23–30 depend directly or indirectly from claim 9. *See id.* at 22:56–24:33. Claim 9 is reproduced below:

> 9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
>
> (a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
> (i) a denaturant;
> (ii) a reductant; and
> (iii) a surfactant;
>
> (b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
>
> (i) a denaturant;
> (ii) an aggregation suppressor;
> (iii) a protein stabilizer; and
> (iv) a redox component;
>
> (c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
>
> (d) washing the separation matrix; and
>
> (e) eluting the protein from the separation matrix.

Ex. 1001, 22:36–55.

D. *The Prior Art*

Petitioner advances the following references as the prior art upon which it relies for the asserted grounds challenging the claims of the '997 patent:

1. Chaozhan Wang et al., *Solubilization and Refolding with Simultaneous Purification of Recombinant Human Stem Cell Factor*, 144 APPL. BIOCHEM. BIOTECHNOL. 181–89 (2008) (Ex. 1003, "Wang");

2. Paul Cutler, ed., *Protein Purification Protocols*, 2nd. ed. (2004) (Ex. 1028, "Cutler");

3. Brian J. Reardon et al., *FGF18 Production in Prokaryotic Hosts*, US 2006/0172384 A1 (published Aug. 3, 2006) (Ex. 1004, "Reardon");

4. Arndt Dietrich et al., *Method for the Purification of G-CSF*, US 2008/0260684 A1 (published Oct. 23, 2008) (Ex. 1005, "Dietrich");

5. Uma Komath et al., *Process for the purification of recombinant granulocyte-colony stimulating factor*, WO 2006/097944 A2 (published Sept. 21, 2006) (Ex. 1006, "Komath '944"); and

6. Uma Komath et al., *Process for preparing G-CSF*, WO 2004/001056 A1 (published Dec. 31, 2003) (Ex. 1007, "Komath '056").

E. *Asserted Grounds of Unpatentability*

Petitioner challenges the patentability of claims 9, 10, 13–21, and 23–30 of the '997 patent on the following grounds:

Claims challenged	**35 U.S.C. §**	**Reference(s)**
9, 10, 13–21, 23–30	102	Wang
9, 10, 13–21, 23–30	103	Wang, Cutler
9, 10, 13–21, 23–30	102	Reardon
9, 10, 13–21, 23–30	102	Dietrich
9, 10, 13–21, 23–30	103	Komath '944, Komath '056

Petitioner further relies upon the declaration of Peter Tessier, Ph.D., to support its grounds of unpatentability. *See* Ex. 1002; Pet. 1.

III. DISCRETION UNDER 35 U.S.C. § 325(d) AND § 314(a)

Patent Owner argues that we should exercise our discretion to deny institution under 35 U.S.C. § 325(d) because "the same or substantially the same prior art or arguments previously were presented to the Office." Prelim. Resp. 7–11 (quoting 35 U.S.C. § 325(d)). Patent Owner also argues that we should exercise our discretion under 35 U.S.C. § 314(a) to deny institution, pointing out that "the PTO is permitted, but never compelled, to institute an IPR proceeding." *Id.* at 12–21 (quoting *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016)).

In evaluating whether to exercise our discretion under § 325(d), we weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art

evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("the *Becton*, *Dickinson* factors").

And, in evaluating whether to exercise our discretion under § 314(a), we weigh these non-exclusive factors: (1) whether the same petitioner previously filed a petition directed to the same claims of the same patent; (2) whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it; (3) whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition; (4) the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition; (5) whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent; (6) the finite resources of the Board; and (7) the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director

notices institution of review. *General Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 9–10 (PTAB Sept. 6, 2017) (precedential as to § II.B.4.i) ("the *General Plastic* factors").

For ease of discussion, we group Patent Owner's arguments into two sections: whether the Petition should be denied based on prior examination of the application leading to the '997 patent, and whether the Petition should be denied based on a prior petition challenging the patentability of the claims of the '997 patent. We analyze the former under § 325(d). *See Becton, Dickinson*, Paper 8, 17–18. We analyze the latter under both § 325(d) and § 314(a). *See General Plastic*, Paper 19 at 9–10 (applying discretion under § 314(a) to deny institution due to prior petition); *see also Medtronic, Inc. v. NuVasive, Inc.*, IPR2014-00487, Paper 8 at 5–7 (PTAB Sept. 11, 2014) (applying discretion under § 325(d) to deny institution due to prior petition).

A. *§ 325(d)—Examination*

Patent Owner does not analyze the individual *Becton, Dickinson* factors in connection with the examination of the application leading to the '997 patent. Instead, Patent Owner argues generally that the Board should deny institution because Petitioner "made no effort to distinguish their supposedly invalidating references from those considered in initial prosecution." Prelim. Resp. 8. But we observe that, in the Petition, Petitioner represents that most of the prior-art references relied upon for its asserted grounds of unpatentability were not considered during prosecution. *See* Pet. 20 (Wang); *id.* at 33 (Reardon), *id.* at 48 (Komath '944); *id.* at 49 (Komath '056). We further note that Cutler does not appear to be listed on the face of the '997 patent. *See* Ex. 1001, code (56). And, although Dietrich

is listed, *id.*, we have no evidence about the extent to which the Examiner evaluated Dietrich during examination. Patent Owner also does not point us to where in the prosecution history the Examiner considered the arguments relied upon in the Petition. For these reasons, we are not persuaded that the factors weigh in favor of exercising our discretion under 35 U.S.C. § 325(d) based on the examination of the application leading to the '997 patent.

B. *§§ 314(a), 325(d)—Prior Petition*

We now turn to Patent Owner's argument that we should deny the Petition because it is duplicative of the petition filed in IPR2019-00797 ("the '797 IPR").[1] Patent Owner argues that we should exercise our discretion under both § 325(d) and § 314(a) to deny institution because several of the Petition's prior-art references and arguments for unpatentability were previously presented in the '797 IPR, and because the prior-art references not previously presented in the '797 IPR are nevertheless cumulative to those that were presented. Prelim. Resp. 8–21.

