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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.,
Petitioner,

v.

GLAXOSMITHKLINE BIOLOGICALS SA,
Patent Owner.

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Case IPR2018-01237
Patent No. 9,265,839 B2

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Before SHERIDAN K. SNEDDEN, JO-ANNE M. KOKOSKI, and RICHARD J. SMITH, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

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

## I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–10 of U.S. Patent No. 9,265,839 B2 (Ex. 1001, "the '839 patent"). Paper 1 ("Pet."). GlaxoSmithKline Biologicals SA ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). In its Preliminary Response, Patent Owner raised the issue of whether Petitioner identified all of the real parties-in-interest. Prelim. Resp. 17–24. Petitioner thereafter requested permission to file a reply to the Preliminary Response to address the real parties-in-interest issue. We granted Petitioner's request, allowing Petitioner to file a reply, and also allowing Patent Owner to file a sur-reply. Paper 9. Petitioner filed its reply (Paper 10, "Reply") accompanied by a Declaration of John T. Haines ("Haines Declaration," Ex. 1061), and Patent Owner filed its sur-reply (Paper 12, "Sur-Reply").

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the evidence and arguments presented in the Petition, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least claim 1 of the '839 patent is unpatentable. Accordingly, an *inter partes* review of all of the claims and all of the grounds presented in the Petition is hereby instituted.

In this Decision, we address all issues raised by the parties in the pre-trial briefing. Our factual findings and conclusions at this stage of the proceeding are based on the evidentiary record developed thus far. This is not a final decision as to the patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the record as fully developed during trial.

*A. Related Matters*

The parties represent that they are not aware of litigations involving the '839 patent. Pet. xii; Paper 4, 2.

The '839 patent is concurrently challenged in IPR2018-01234 by Petitioner on different grounds.

The '839 patent is a continuation of U.S. Patent Application No. 13/581,824, which issued as Patent No. 8,753,645. The '645 patent is concurrently challenged in IPR2018-01229 and IPR2018-01236 by Petitioner.

*B. The '839 patent*

The '839 patent describes a "[p]rocess for conjugation of bacterial saccharides including *Streptococcus pneumoniae and Haemophilus influenzae* saccharides by reductive amination[.] Ex. 1001, Abst. "Reductive amination involves two steps, (1) oxidation of the antigen, (2) reduction of the antigen and a carrier protein to form a conjugate." *Id.* at 1:43–45.

The oxidation step may involve reaction with periodate, which "may lead to size reduction." *Id.* at 46–47. However, according to the '839

patent, "using lower concentrations of periodate in the presence of low phosphate may lead to retention of size and/or the retention of epitopes." *Id.* at 51–53. In this regard, the claims of the '839 patent require "reacting the bacterial saccharide with 0.001–0.7 molar equivalents of periodate to form an activated bacterial saccharide." *Id.* at 26:32–44 (claim 1). The '839 patent discloses that the buffer used in this reaction step should not contain an amine group. *Id.* at 4:41–42. Suitable buffers include the "phosphate buffer, borate buffer, acetate buffer, carbonate buffer, maleate buffer and citrate buffer." *Id.* at *Id.* at 4:42–48.

The bacterial saccharide may be an *S. pneumoniae* capsular saccharide 6B. *Id.* at 5:1–33, 8:16–10:60.

The carrier protein used to form the conjugate may be "any peptide or protein." *Id.* at 6:28–30. Suitable carrier proteins include tetanus toxoid, fragment C of tetanus toxoid, diphtheria toxoid, CRM197, Pneumolysin, protein D, PhtD, PhtDE and N19." *Id.* at 7:4–9.

"Reducing agents which are suitable for use in the process of the invention include the cyanoborohydrides, such as sodium cyanoborohydride, borane-pyridine, or borohydride exchange resin." *Id.* at 12:7–10.

The '839 patent states that the inventors "have surprisingly found that using lower concentrations of periodate in the presence of low phosphate may lead to retention of size and/or the retention of epitopes." *Id.* at 1:51–53. The '839 patent further describes that "[t]reatment with periodate may lead to a reduction in the size of the bacterial saccharide (sizing effect)." *Id.* at 6:14–15. Additionally, the '839 patent states: "When low concentrations

of buffer . . . and low amounts of periodate are used, this may reduce the sizing effect described above." *Id*. at 8:11–13.

*C. Illustrative Claims*

Independent claim 1, reproduced below, is illustrative of the challenged claims:

> 1. A process for conjugating a bacterial saccharide and reducing the sizing effect on bacterial saccharide comprising the steps of
>
> a) reacting the bacterial saccharide with 0.001–0.7 molar equivalents of periodate to form an activated bacterial saccharide;
>
> b) mixing the activated bacterial saccharide with a carrier protein;
>
> c) reacting the activated bacterial saccharide and the carrier protein with a reducing agent to form a conjugate;
>
> wherein step a) occurs in a buffer which does not contain an amine group, and the buffer has a concentration between 1–100 mM and wherein the bacterial saccharide is *S. pneumoniae* capsular saccharide 6B.