Under the particular circumstances of this case, we decline to exercise our discretion under § 325(d) or § 314(a) to deny institution. In coming to our decision, we are mindful "that an objective of the AIA is to provide an effective and efficient alternative to district court litigation." *General Plastic*, Paper 19 at 16. We are also mindful that we must "recognize the potential for abuse of the [*inter partes*] review process by repeated attacks

[1] As noted above, Kashiv petitioned for an *inter partes* review of the '997 patent, *supra* § II.A, specifically challenging the patentability of claims 9, 10, 13–15, 17–21, 23, and 26–30, *see Kashiv BioSciences, LLC v. Amgen Inc.*, IPR2019-00797, Paper 16 at 2 (PTAB Sept. 11, 2019).

on patents." *Id.* at 16–17. Indeed, factors articulated in *Becton, Dickinson* and *General Plastic* encapsulate these concerns.

But a decision whether to exercise discretion is based on "a balanced assessment of all relevant circumstances in the case, including the merits." Update to Trial Practice Guide (July 2019), at 25, available at https://www.uspto.gov/sites/default/files/documents/trial-practice-guide-update3.pdf. And here, upon consideration of the factors and the merits of Petitioner's grounds of unpatentability, we find that the relative strength of the preliminary merits as discussed below, combined with the broad scope of the claims at issue, signals a need for an effective and efficient *inter partes* review of the '997 patent that outweighs the potential for abuse by instituting the instant Petition.

It is true that the Board has denied institution of so-called "follow-on" petitions—whether filed by the original petitioner or another—particularly where the follow-on petition relies on the same or cumulative prior-art references. *See, e.g.*, *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, IPR2013-00324, Paper 19 at 5–7 (PTAB Nov. 21, 2013) (informative); *Unified Patents, Inc. v. PersonalWeb Techs., LLC,* IPR2014-00702, Paper 13 at 6–9 (PTAB July 24, 2014) (informative). Indeed, as Patent Owner points out, the Board exercised its discretion under § 314(a) to deny institution of Petitioner's follow-on petition challenging Amgen's U.S. Patent No. 9,856,287 ("the '287 patent") in IPR2019-00971, because that patent had already been challenged by Kashiv[2] in a petition for a post-grant

[2] Although Adello Biologics, LLC ("Adello") initially filed the petition for post-grant review in PGR2019-00001, Kashiv BioSciences, LLC is a real party-in-interest in that case. *See Adello Biologics, LLC v. Amgen*

review designated PGR2019-00001. *See Fresenius Kabi USA, LLC v. Amgen, Inc.*, IPR2019-00971, Paper 13 at 6–11 (PTAB Oct. 16, 2019); *see also* Prelim. Resp. 12–14.

But here, we are of the opinion that the potential for abuse by instituting an arguably follow-on Petition in this case has been ameliorated by the termination of the '797 IPR proceeding. Specifically, the parties to the '797 IPR filed a joint motion to terminate on December 3, 2019, and the Board terminated the proceeding on December 6, 2019. *Kashiv BioSciences, LLC v. Amgen Inc.*, IPR2019-00797, Paper 23 at 3 (PTAB Dec. 6, 2019). In its Decision granting the parties' joint motion to terminate, the Board noted that termination was appropriate because the '797 IPR was in its early stages, none of the stipulated due dates had passed, and Patent Owner had yet to file a Patent Owner Response. *Id.* at 2–3. And, although the petition in the '797 IPR was already filed when Petitioner filed the instant Petition, Amgen's preliminary response in that case was not. Thus, Petitioner did not gain an unfair advantage from the proceedings in the '797 IPR. *See General Plastic*, Paper 19 at 17 (explaining the concern "directed to Petitioner's potential benefit from receiving and having the opportunity to study Patent Owner's Preliminary Response, as well as our institution decisions on the first-filed petitions, prior to its filing of follow-on petitions").

Finally, we consider the finite resources of the Board, but find that they do not weigh in favor of denial in this case because there are no longer

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Inc., PGR2019-00001, Paper 7 at 2 (PTAB Jan. 23, 2019) (Updated Mandatory Notices listing Kashiv BioSciences, LLC as a real party-in-interest). According to Patent Owner, Kashiv Pharma, LLC, acquired Adello on January 1, 2019, and the resulting entity was renamed Kashiv BioSciences, LLC. Prelim. Resp. 12 n.3 (citing Ex. 2050, 1).

multiple petitions challenging the same patent. Thus, for the reasons discussed above, we determine that the factors in this particular case do not weigh in favor of exercising our discretion under 35 U.S.C. § 314(a) and 35 U.S.C. § 325(d). We therefore decline Patent Owner's request to deny the Petition.

IV. PATENTABILITY ANALYSIS

We organize our patentability analysis into five sections. First, we address the level of ordinary skill in the art. Second, we address claim construction. Third, we provide an overview of the asserted references. Fourth, we consider the printed publication status of several references. And fifth, taking account of the information presented, we consider whether the Petition satisfies the threshold requirement for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. *Level of Ordinary Skill in the Art*

Relying on Dr. Tessier's declaration, Petitioner contends that a person of ordinary skill in the art for the '997 patent "would have had a Ph.D. in biochemistry, biology, chemical engineering, biomedical engineering or bioengineering and several years' experience in the recovery and purification of recombinant proteins from non-mammalian expression systems." Pet. 13. Alternatively, Petitioner contends, an ordinarily skilled artisan "would have had an equivalent level of education and experience, including a Bachelor's or Master's degree with more practical work experience in the above fields." *Id.* (citing Ex. 1002 ¶¶ 66–67). Petitioner further contends that an ordinarily skilled artisan "would have worked in collaboration with other scientists and/or clinicians with experience in the design and expression of recombinant proteins, biochemical manufacturing,

pharmaceutical development of biologics, therapeutic use of biologics, or related areas." *Id.* at 13–14.

Patent Owner does not propose a definition for the level of ordinary skill in the art in its Preliminary Response or otherwise dispute Petitioner's definition. *See generally* Prelim. Resp. Petitioner's definition appears consistent with the level of ordinary skill in the art reflected in the prior art, and we apply it for our analysis in this Decision. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. *Claim Construction*

Because the Petition was filed after November 13, 2018, we interpret the claims "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (as amended Oct. 11, 2018). Under this standard, we construe a claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.* Furthermore, at this stage in the proceeding, we need only construe the claims to the extent necessary to determine whether to institute *inter partes* review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

Petitioner proposes constructions for the terms "applying the refold solution to the separation matrix," "washing," "eluting" (or "elution"), and "isolated after elution." Pet. 14–19. Patent Owner responds[3] with constructions for "refold buffer," "applying the refold solution to a separation matrix," "aggregation suppressor," and "protein stabilizer," and further argues that the recited elements in certain dependent claims are required limitations. Prelim. Resp. 21–37. For this Decision, we determine that we need only construe the claim terms "refold buffer," "aggregation suppressor," and "protein stabilizer." We also discuss the scope of dependent claims 14–19 and 23–27 as a claim construction issue arising from the parties' respective arguments.

1. *Refold buffer*

Claim 9 recites a step of "forming a refold solution comprising the solubilization solution and a refold buffer." Ex. 1001, 22:44–45. The "refold buffer" comprises "one or more of" a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. Ex. 1001, 22:45–

[3] Patent Owner also argues that the Petition should be denied for Petitioner's failure to provide express constructions for "at least 'aggregation suppressor,' 'protein stabilizer,' and 'refold buffer.'" Prelim. Resp. 21–22 (citing 37 C.F.R. § 42.104(b)(3)–(4)). We decline to deny the Petition on this basis. Petitioner states in the Petition that each claim term "not expressly defined in the specification or discussed below [in the Petition]" "should be given its ordinary and customary meaning" under the *Phillips* standard. Pet. 14. Moreover, as discussed *infra*, we determine that the claim terms "aggregation suppressor," and "protein stabilizer" are expressly defined in the '997 patent's written description. Thus, under the particular circumstances of this case and for this Decision, we find Petitioner's general statement on claim construction sufficient to satisfy the requirements of 37 C.F.R. § 42.104(b)(3)–(4).

50. Patent Owner proposes the following construction for refold buffer: "a pH-buffered solution that provides conditions for the protein to refold into its biologically active form, comprising one or more of a denaturant, an aggregation suppressor, a protein stabilizer and a redox component." Prelim. Resp. 22. As to "pH-buffered," Patent Owner argues that "the refold buffer should be construed so as to require that it be pH-*buffered*." *Id.* at 23. And, as to "conditions for the protein to refold into its biologically active form," Patent Owner argues that the "refold buffer must actually provide conditions suitable so that the protein refolds into its biologically active form." *Id.* at 26.

The '997 patent states that "[t]he function of the buffer component of the refold solution is to maintain the pH of the refold solution and can comprise any buffer that buffers in the appropriate pH range." Ex. 1001, 15:5–7. Given this statement, we agree with Patent Owner that the "refold buffer" is "a pH-buffered solution." *See* Prelim. Resp. 24–25.

On the other hand, we disagree with Patent Owner—based on the present record—that "refold buffer" must be construed as requiring that the buffer "actually provide conditions suitable so that the protein refolds into its biologically active form." *Id.* at 26. It is not clear to us on this record that the protein must refold into its *biologically active form* before the refold solution is applied to a separation matrix. The written description of the '997 patent suggests otherwise: in the "Summary of the Invention" section, the '997 patent states that "[a]lthough not required, the method can *further comprise* refolding the protein to its native form *after* it is eluted from the separation matrix." Ex. 1001, 2:17–20 (emphases added). Thus, it appears to us that the refold buffer need not necessarily "provide conditions suitable

so that the protein refolds into its biologically active form," as Patent Owner argues. Prelim. Resp. 26.

We agree with Patent Owner that the refold buffer must comprise one or more of a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. *Id.* at 22. But, again, it is not clear to us on this record that those components cause the protein to refold into its biologically active form. In describing the functions of these components, the '997 patent states that the denaturant "can be included as a means of modifying the thermodynamics of the solution, thereby shifting the equilibrium towards an optimal balance of native form," "[t]he aggregation suppressor can be included as a means of preventing non-specific association of one protein with another, or with one region of a protein with another region of the same protein," and "[t]he protein stabilizer can be included as a means of promoting stable native protein structure and may also suppress aggregation." Ex. 1001, 14:27–40. None of these descriptions, however, suggest that the protein must completely refold into its biologically active form before it is purified on the separation matrix, contrary to Patent Owner's arguments otherwise. *See* Prelim. Resp. 27 (arguing that "what the inventors actually invented and intended to envelop with the claim includes a refold buffer that provides conditions so that the protein refolds into its biologically active native form in the refold solution" (quotation omitted)). Again, the '997 patent suggests that the claimed invention does not require complete refolding for protein purification on a separation matrix. *See id.* at 8:43–48 (discussing the need for a protein to have "*enough structure* to associate with the affinity separation matrix" (emphasis added)).

2. *Aggregation suppressor and protein stabilizer*

Claim 9 recites a refold buffer comprising "one or more of" a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. Ex. 1001, 22:44–50. Patent Owner argues that an aggregation suppressor "must actually disrupt or decrease or eliminate interactions between two or more proteins at the concentration used," such that "[i]f it does not 'disrupt and decrease or eliminate interactions between two or more proteins' when in the presence of proteins, then it is not an 'aggregation suppressor.'" Prelim. Resp. 32–33 (quoting Ex. 1001, 5:45–47). Similarly, for protein stabilizer, Patent Owner argues that "a protein stabilizer must actually stabilize protein in the refold solution at the concentration used," such that "[i]f it does not 'change a protein's reaction equilibrium state, such that the native state of the protein is improved or favored,' it is not a protein stabilizer." *Id.* (quoting Ex. 1001, 5:54–57) (emphasis omitted).

We discern Patent Owner's argument to be that claim 9 requires the aggregation suppressor and protein stabilizer to be present in the refold buffer at concentrations necessary for the aggregation suppressor to suppress aggregation and for the protein stabilizer to stabilize protein interactions. We decline, however, to impose a concentration requirement on the constructions of "aggregation suppressor" and "protein stabilizer" based on the present record.

The '997 patent expressly sets forth the definitions of these terms in the written description. Specifically, the '997 patent states that, "[a]s used herein, the term 'aggregation suppressor' means any compound having the ability to disrupt and decrease or eliminate interactions between two or more proteins." Ex. 1001, 5:45–47. And as to "protein stabilizer," the '997 patent

similarly states that, "[a]s used herein, the term 'protein stabilizer' means any compound having the ability to change a protein's reaction equilibrium state, such that the native state of the protein is improved or favored." *Id.* at 5:54–57.