Ex. 1001, 26:32–44.

*D. Evidence Relied Upon*

Petitioner relies upon the following prior art references:

Ex. 1005, Frasch, *Preparation of Bacterial Polysaccharide-Protein Conjugates: Analytical and Manufacturing Challenges*, 27 VACCINE 6468–70 (2009) ("Frasch").

Ex. 1006, Lees, et al., "Conjugation Chemistry," Pneumococcal Vaccines: The Impact of Conjugate Vaccine, Chap. 11, 163-74 (ASM Press, Washington, D.C., 2008) ("Lees")

Ex. 1007, Biemans et al., PCT Patent Application Publication No. WO 2009/000825 A2, published Dec. 31, 2008 ("Biemans" or "GSK 2009 PCT").

Ex. 1015, Anderson et al., U.S. Patent No. 4,902,506, issued Feb. 20, 1990 ("Anderson").

Ex. 1016, Kuo et al., U.S. Patent No. 5,565,204, issued Oct. 15, 1996 ("Kuo").

Petitioner also relies upon the Declaration of Fikri Avci, Ph.D. (Ex. 1009) to support its contentions.

*E. Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability (Pet. 5–6):

| Ground | Claims | Basis | References |
|---|---|---|---|
| 1 | 1–10 | § 103(a) | Anderson and Kuo |
| 2 | 1–10 | § 103(a) | Anderson, Kuo, Frasch and Lees |
| 3 | 4 | § 103(a) | Anderson, Kuo, Frasch, Lees, and GSK 2009 PCT |

## II. DISCUSSION

*A. Real Parties-in-Interest*

The statute governing *inter partes* review proceedings sets forth certain requirements for a petition, including that "the petition identif[y] all real parties in interest." 35 U.S.C. § 312(a)(2); *see also* 37 C.F.R. § 42.8(b)(1) (requirement to identify real parties-in-interest in mandatory notices). Pursuant to 35 U.S.C. § 312(a)(2) and 37 C.F.R. § 42.8(b)(1), Petitioner states that "[t]he real parties-in-interest are Petitioner Merck Sharp & Dohme Corp., and Merck & Co., Inc. (collectively, "Merck")." Pet. xii.

In its Preliminary Response, Patent Owner argues that Pfenex Inc. ("Pfenex") also qualifies as a real party-in-interest ("RPI") "due at least in part to its exclusive license to assist in developing a vaccine related to the claimed invention," and that Petitioner's failure to identify Pfenex as an RPI requires that we deny the Petition. Prelim. Resp. 17–24. Patent Owner relies on the recent decisions of our reviewing court in *Applications in Internet Time, LLC v. RPX Corp*., 897 F.3d 1336 (Fed. Cir. 2018) ("*AIT*") and *Worlds Inc. v. Bungie, Inc*., 903 F.3d 1237 (Fed. Cir. 2018) ("*Worlds*"). *Id*. Patent Owner also cites to "publicly available information"[1] as showing that "Pfenex granted Merck an exclusive worldwide license to Pfenex Expression Technology™ *Pseudomonas*-based recombinant protein expression technology for the production of specific proteins to be used in the development of Merck's vaccine product." *Id.* at 20–21.

Petitioner bears the burden of persuasion regarding the real party-in-interest contention advanced by Patent Owner. *See Worlds*, 903 F.3d at 1241–42. .

*1. Petitioner's Arguments*

Petitioner's reply challenges the factual and legal bases for Patent Owner's contention that Pfenex should have been named as an RPI. Reply 1–5. Petitioner[2] states that, even if one were to accept Patent Owner's

[1] Patent Owner submits several web pages (Exs. 2003, 2004, 2007, 2008 and 2010), a journal article (Ex. 2005), a Statement of Claim from a Canadian legal proceeding (Ex. 2006), and a Pfenex Corporate Presentation (Ex. 2009).

[2] Both the Reply and Haines Declaration also refer to Petitioner as "Merck."

characterization of Pfenex's press releases and other evidence as true, they "show nothing more than that Pfenex has licensed certain technology to Merck for Merck to use in Merck's proposed V114 product." *Id.* at 1–2 (citing Patent Owner's Exhibits 2003, 2005, and 2007–2010). According to Petitioner:

> The RPI requirement should not be (and never has been before) expanded to capture all third parties who license technology to a petitioner, or who otherwise might indirectly derive revenue from the sale of a petitioner's proposed product. Such an impractical, overreaching rule would have the effect of ensnaring suppliers and contract research organizations with no connection to the Petition. It would also create unnecessary and unreasonable uncertainty as to which entities should be named as RPI.