Because the written description expressly defines these terms, we find those definitions to govern, at least for our analysis in this Decision. *See Inventio AG v. ThyssenKrupp Elevator Americas Corp.*, 649 F.3d 1350, 1356–57 (Fed. Cir. 2011) (stating that express definitions of claim terms in the written description "govern the construction of the claims" (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005))), overruled on other grounds by *Williamson v. Citrix Online, LLC*, 792 F.3d 1339 (Fed. Cir. 2015).

3. *Dependent claims 14–19 and 23–27*

Claims 14–19 and 23–27 depend, directly or indirectly, from claim 9. Claim 9 recites a solubilization solution comprising "one or more of" (i) a denaturant, (ii) a reductant, and (iii) a surfactant, and a refold buffer comprising "one or more of" (i) a denaturant, (ii) an aggregation suppressor, (iii) a protein stabilizer, and (iv) a redox component. *Id.* at 22:39–50. Each of the dependent claims recite a particular kind of denaturant, reductant, surfactant, aggregation suppressor, protein stabilizer, or redox component. *Id.* at 22:66–23:22, 24:1–21. For example, claim 14 depends directly from claim 9, and recites "wherein the denaturant of the solubilization solution or the refold buffer comprises one or more of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea." *Id.* at 22:66–23:2.

Although not framed as a claim-construction issue, Petitioner contends that "because claim 9 recites the components of the solubilization

solution and refold buffer in the alternative," the dependent claims "under a plain reading . . . do not require use of one of the recited chemicals, so long as one of the alternative components recited in claim 9 is present in the solubilization solution or refold buffer." Pet. 13. Patent Owner responds that "these dependent claims should be construed to mean that the group member recited by the dependent claim *must* be present (and further limited as the dependent claim specifies), while *one or more (or none) of the other remaining members* of the independent claim's group may also be present." Prelim. Resp. 35.

We need not determine the precise scope of dependent claims 14–19 and 23–27 at this stage of the proceeding and for this Decision. Petitioner and Patent Owner are requested to address further in Patent Owner's Response and Petitioner's Reply whether those dependent claims require use of one of the recited chemicals. We offer the following observations, based on the present record, to help guide the parties' briefing on this issue.

Taking claim 16 as an example, it appears that the plain language of claim 16 limits the "surfactant" of claim 9 by specifying that the surfactant comprises at least one of sarcosyl and sodium dodecylsulfate. Claim 16, however, but does not appear to narrow the scope of the "solubilization solution" of claim 9, because claim 16's plain language does not expressly require the solubilization solution to include *any* surfactant. *See* Ex. 1001, 23:6–7. In this regard, claim 16 does not state that the solubilization solution of claim 9 comprises a surfactant, and the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate. Thus, as Petitioner observes, the plain language of claim 16 appears to encompass a solubilization solution comprising, e.g., only a denaturant. Pet. 13.

On the other hand—and as Patent Owner points out—this reading of claim 16 appears to ignore the prosecution history and, perhaps, how an ordinarily skilled artisan would understand claim 16. For example, during prosecution, both the applicant and the Examiner considered claim 16 to require the presence of a surfactant in the refold buffer. *See* Ex. 1033, 76–78 (applying new reference disclosing sodium dodecylsulfate to reject claim 16). The parties' briefing and arguments should keep in mind the appropriate burdens, and set forth the most applicable claim-construction canons and case law.

C. *The Prior Art*

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. *Wang (Ex. 1003)*

Wang relates to a "new protocol to recover active rhSCF [recombinant human stem cell factor] from inclusion bodies . . . for the production of rhSCF from *E. coli*." Ex. 1003, 182. Wang states that rhSCF is typically expressed in *E. coli*, but that the rhSCF protein "often forms insoluble and inactive inclusion bodies in *E. coli*." *Id.* "A general strategy for recovery of active rhSCF from inclusion bodies involves cell lysis, extraction and cleaning of inclusion bodies, solubilization of inclusion bodies, and refolding into its native conformation." *Id.* Wang states that, following solubilization, "the denatured protein is transferred into a nondenaturating environment to shift the folding equilibrium toward its native conformation," which "is normally achieved by removing the denaturants through dilution or dialysis." *Id.* This process, however, results in "refolding yields [that] are typically low." *Id.*

To obtain higher yields of refolded protein, Wang utilizes ion-exchange chromatography (IEC), a type of liquid chromatography (LC). *Id.* "The main advantage of the LC refolding method is that it not only prevents the unfolded protein molecules from aggregating with each other but also simultaneously purifies or partially purifies the protein during the chromatographic process." *Id.* Wang states that, "[i]n the presented work, high pH buffers were used to solubilize rhSCF expressed in *E. coli* as inclusion bodies; the high pH buffer component and the solubilization conditions were optimized, then the solubilized rhSCF was refolded by dilution, dialysis, and IEC, respectively, and the refolding results were compared with the urea solubilized rhSCF." *Id.* Wang reports that "rhSCF solubilized by high pH solution containing low concentration of urea is easier to be renatured than that solubilized by high concentration of urea, and the IEC refolding method was more efficient than dilution refolding and dialysis refolding for rhSCF." *Id.* at 181. Wang states that the IEC refolding method "may have great potential for large-scale production of rhSCF." *Id.*

2. *Cutler (Ex. 1028)*

Cutler provides an overview of, and methods for, ion-exchange chromatography, "one of the most widely used forms of column chromatography." Ex. 1028, 125. In a protocol for IEC, Cutler teaches applying a sample to an ion-exchange column, washing the column with binding buffer "to ensure that all nonbound proteins are washed out of the column," eluting bound proteins "by washing the column with an increasing salt gradient," collecting the eluted protein in fractions, and determining in which fractions "the protein of interest has been isolated and whether contaminants have coeluted." *Id.* at 129.

3. *Reardon (Ex. 1004)*

Reardon relates to methods for the large-scale production of fibroblast growth factor 18 ("FGF18") from *E. coli*. Ex. 1004, code (57) (Abstract). In one embodiment, a method for "isolating insoluble FGF18" comprises collecting inclusion bodies, dissolving the insoluble protein in a chaotropic solvent, diluting the chaotropic solvent by adding a refolding buffer, isolating the protein by filtration, and purifying the refolded FGF18 protein on a cation-exchange column. *Id.* ¶ 14.