*Id.* at 2. Petitioner further argues that the "heart" of an RPI inquiry involves two questions: whether a petition "has been filed at a nonparty's 'behest'" and whether a non-party "desires review of the patent." *Id.* (quoting *Applications in Internet Time*, 897 F.3d at 1351). Petitioner also explains that it did not file the Petition at the behest of Pfenex and that Pfenex has no reason to desire review of the '839 patent. *Id.* at 3–5.

According to the Haines Declaration, Petitioner has a proposed vaccine product (V114) for preventing pneumococcal disease, which is currently undergoing clinical trials, and contains a protein called CRM197. Ex. 1061 ¶ 3. The Haines Declaration indicates that Petitioner and Pfenex "have entered into a license to Pfenex Expression Technology™ that relates to a production strain capable of producing the CRM197 protein in Merck's

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Reply 1; Ex. 1061 ¶ 2.

proposed vaccine product." *Id.* ¶ 5. The Haines Declaration further states that "Pfenex's only role in Merck's proposed vaccine product is the licensing of this technology and related intellectual property to Merck. Pfenex has not been, and will not be, involved in making, using, offering to sell, selling or importing Merck's proposed vaccine product or any portion of that product," including the protein known as CRM197. *Id*. ¶ 6. Moreover, assuming FDA approval, Petitioner's proposed vaccine product and "the materials used to make it, including CRM197, will be manufactured and sold by Merck or other entities that do not include Pfenex." *Id*. ¶ 7.

Petitioner thus denies Patent Owner's contentions that "Petitioner and Pfenex are involved in making the clinical candidate V114 that contains 23F-CRM197" and are "similarly at risk of infringing" the '839 patent. Reply 1. Petitioner also submits a journal article[3] showing that carrier protein CRM197 was first disclosed 45 years ago. *Id.* at 5, n.4. Petitioner also argues, contrary to Patent Owner's allegation, that CRM197 is not covered by the claims of the challenged patent. *Id*. Petitioner further argues that "Merck and Pfenex have no similar common ownership, management overlap, or history of coordinating legal matters suggesting that Merck filed this Petition at Pfenex's behest." *Id.* at 4.

*2. Patent Owner's Arguments*

Patent Owner argues that, according to Petitioner's press release in 2009, "Pfenex granted Merck an exclusive worldwide license to Pfenex

[3] Uchida et al., *Diphtheria Toxin and Related Proteins,* 248 J. BIOLOGICAL CHEMISTRY 11, 3838–44 (1973). Ex. 1062.

Expression Technology™ *Pseudomonas*-based recombinant protein expression technology for the production of specific proteins to be used in the development of Merck's vaccine product." Prelim. Resp. 21 (citing Ex. 2003, 1). Patent Owner also argues that Merck paid Pfenex upfront licensing fees and milestone payments, and that Pfenex is entitled to royalty payments "on any product sales derived from the agreement." *Id.* at 22 (citing Ex. 2003, 1; Ex. 2010, 1). Patent Owner also contends that these facts satisfy the statement in *AIT* that the RPI inquiry involves "determining whether the non-party is a clear beneficiary that has a preexisting, established relationship with the petitioner." *Id.* at 19 (quoting *Applications in Internet Time*, 897 F.3d at 1351 (Patent Owner's emphasis omitted)).

Patent Owner further argues that the carrier protein CRM197 is covered by dependent claim 5 of the '839 patent. Prelim. Resp. 21–22. Petitioner also points to Canadian litigation involving Petitioner, and Petitioner's allegation that it "has a reasonable basis to believe that the manufacture, use, and/or sale of V114 in Canada will be impugned by [Patent Owner] as an infringement of" the Canadian counterpart of the '839 patent, and further argues that both Petitioner and Pfenex "are involved in making the clinical candidate V114 that contains 6B-CRM197" and are "similarly at risk of infringing" the '839 patent. Prelim. Resp. 23 (citing Ex. 2006 ¶ 18 and Ex. 2004, 1).

In its Sur-Reply, Patent Owner argues that the RPI inquiry "is not limited to entities that are subject to potential infringement liability with respect to a challenged patent," and that Petitioner "fails to establish why Pfenex should not be named as an RPI in view of its relationship with

Petitioner and Pfenex's potential to benefit from these IPR proceedings." Sur-Reply 1–2. Patent Owner reasserts that Pfenex has an established relationship with Petitioner, that Pfenex stands to benefit from Petitioner's IPRs, and that this satisfies "[t]he proper test for RPI." *Id.* at 3–5.

*3. Analysis*

On the record before us and for the reasons set forth below, we are persuaded that Petitioner has satisfied its burden of establishing that Pfenex is a real party-in-interest under 35 U.S.C. § 312(a)(2).[4]

"Determining whether a non-party is a 'real party in interest' demands a flexible approach that takes into account both equitable and practical considerations, with an eye toward determining whether the non-party is a clear beneficiary that has a preexisting, established relationship with the petitioner." *Applications in Internet Time*, 897 F.3d at 1351. Whether a particular entity is a real party-in-interest is a "highly fact-dependent question" that is assessed "on a case-by-case basis." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,759 (Aug. 14, 2012) (citing *Taylor v. Sturgell*, 553 U.S. 880, 893–95 (2008)). Although multiple factors may be relevant to the inquiry, "[a] common consideration is whether the non-party exercised or could have exercised control over a party's participation in a proceeding." *Id.* The two questions lying at the heart of the RPI inquiry

[4] Unlike *AIT* or *Worlds*, the RPI considerations in this case arise under 35 U.S.C. § 312(a)(2) rather than 35 U.S.C. § 315(b). The Director can allow the petitioner to add a real party in interest if a petition fails to identify all real parties in interest under Section 312(a)(2). *Wi-Fi One, LLC v. Broadcom Corp.*, 878 F.3d 1364, 1374 n.9 (Fed. Cir. 2018) (*en banc*).

are "whether a non-party 'desires review of the patent' and whether a petition has been filed at a non-party's 'behest.'" *Applications in Internet Time,* 897 F.3d at 1351 (quoting Trial Practice Guide, 77 Fed. Reg. at 48,759).

The present Petition relates to the question of whether claims directed to a "process for conjugating a bacterial saccharide and reducing the sizing effect on bacterial saccharide" are invalid under Sections 102 and/or 103. Paper 1. Although claim 5 refers to CRM197 as one of several carrier proteins that may be used in the process of claim 1, we agree with Petitioner that none of the claims at issue "cover" the protein identified as CRM197.

The evidence submitted by Petitioner establishes that Petitioner has a proposed vaccine product (V114) for preventing pneumococcal disease, which is currently undergoing clinical trials, and contains a protein called CRM197. Ex. 1061 ¶ 3. The evidence presented by Petitioner further establishes that, although Pfenex granted Merck a license to technology and intellectual property related to "a production strain capable of producing the CRM197 protein in Merck's proposed vaccine product[,]" . . . "Pfenex has not been, and will not be, involved in making, using, offering to sell, selling or importing Merck's proposed vaccine product or any portion of that product," including the protein known as CRM197. *Id*. ¶¶ 5–6. The information submitted by Patent Owner indicates that this license agreement was entered into prior to the filing of the application giving rise to the '839 patent, and included the payment of upfront licensing fees, milestone payment(s), and "royalty payments on any product sales derived from the

agreement." Prelim. Resp. 21–22. Petitioner does not dispute those contentions.

Patent Owner's contention that Pfenex is an RPI solely because Pfenex has a preexisting, established relationship with Petitioner and is a clear beneficiary of the Petition, is an insufficient reading of *AIT* and unavailing. *See Unified Patents, Inc. v. Realtime Adaptive Streaming, LLC*, IPR2018-00883 (PTAB Nov. 27, 2018 (Public Version)) (Paper 36, 14–15) ("We agree with Petitioner that Patent Owner is overextending the reasoning of *AIT*. The RPI analysis set out in *AIT* and the common law require more than simply confining the analysis to determining whether a party benefits generally from the filing of this Petition and also has a relationship with the Petitioner.").

Here, we agree with Petitioner that if the sole requirement for being named an RPI was as argued by Patent Owner, it would ensnare third parties, such as suppliers and contract research organizations, with no connection to the Petition.[5] Reply 2. Moreover, given the nature of the relationship with Pfenex, as established by Petitioner, Patent Owner's contention that Pfenex is a clear beneficiary of the Petition is seemingly based on assumptions and speculation that a negative outcome for Petitioner in challenging the validity of the '839 patent will result in depriving Pfenex

[5] If the RPI test were simply a preexisting relationship and benefit from a successful Petition, it might also ensnare shareholders of Petitioner. Such a result would not meet the practicality or equity considerations stated in *AIT*.

of the benefit of its license agreement with Petitioner. The record before us does not support such assumptions or speculation.

Petitioner has persuaded us that the nature of its relationship with Pfenex is such that Pfenex is not exercising, nor could it exercise, control over Petitioner's participation in the present *inter partes* review, that the Petition has not been filed at the behest of Pfenex, and that Pfenex does not desire review of the '839 patent. Accordingly, based on the entirety of the record before us at this stage of the proceeding, we find that Petitioner has persuasively established that Pfenex need not be named as an RPI in connection with the Petition.