4. *Dietrich (Ex. 1005)*

Dietrich relates to methods for purifying recombinant granulocyte-colony stimulating factor ("G-CSF") using cation exchange chromatography and hydrophobic interaction chromatography, "wherein [the] two chromatographic steps are immediately consecutive in optional order." Ex. 1005, code (57) (Abstract).

Dietrich states that "a frequently occurring problem in the production of recombinant proteins" such as G-CSF in *E. coli* is "the formation of hardly soluble intracellular aggregates of denatured forms of the protein expressed, the so-called inclusion bodies." *Id.* ¶ 5. According to Dietrich, the disclosed method provides for the purification of G-CSF "with satisfactory purity and yield," but "with as few chromatographic steps as possible in order to keep technical complexity and costs on a low level." *Id.* ¶ 13.

In the examples, Dietrich teaches a solubilization step wherein the inclusion bodies containing G-CSF were solubilized in solubilization buffer containing 30 mM Tris, 1 mM EDTA, 6.0 M guanidine-HCl, 100 mM GSH (glutathione), pH 8.0. *Id.* ¶ 68. Next, Dietrich teaches forming a refolding

solution comprising the solubilization buffer and a refolding buffer, the refolding buffer containing 30 mM Tris, 2 mM GSSG (glutathione disulfide), 2 mM GSH, and 3 M urea at pH 7.5. *Id.* ¶ 69. Dietrich teaches filtering the refolding solution after refolding and "before the first chromatographic step." *Id.* ¶ 70. Dietrich teaches, in a first chromatographic step, applying the filtered solution to a cation exchange chromatography column SP Sepharose XL matrix, washing the column with sodium acetate, and subsequently eluting G-CSF with an elution buffer of 20 mM sodium acetate and 200 mM NaCl, pH 5.0. *Id.* ¶¶ 71–72.

Dietrich teaches that second and third chromatography steps provide for the further purification of G-CSF. Specifically, the second step involves hydrophobic interaction chromatography, *id.* ¶¶ 73–76, and the third step involves a second cation exchange chromatography, *id.* ¶¶ 77–81.

5. Komath '944 (Ex. 1006)

Komath '944 relates to "[a] a novel process for large scale purification of therapeutic grade quality of recombinant human G-CSF from microbial cells, wherein the protein is expressed as inclusion bodies." Ex. 1006, code (57). According to Komath '944, the process "involves the novel use of Hydrophobic Interaction Chromatography (HIC) step to purify G-CSF eluted from a cation exchange column." *Id.* Komath '944 states that the isolation and purification process comprises "isolating inclusion bodies containing G-CSF from microbial cells," "solubilizing said G-CSF protein from isolated inclusion bodies," "refolding the said solubilized G-CSF protein to obtain active folded protein," and "subjecting the said refolded G-CSF protein to two step chromatography wherein the said refolded G-CSF

protein is first subjected to cation exchange chromatography followed by hydrophobic interaction chromatography." *Id.* at 4–5.[4]

6. *Komath '056 (Ex. 1007)*

Komath '056 relates to "[a] simple, economic and scalable process for the purification of recombinant human G-CSF expressed in *E.coli*." Ex. 1007, code (57). According to Komath '056, hG-CSF was purified "by a simple three step procedure involving lysis of the cells, washing of inclusion bodies and ion exchange chromatography." *Id.* at 8. As to the washing step, Komath '056 states that "[t]he final washed [inclusion body] pellet . . . is essentially free of endotoxins, host cell proteins and host DNA," and "ready to be solubilized, refolded into native form and concentrated by ion exchange chromatography." *Id.* Komath '056 states that the washed inclusion-body pellet "is solubilized using a combination of a denaturant and high alkaline pH." *Id.* at 9. In one example, the washed inclusion body pellet "is solubilized with urea at concentrations ranging from 2M to 6M." *Id.* at 11. Table 1 of Komath '056 presents the "percentage recovery of the protein with various sodium chloride concentrations." *Id.* Table 1 shows that, at 25 mM and 50 mM of NaCl, no elution was observed, and at 100 mM, 250 mM, and 500 mM, less than 1% recovery of the protein was observed. *Id.* at 12 (Table 1).

D. *Printed Publication Status of Certain References*

Patent Owner argues that the Petition should be denied because it fails to establish that Wang, Cutler, and several other references (i.e., Exhibits

[4] For clarity, we refer to page numbers in the original document, rather than the page numbers added by Petitioner.

1008–1012, 1014–1021, 1027–1028, 1031, and 1036–1038) qualify as prior-art printed publications. Prelim. Resp. 38–39, 60–61.

At the institution stage, the Board has required the petitioner to make a "threshold showing" that any reference relied upon was publicly accessible before the effective filing date of the challenged patent. *See, e.g.*, *Frontier Therapeutics, LLC v. Medac Gesellschaft Für Klinische Spezialpräparate mbH*, IPR2016-00649, Paper 10 at 22 (PTAB Sept. 1, 2016) (denying institution upon finding that petitioner failed to make a threshold showing that an alleged "printed package insert" was a printed publication); *Instradent USA, Inc. v. Nobel Biocare Servs. AG*, IPR2015-01786, Paper 14 at 16–17 (PTAB Feb. 19, 2016) (finding that deposition testimony from the challenged patent's co-inventor stating that hundreds of copies of a catalog may have been printed and distributed to customers was sufficient to make a threshold showing of public accessibility). Upon review of the evidence and arguments in the current record, we are persuaded that Petitioner has made the requisite threshold showing.

Wang, on its face, appears to be a scientific article published in the journal *Applied Biochemistry and Biotechnology*. Ex. 1003, 181. As with most scientific articles, the publication year is included as part of the citation itself: "*Appl Biochem Biotechnol* (2008), 144:181–189." *Id.* Moreover, the face of the journal article indicates that the authors submitted the article for review on June 14, 2007, and that the article was accepted on November 21, 2007 and published online on January 5, 2008. *Id.* These indicia are conventional markers that, in this case, signal that Wang was published in early 2008, at least one year before the earliest-possible priority date of June 25, 2009, for the '997 patent. *See* Ex. 1001, code (60). Similarly, Cutler, on

its face, appears to be an excerpt from *Methods in Molecular Biology*, a well-known laboratory manual having a copyright date of 2004. *See* Ex. 1028; *see also* Ex. 1002 ¶ 137. Although we acknowledge that a copyright date is not always probative of publication, we find this indicia sufficient—based on the present record—to signal that Cutler was published in 2004.