*B. Person of Ordinary Skill in the Art*

Petitioner asserts that a person of ordinary skill in the art at the time of the invention would have would have had a Ph.D. degree in Biochemistry, Chemistry, or a comparable discipline, and at least 2–3 years of research experience focused on carbohydrate chemistry. Pet. 7 (citing Ex. 1009 ¶ 21).

At this stage of the proceeding, and absent opposition from Patent Owner, we adopt Petitioner's definition of the level of ordinary skill in the art. Moreover, the prior art itself is sufficient to demonstrate the level of skill in the art at the time of the invention. *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)).

*C. Claim Construction*

For petitions filed before November 13, 2018, we interpret the claims of an unexpired patent that will not expire before issuance of a final written decision using the broadest reasonable interpretation in light of the specification. *See* 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms that are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner proposes constructions for the terms "reducing the sizing effect," "molar equivalents," and "average molecular weight." Pet. 25–31. At this stage of the proceeding, Patent Owner disputes only Petitioner's construction of "reducing the sizing effect" and "average molecular weight." Prelim. Resp. 5–17. We address the parties proposed claim constructions below. Based on the record before us, we determine that no other claim terms require an explicit construction at this time.

We emphasize that the following constructions are preliminary and invite the parties to address them as necessary during trial.

*1. "reducing the sizing effect"*

Preamble language that merely states the purpose or intended use of an invention is generally not treated as limiting the scope of the claim. *See*

*Boehringer Ingelheim Vetmedica, Inc. v. Schering–Plough Corp*., 320 F.3d 1339, 1345 (Fed. Cir. 2003); *Rowe v. Dror*, 112 F.3d 473, 478 (Fed.Cir.1997). "In considering whether a preamble limits a claim, the preamble is analyzed to ascertain whether it states a necessary and defining aspect of the invention, or is simply an introduction to the general field of the claim." *On Demand Mach. Corp. v. Ingram Indus., Inc*., 442 F.3d 1331, 1343 (Fed. Cir. 2006), *cert. denied*, 549 U.S. 1054 (2006). For example, "preamble language merely extolling benefits or features of the claimed invention does not limit the claim scope without clear reliance on those benefits or features as patentably significant." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc*., 289 F.3d 801, 809 (Fed. Cir. 2002) (citations omitted).

A preamble may be limiting, however, if: "it recites essential structure or steps"; claims "depend[ ] on a particular disputed preamble phrase for antecedent basis"; the preamble "is essential to understand limitations or terms in the claim body"; the preamble "recit[es] additional structure or steps underscored as important by the specification"; or there was "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art." *Catalina Mktg*., 289 F.3d at 808.

Petitioner contends that the preamble phrase "reducing the sizing effect on bacterial saccharide" in claim 1 is not limiting. Pet. 1, 25–28. Petitioner argues that the body of claim 1 itself sets forth the steps required to practice the claimed process, and that those steps in and of themselves would lead to a reduction in the sizing effect. *Id.* at 25.

Patent Owner contends that "[t]he prosecution histories of both the '839 patent and the [related] '645 patent[6] illustrate that 'reducing the sizing effect' is not merely an intended purpose but an important characteristic of the claimed process." Prelim. Resp. 10. Patent Owner notes that during prosecution of the '839 patent, "Applicant argued that the claimed range of 0.001–0.7 molar equivalents of periodate was not obvious over the cited prior art because the claimed range 'has previously ***unexpected properties***' for the 6B saccharide, i.e., 'the saccharide[] [is] ***not reduced in size*** by the activation process.'" *Id.* at 10–11 (citing Ex. 2002, 508 (Response dated November 20, 2013) (emphases added)). Patent Owner further contends that the "reducing the sizing effect" language was added by Examiner Amendment, which accompanied the statement that, "***[i]n view of amendment to the claim 1*** and arguments of record, the rejection of claims 1, 2, 6, 14-6, 33, 46, 51, 62 and 67 . . . under 35 USC § 103 . . . is withdrawn.'" *Id.* at 12 (citing Ex. 2002, 519 (Notice of Allowance) (emphasis added)). Patent Owner also directs our attention to the Examiner's statement in the Notice of Allowance under the heading "Reasons for Allowance," which provides as follows:

> None of the prior art teaches or suggests the claimed process. The current process is drawn for not only conjugating *S. pneumoniae* capsular saccharide 23F or 6B by using 0.001–0.7 molar equivalents of periodate but also for reducing the [sizing effect][7] of the capsular saccharide by using low 0.001–0.7 molar equivalents of periodate.

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[6] U.S. Patent No. 8,753,645.

[7] The parties agree that the original language "reducing the size" was a

*Id*. at 11–12 (citing Ex. 2002, 520).

Anticipating Patent Owner's reliance on the Examiner's Reasons for Allowance, Petitioner contends that "[t]he Examiner's statement clearly demonstrates that 'reducing the sizing effect' is not an additional limitation because the Examiner recognized that the step needed to achieve such reduction, i.e., step a), was already recited in the claim body." Pet. 27. That is, "'reducing the sizing effect' is a result of using the 0.001–0.7 MEq of periodate of step a), which was already recited in the body of claim 1 before the addition of this claim term." *Id.* "Thus, "reducing the sizing effect" was included in the preamble for the same reasons that 'conjugating a bacterial saccharide' was—to state the purpose of the process." *Id.* at 28.

Upon consideration of the parties' positions and a review of the current record, we are persuaded by Petitioner that the preamble of claim 1 is non-limiting. Patent Owner relies on *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc*., 868 F.2d 1251 (Fed. Cir. 1989), where the Federal Circuit found that the preamble "optical waveguides" was limiting. Prelim. Resp. 8–9. The present case is distinguishable from *Corning*, however, because in concluding that the preamble was limiting, the court determined that "[t]he claim requires . . . the particular structural relationship defined in the specification for the core and cladding to function as an optical waveguide." *Corning*, 868 F.2d at 1257. That structural relationship was relevant when

typographical error made by the Examiner. Pet. 25, n.12; Prelim. Resp. 12, n.5.

distinguishing the claimed optical waveguides from "all types of optical fibers." *Id.*

In contrast to the preamble phrase in *Corning*, the preamble phrase "reducing the sizing effect" in this case is not defined structurally by the specification, but merely identifies the particular problem solved by the inventors of the '839 patent. While the '839 patent discloses that the inventors "surprisingly found" a way to achieve the "retention of size and/or the retention of epitopes," the '839 patent discloses also that this size reduction effect is accomplished by "using lower concentrations of periodate in the presence of low phosphate." Ex. 1001, 1:51–53. In this regard, the steps recited in the method of claim 1 set forth limitations for concentrations of both periodate and buffer. That is, "'reducing the sizing effect' is a result of using the 0.001–0.7 MEq of periodate of step a), which was already recited in the body of claim 1 before the addition of this claim term." Pet. 27.

Clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention. *See generally Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375, 58 USPQ2d 1508, 1513 (Fed.Cir.2001) (A preamble may limit when employed to distinguish a new use of a prior art apparatus or process.). In this regard, we acknowledge that the preamble phrase was added by Examiner's Amendment, but we are not persuaded that the language was added clearly for the purpose of distinguishing the claimed invention from the prior art. First, the

amendment was not limited to adding language to the preamble, but also deleted text from the body of the claim. Ex. 2002, 518. Second, the Examiner's Reasons for Allowance acknowledges that the purpose of the claims process is "for reducing the [sizing effect] of the capsular saccharide," which is achieved "by using low 0.001–0.7 molar equivalents of periodate." *Id.* at 519. On the current record, we are persuaded by Petitioner's argument that the Examiner's Reasons for Allowance suggests that "'reducing the sizing effect' was included in the preamble for the same reasons that 'conjugating a bacterial saccharide' was—to state the purpose of the process." *Id.* at 28. The language adds context and purpose, but does not otherwise limit the claim.

*2. "average molecular weight"*

A clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited. *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed.Cir.1993). However, when a "clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

Claim 4 recites "[t]he process of claim 1 wherein the average molecular weight of the bacterial saccharide is between 1–1100 kDa after step a)." (Ex. 1001, 26:50-52). Petitioner contends that the term "molecular weight" is non-limiting and merely reflects the "intended results that follow from practicing the claimed method." Pet. 30.

Patent Owner contends that "the only difference between claim 1 and claim 4 is that claim 4 further recites a range of post-activation and pre-conjugation 'average molecular weight' of 6B" and that "[t]his indicates that the recited molecular weight limitation represents a meaningful manipulative difference in the recited steps compared to claim 1." Prelim. Resp. 16 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) ("the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.")). Additionally, Patent Owner contends that "[t]he average molecular weight recited in claim 4 further limits the claim scope to cover certain activation conditions and certain levels of reduction of the sizing effect." Prelim. Resp. 17.

We are persuaded by Patent Owner's rationale, which we adopt as our own, that the wherein clause of claim 4 further limits independent claim 1. *Id.* at 16–17. We construe the term "average molecular weight," for the purposes of this Decision, to have the express definition set forth in the '839 patent, i.e., "the weight-average molecular weight (Mw) of the bacterial saccharide measured prior to conjugation and is measured by MALLS." Ex. 1001, 5:61-64;[8] *see Sinorgchem Co., Shandong v. Int'l Trade Comm'n*, 511

[8] We note that the terms "average molecular weight" and "weight-average molecular weight" are used synonymously in the '839 patent. *See* Ex. 1001, 5:61–64 ("The molecular weight or average molecular weight of a saccharide herein refers to the weight-average molecular weight (Mw) of the bacterial saccharide measured prior to conjugation and is measured by MALLS.").