Because we find that Petitioner has made a sufficient threshold showing that Wang and Cutler qualify as prior-art printed publications for institution, and because institution is an all-or-nothing decision, we will make our determination as to whether Petitioner has satisfied its burden of proving public accessibility of the relevant challenged references in our final written decision based on the entire record. Thus, to the extent Patent Owner continues to challenge the printed-publication status of these references after institution, the parties are requested to further develop the record on this issue.

E. *Asserted Anticipation by Wang*

Petitioner contends that Wang anticipates claims 9, 10, 13–21, and 23–30 of the '997 patent. Pet. 20–31. A claim is anticipated, and therefore unpatentable under 35 U.S.C. § 102, if all its limitations are disclosed either explicitly or inherently in a single prior art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all the limitations of the claim "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

Petitioner contends that Wang teaches the preamble of claim 9, because Wang "discloses a method for purifying a protein, i.e.[,]

'[r]ecombinant human stem cell factor (rhSCF)' expressed in a non-native limited-solubility form, i.e.[,] inclusion bodies, in a non-mammalian expression system, i.e.[,] '*Escherichia coli*.'" Pet. 22 (citing Ex. 1003, 181; Ex. 1002 ¶ 98). Petitioner also contends that Wang teaches the method steps of claim 9, because Wang discloses solubilizing rhSCF inclusion bodies with urea, forming a refold solution comprising a refold buffer comprising Tris (an aggregation suppressor and protein stabilizer) and GSH and GSSG (redox components), applying the refold solution to a separation matrix (IEC), and washing the IEC column to elute the protein. *Id.* at 23–26 (citing Ex. 1003, 183–184, 187 (Table 1); Ex. 1002 ¶¶ 101, 103–105, 141–154, 165; Ex. 1001, 2:48–58, 2:60–65, 4:10–15, 14:44–58).

Having considered the arguments and evidence before us, we find that the record establishes a reasonable likelihood that Petitioner would prevail on its asserted ground of anticipation by Wang. As to the preamble ("method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system"), Wang discloses purifying a protein—recombinant human stem cell factor (rhSCF)—that is expressed as "insoluble and inactive inclusion bodies in *E. coli*." Ex. 1003, 182. Dr. Tessier testifies, and we agree, that *E. coli* is a well-known bacterial (or non-mammalian) expression system. *See* Ex. 1002 ¶ 141. As to the first method step ("solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant"), Wang teaches that the "rhSCF inclusion bodies were solubilized in 20 ml" of various solutions, including solution II containing Tris, disodium phosphate (Na_2HPO_4), and urea. *Id.* at 183–184. The present

record shows that urea is well known in the art as a denaturant. *See, e.g.*, Ex. 1001, 2:38–39, 4:35–37, 5:29–30, 13:49–51, 22:38–41; Ex. 1002 ¶ 142.

Turning to the second method step ("forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component"), we agree with Petitioner—on this record and for institution—that an ordinarily skilled artisan would have understood that Wang, in a section titled "Refolding of rhSCF by Dilution," describes forming a refold solution by diluting the solubilizing solution containing denatured rhSCF with a refold buffer containing Tris (pH 8.0), EDTA, GSH (reduced glutathione), and GSSG (oxidized glutathione). Ex. 1003, 182, 184; *see also* Pet. 20–21, 23–24.

We also agree with Petitioner—on this record and for institution—that an ordinarily skilled artisan would have understood that Wang's disclosure meets the claim language of "the refold buffer comprising one or more" of the selected ingredients, because: (1) Tris is a well-known buffer that stabilizes proteins and suppresses protein aggregation, *see* Ex. 1001, 2:43–60, 14:44–54 (the '997 patent listing Tris as an example of a protein stabilizer and as an example of an aggregation suppressor), Ex. 1002 ¶ 144 (testimony of Dr. Tessier that Tris is "a buffer that controls solution pH"); and (2) GSH and GSSH, together, form a glutathione redox agent, *see* Ex. 1001, 2:57–60 (the '997 patent describing "the redox component" as comprising "one or more of glutathione-reduced, glutathione-oxidized"); Ex. 1002 ¶ 143 (testimony of Dr. Tessier that GSH and GSSG form "a mixture that is commonly used as a redox agent").

We do not agree—on this record and for institution—with Patent Owner's argument that Petitioner fails "to clearly map Wang to the claim elements," and improperly "mix[es] and match[es]" various embodiments of Wang to achieve the limitations of claim 9. Prelim. Resp. 39–40. In the Petition, Petitioner describes Wang's experiments generally, Pet. 20–21, and explains that Wang's experiments compare three procedures used to refold and purify rhSCF: (1) simultaneous refolding and purification by direct injection of the sample solution into an IEC column, (2) refolding by dilution of the sample solution followed by IEC purification, and (3) refolding by dialysis of the sample solution followed by IEC purification. *See id.* at 21–22 (contending that "[t]he experiment in Wang also compares the results of a 'Refolding with Simultaneous Purification' method with two more traditional methods involving sequential solubilization, refolding, and purification steps" (emphases omitted)). In this regard, Petitioner identifies differences in the procedures Wang utilized to refold and purify rhSCF by section title (i.e., "Refolding of rhSCF by Dilution" and "Refolding with Simultaneous Purification of rhSCF by IEC") and by page, *id.* at 21 (emphases omitted) (citing Ex. 1004, 184). Petitioner then maps the limitations of claim 9 to Wang's teachings, and specifically maps claim 9's refolding and purification steps to Wang's second "refolding by dilution" experiment. *Id.* at 22–23 (contending that "Wang describes a process of refolding by dilution . . . ." and "Wang teaches that, for the refold by dilution method . . . ."). Thus, we find that Petitioner's presentation of this ground of unpatentability is sufficient for institution.

We also do not read certain limitations into claim 9 as Patent Owner suggests, for the reasons explained above in our claim construction analysis.