F.3d 1132, 1138 (Fed. Cir. 2007) ("We have frequently found that a definition set forth in the specification governs the meaning of the claims.").

*3. "molar equivalents"*

Petitioner contends that the term "molar equivalents of periodate" should be construed to mean "the ratio of moles of periodate to the moles of saccharide repeating unit." Pet. 26. At this stage of the proceeding, for purposes of this decision, we adopt Petitioner's unopposed constructions.

### *D. Ground 1: Obviousness of Claims 1–10 over the Combination of Anderson and Kuo*

Petitioner asserts that claims 1–10 are unpatentable under § 103 as obvious over the combination of Anderson and Kuo. Pet. 31–49. Patent Owner does not substantively address Petitioner's unpatentability contentions.

Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–10 are unpatentable as obvious over the combination of Anderson and Kuo.

*1. Anderson*

Anderson discloses a reductive amination method for making conjugates of pneumococcal saccharides, including serotypes 3, 6A, 12, 14 and 23, and carrier proteins. Ex. 1015, 23:23–55. In particular, Anderson's Example 11 discloses a method for conjugating pneumococcal saccharide 6A by: (a) reacting 6A with 0.27 MEq of periodate, (b) mixing the activated 6A with diphtheria toxoid, a carrier protein, and (c) reacting the activated 6A

and carrier protein with the reducing agent sodium cyanoborohydride ($NaCNBH_3$) to form a conjugate. *Id.*

Anderson discloses using a buffer in other conjugation reactions, in particular, 0.2 M phosphate buffer. Ex. 1015, 20:1–5.

*2. Kuo*

Kuo discloses methods for making conjugates of an oxidized polysaccharide derived from the capsular polysaccharide of *S. pneumoniae*. and a protein carrier. Ex. 1016, 1:66–2:7. In particular, Kuo discloses that the bacterial saccharide may be *S. pneumoniae* capsular saccharide 6B. *Id.* at 4:40–42, 5:18–22.

Kuo's process using sodium periodate to activate the pneumococcal saccharides is summarized in the following excerpt:

> In its native form, the polysaccharides from pneumococcal organisms do not contain reactive reducing groups. In order to create each reactive polysaccharide containing reducing groups, the polysaccharide is partially hydrolyzed with controlled amounts of sodium periodate to produce reducing groups by cleavage of the cis-vicinal hydroxyl group of the polysaccharide by oxidizing with a periodate, to generate aldehyde functions following the process of Parikh, et al. (14). The purified pneumococcal polysaccharides are treated in the dark with 0.2-50 mM of sodium periodate at 4 ° C. or at room temperature for various lengths of time.

*Id.* at 4:26–39. Once activated, the oxidized polysaccharide is conjugated to a protein carrier using cyanoborohydride for reductive amination by conventional means. *Id.* at 5:5–17.

Example 3 of Kuo describes periodate activation of pneumococcal Type 14 polysaccharide using a 4 mg portion of sodium periodate and 0.1M

sodium acetate buffer (pH 5.0). *Id.* at 10:43–59. Example 5 of Kuo describes conjugation to a recombinant pneumolysin carrier protein using sodium cyanoborohydride. *Id.* at 11:20–39. Kuo also disclosed a similar method of periodate activation and conjugation for saccharide Type 18C. *Id.* at 10:65–11:15, 12:41–60 (Examples 4, 7).

*3. Analysis*

In support of its assertion that the combination of Anderson and Kuo renders claims 1–10 obvious, Petitioner sets forth the foregoing teachings of Anderson and Kuo and provides a detailed discussion explaining how each claim limitation is disclosed in the combination of references. Pet. 31–49. In particular, Petitioner contends that Anderson discloses methods for conjugating pneumococcal saccharides to carrier proteins. *Id.* at 33 (citing Ex. 1015, 23:23–43; Ex. 1009 ¶ 114). Regarding step a) of claim 1, Petitioner contends that Anderson's Example 11 is directed to pneumococcal saccharide 6A and discloses activation with periodate in the claimed range. *Id.* at 36–37. Specifically, Anderson teaches that saccharide 6A was activated with 0.27 MEq of periodate, which is within the claimed range. *Id.* (citing Ex. 1015, 23:36–55). Petitioner contends that "reducing the sizing effect" is the natural result of treating the bacterial saccharide with 0.001–0.7 MEq of periodate in 1–100 mM buffer. *Id.* at 33–36.

Regarding step b) and c) of claim 1, Petitioner contends that Anderson teaches that the activated 6A saccharide is reacted with a carrier protein, diphtheria toxoid, by mixing them together with a reducing agent to form a conjugate. *Id.* at 38 (citing Ex. 1015, 23:36–55; Ex. 1009 ¶¶ 126, 128).