See supra § IV.B; *see also* Prelim. Resp. 40 (arguing that "Petitioners did not provide any analysis of Wang under the proper construction of 'protein stabilizer' or 'aggregation suppressor'"); *id.* at 42 (arguing that "Petitioners further failed to address the requirement that the 'refold buffer' under the correct construction must have a pH buffering capacity and provide conditions for the protein to refold into its biologically active form"). And, having considered the arguments and evidence before us, we are of the opinion that Patent Owner's arguments demonstrate that there are disputed genuine issues of material fact about how an ordinarily skilled artisan would have understood Wang's teachings; for example, whether an ordinarily skilled artisan would have understood $mmol \cdot l^{-1}$ Tris to be a protein stabilizer and/or an aggregation suppressor as recited in the claims, and whether Wang's Tris-EDTA-GSH-GSSG solution acts as a buffer. Dr. Tessier's testimony that skilled artisans would have understood that Tris is a "buffer that controls solution pH" and also acts as an aggregation suppressor and protein stabilizer is currently unrebutted and supported by the written description of the '997 patent. Ex. 1002 ¶ 144 (citing Ex. 1001, 2:57–60); *see also* 37 C.F.R. § 42.108(c) (requiring certain "genuine issue[s] of material fact" to "be viewed in the light most favorable to the petitioner . . . for purposes of deciding whether to institute an *inter partes* review").

Turning to method steps three ("applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix"), four ("washing the separation matrix"), and five ("eluting the protein from the separation matrix"), we are satisfied on this record that Wang teaches these limitations by disclosing that, in the "refolding by dilution" experiment, "after refolding, the rhSCF was purified by IEC."

Ex. 1003, 184. Although Wang does not elaborate in the "Refolding of rhSCF by Dilution" section the specific steps taken for IEC purification, Wang elsewhere states that chromatographic runs were performed by "directly inject[ing]" the sample solution into the IEC column, washing the column, and then eluting the protein. *Id.*; *see also* Pet. 23–26.

In summary, based on the record before us and the application of the reasonable likelihood standard, we are satisfied that Petitioner has shown sufficiently for instituting trial that it would prevail in showing claim 9 unpatentable for anticipation by Wang. And, having determined that Petitioner has met its burden under § 314(a) as to its challenge of claim 9 for anticipation by Wang, it is appropriate to institute *inter partes* review as to all claims challenged in the Petition, and on all grounds presented, pursuant to *SAS* and the USPTO Guidance. Thus, we also institute *inter partes* review of claims 10, 13–21, and 23–30 based on anticipation by Wang.

As noted above in our claim-construction analysis, however, we do not decide at this stage of the proceeding whether certain dependent claims require the solubilization solution of claim 9 to have the particular kind of reductant, surfactant, aggregation suppressor, protein stabilizer, or redox component recited in those dependent claims. We note that Wang does not teach a solubilization solution comprising a surfactant, and thus, under Patent Owner's construction, would not anticipate claims 16 and 24. *See supra* § IV.B.3. Again, the parties are requested to fully brief the scope of the dependent claims during trial.

F. *Asserted obviousness over Wang in view of Cutler*

Petitioner contends that claims 9, 10, 13–21, and 23–30 of the '997 patent would have been obvious over Wang in view of Cutler. Pet. 31–32.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007).

Having determined that Petitioner has met its burden under § 314(a) as to its challenge of claim 9 for anticipation by Wang, it is appropriate to also institute *inter partes* review of claims 9, 10, 13–21, and 23–30 based on obviousness over Wang and Cutler pursuant to *SAS* and the USPTO Guidance, notwithstanding Patent Owner's argument that Petitioner's analysis is conclusory. *See* Prelim. Resp. 43–45.

We acknowledge Patent Owner's argument that Petitioner has "failed to explain why the [ordinarily skilled artisan] would be motivated to make any proposed modification" in Wang. Prelim. Resp. 44. But we observe at this stage of the proceeding that Petitioner appears to contend only that an ordinarily skilled artisan would look to Cutler for specific instructions on how to perform the IEC purification used in Wang's "refolding by dilution" experiment. Pet. 31. Specifically, Petitioner contends that, "should [Patent Owner] contend that a [ordinarily skilled artisan] reading Wang would not have understood each of the steps of purifying a protein by IEC to be disclosed, such a [ordinarily skilled artisan] would have looked to a standard reference on protein purification such as Cutler." *Id.* This issue—i.e., whether an ordinarily skilled artisan would have looked to Cutler for the teachings arguably missing from Wang—is one best resolved following trial with the benefit of a full evidentiary record.

G. *Asserted anticipation by Reardon or by Dietrich*

Petitioner contends that each of Reardon and Dietrich anticipates claims 9, 10, 13–21, and 23–30 of the '997 patent. Pet. 33–48. Again, in light of *SAS* and USPTO Guidance, we institute an *inter partes* review on the ground of anticipation by Reardon and on the ground of anticipation by Dietrich, for all challenged claims.

Before leaving these grounds, however, we briefly address Patent Owner's arguments that neither Reardon nor Dietrich discloses the claimed limitation of "applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix," because both references disclose adjusting the pH before applying the solution to the separation matrix. According to Patent Owner, adjusting the pH would cause precipitation of components out of solution. Prelim. Resp. 46, 48–49.

Petitioner asserts that Reardon satisfies this claim limitation by disclosing "dilution in a refold buffer comprising 50 mM Tris and 120 mM NaCl." Pet. 35 (citing Ex. 1004 ¶ 79; Ex. 1002 ¶ 177). And Petitioner contends that Dietrich discloses "applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix" by adjusting the pH of the refold solution and equilibrating the ion-exchange column before loading the refold solution onto the column. Pet. 43–44 (citing Ex. 1004 ¶¶ 35–36, 70–72; Ex. 1002 ¶ 207). Relying on the Declaration of Dr. Tessier, Petitioner contends that an ordinarily skilled artisan "would have understood that the purpose of such steps was to optimize the condition for proteins to bind to the separation matrix." *Id.* at 44 (citing Ex. 1002 ¶ 207).

We understand Patent Owner's argument to be that, because the pH adjustment would precipitate components out of solution, neither Reardon nor Dietrich teaches applying the claimed "refold solution"—which comprises at least "one or more of" a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component—to the separation matrix. At this stage of the proceeding, however, Patent Owner points to no evidentiary support for that argument. We also observe that Patent Owner has yet to submit expert testimony supporting its attorney arguments as to the ordinarily skilled artisan's understanding of the teachings of Reardon and Dietrich. *See* Prelim. Resp. 34–40. Thus, we again determine that these issues are best resolved following trial with the benefit of a full record. *See* 37 C.F.R. § 42.65(a) (opinion testimony that does not disclose underlying facts "is entitled to little or no weight").

H. *Asserted obviousness over Komath '944 and Komath '056*

Petitioner contends that claims 9, 10, 13–21, and 23–30 of the '997 patent would have been obvious over the combination of Komath '944 and Komath '056. Pet. 48–58. Specifically, Petitioner contends that Komath '944 teaches each and every limitation of claim 9, except for the components of the refold buffer. *See id.* at 48–49 (citing Ex. 1006, 8; Ex. 1002 ¶ 227). Petitioner contends that Komath '056 makes up for this omission by "specifically disclos[ing] forming a refold solution by diluting the solubilization solution with 0.1% polysorbate 20—an aggregation suppressor." *Id.* at 49 (citing Ex. 1007, 9, 11; Ex. 1002 ¶ 228). Petitioner contends that an ordinarily skilled artisan would have been motivated to combine the teachings of Komath '944 and Komath '056 because, *inter alia*, Komath '944 "cites to Komath '056 and teaches that it 'addressed most of

the limitations of lengthy processes described in scientific literature.'" *Id.* at 49 (quoting Ex. 1006, 1–2).

Again, in light of *SAS* and USPTO Guidance, we institute an *inter partes* review on the ground of obviousness over Komath '944 and Komath '056, for all challenged claims. Both Komath '944 and Komath '056 disclose methods for purifying recombinant human G-CSF in *E. coli* expressed as inclusion bodies. Ex. 1006, code (57); Ex. 1007, code (57). As to the limitations of claim 9, for example, Komath '944 teaches that the isolation and purification process comprises "isolating inclusion bodies containing G-CSF from microbial cells," "solubilizing said G-CSF protein from isolated inclusion bodies," "refolding the said solubilized G-CSF protein to obtain active folded protein," and "subjecting the said refolded G-CSF protein to two step chromatography wherein the said refolded G-CSF protein is first subjected to cation exchange chromatography followed by hydrophobic interaction chromatography." Ex. 1006, 4–5. Komath '944 states that, for the refolding step, "[t]he pH of the refolded protein solution is maintained in the range of 3.5 to 5.5 using any appropriate buffer suitable for maintaining pH in the acidic range." *Id.* at 8. Komath '056 specifies that an appropriate refold buffer comprises 0.1% polysorbate 20. Ex. 1007, 9 ("The protein solution is diluted further with 0.1 % polysorbate 20 for refolding.").

We offer the following observations on Patent Owner's arguments that Petitioner has failed to show a reasonable likelihood of prevailing on its ground of unpatentability based on Komath '944 and Komath '056. *See* Prelim. Resp. 50–60 (emphases omitted). First, similarly to its argument with respect to the ground of unpatentability based on Wang in view of

Cutler, Patent Owner argues that Petitioner has "failed to explain why and how a[n] [ordinarily skilled artisan] would have modified Komath '944." *Id.* at 52. We observe at this stage of the proceeding, however, that Petitioner appears to contend that an ordinarily skilled artisan would look to Komath '056 only for specific information about the components of the refold buffer. Pet. 48–49. Specifically, Petitioner relies on Komath '056 for teaching a refold buffer comprising polysorbate 20. *Id.*

For example, although we agree with Patent Owner that Komath '056 does not appear to disclose "what, if anything, is added to the solution to achieve a pH of 8.0–8.5, what is added to the solution to achieve a pH of 4.0–5.0," Prelim. Resp. 55, claim 9 also fails to identify the same. Instead, claim 9 recites that the refold buffer need only comprise "one or more of" (i) a denaturant, (ii) an aggregation suppressor, (iii) a protein stabilizer, and (iv) a redox component. Ex. 1001, 22:39–50. And, as Petitioner points out, the '997 patent lists polysorbate 20 as an aggregation suppressor. Pet. 52 (citing Ex. 1001, 5:45–53). Thus, we agree with Petitioner—on this record and for institution—that Komath '056's refold buffer meets the requirements of claim 9.

Second, Patent Owner acknowledges that Komath '944 teaches that the refolded G-CSF protein is "suitable for direct loading on a cation exchange column." Prelim. Resp. 56 (quoting Pet. 52). But Patent Owner appears to argue that Komath '056 teaches away from direct application because "Komath '056 does not disclose using the ion exchange column to purify the protein." *Id.* (emphasis omitted). As an initial matter, we observe that Patent Owner has yet to submit expert testimony supporting its attorney arguments as to the ordinarily skilled artisan's understanding of Komath

'056's teachings. Whether Komath '056's teaching that the inclusion body *pellet* is substantially free of endotoxins, host cell proteins, and host DNA necessarily means that the G-CSF *protein* is not purified using an ion exchange column presents an issue of fact best resolved following trial with the benefit of a full record. 37 C.F.R. § 42.65(a). Komath '056, for example, describes Example 4 as using ion-exchange chromatography "as a final polishing step for the protein." Ex. 1007, 12.

In any event, we note that the method of claim 9 recites the transitional term "comprising," indicating that additional method steps (such as additional purification steps) are encompassed within its scope. *See Solvay S.A. v. Honeywell Int'l Inc.*, 742 F.3d 998, 1005 (Fed. Cir. 2014) ("The well-established meaning of 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." (quotation omitted)). Thus, at this stage of the proceeding, even if the method of Komath '056 utilizes intermediate steps, we do not read claim 9 so narrowly as to exclude additional steps.

For these reasons, we do not find—at least on this record—that Patent Owner's arguments undermine Petitioner's showing of a reasonable likelihood of success.

V. CONCLUSION

After considering the arguments presented in the Petition and the Preliminary Response, as well as the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '997 patent is unpatentable. Thus, in accordance with *SAS* and USPTO Guidance, we institute an *inter partes* review of all challenged claims on all grounds set forth in the Petition. Our

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

VI. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 9, 10, 13–21, and 23–30 of U.S. Patent No. 9,643,997 B2 is instituted with respect to all grounds set forth in the Petition;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, an *inter partes* review of the '997 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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