Petitioner acknowledges a difference between the 6A saccharide disclosed by Anderson and the 6B saccharide required by the claims, but contends that the structure and periodate reactivity of 6A is nearly identical to that of 6B. *Id.* at 38–43; Ex. 1009 ¶¶ 132–136. Petitioner further relies on Kuo, which discloses that 6B saccharide can be used to make conjugates. *Id.* at 38 (citing Ex. 1016, 4:40–44, 5:18–21). Petitioner contends that a person of ordinary skill in the art would have been motivated to combine the teachings of Anderson and Kuo to make conjugates with a reasonable expectation of success because both Anderson and Kuo disclose methods of activating pneumococcal saccharides with periodate and conjugating them to carrier proteins using reductive amination. Pet. 41–42 (citing Ex. 1015, 23:23–55; Ex. 1016, 5:5–9; Ex. 1009 ¶ 140).

With regard to the recited buffer, Petitioner contends that Kuo discloses a method of making 6B conjugates involving periodate activation of saccharides in acetate buffer. Petitioner further contends as follows:

> periodate activations were routinely performed under buffered conditions to prevent pH changes during activation. POSAs were aware that amine-containing buffers should be avoided and used buffers in concentrations within the claimed range of 1–100 mM when activating pneumococcal saccharides. ([Ex. 1009] ¶ 138). In view of the knowledge in the art, POSAs would have been motivated to use Kuo's buffer (100 mM) to prevent pH changes during periodate activation in Anderson's method. ([Ex. 1009] ¶ 139).

Pet. 41–42. Petitioner contends that a person of ordinary skill in the art would have been

> aware of the benefit of using non-amine containing buffers, such as an acetate buffer, as used in Kuo, when performing periodate

> activation. ([Ex. 1009] ¶ 144). Therefore, POSAs would have reasonably expected that a non-amine containing buffer could be successfully used with Anderson's method. (*Id*.). Also, non-amine containing buffers at a concentration of 100 mM, such as those in Kuo, had been used to activate saccharides with periodate in amounts within the claimed range. (*Id*.). Thus, POSAs would have had a reasonable expectation of success in using Kuo's buffer, having the claimed features, in Anderson's method to achieve the claimed process. (*Id*., ¶¶ 144-145).

Pet. 42–43.

With regard to dependent claims 2–10, Petitioner provides a detailed discussion explaining how each claim limitation set forth in dependent claims 2–10 are disclosed in the combination of Anderson and Kuo. For purposes of this Decision, we agree with Petitioner's analyses of claims 2–10 and adopt it as our own.

Having considered the arguments and evidence set forth in the Petition, we are persuaded that Petitioner has shown sufficiently that each limitation of claims 1–10 is taught or suggested by the combination of Anderson and Kuo. Accordingly, we determine Petitioner has shown a reasonable likelihood of prevailing on its assertion that claims 1–10 are unpatentable as obvious over Anderson and Kuo.

### *E. Ground 2: Obviousness of Claims 1–10 over the Combination of Anderson, Kuo, Frasch, and Lees*

Petitioner asserts that claims 1–10 are unpatentable under § 103 as obvious over the combination of Anderson, Kuo, Frasch, and Lees. Pet. 49–59. Patent Owner does not substantively address Petitioner's unpatentability contentions.

Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–10 are unpatentable over the combination of Anderson, Kuo, Frasch, and Lees. We incorporate here our earlier findings and discussion regarding the disclosures of Anderson and Kuo.

*1. Frasch*

Frasch provides a review of the "[a]nalytical and manufacturing challenges" associated with the preparation of bacterial saccharide-protein conjugates. Ex. 1005, 6468 (title). Frasch discloses that "[o]ne important potential problem with use of periodate to activate the [polysaccharides ("PS")] is altering the physical structure of the PS, with loss of important epitopes." *Id.* at 6468–69). Frasch teaches the chemical mechanism for how this structural alteration occurs:

> Sodium periodate oxidizes diols (two adjacent carbons with hydroxyl groups) into aldehydes (C=O) and in the process breaks C-C bonds. Thus, depending upon the PS structure, periodate activation can fragment a PS and open the ring structure of sugars. When the diol is within a ring, the ring sugar is opened possibly altering the PS confirmation. When the diol is in a glycerol or ribitol side chain, the side chain disappears.

*Id.* at 6469.

Frasch further cautions that "[t]he chemistry to be used for PS activation must be carefully considered, because some activation methods can degrade the PS in addition to causing a size reduction." *Id.* at 6469. Frasch further explains that "[t]he size of the purified PS or oligosaccharide should be known, both before and after activation, because the activation chemistry may significantly reduce the size of the polysaccharide." *Id.*

*2. Lees*

Lees discloses that

> The capsular [polysaccharides ("PSs")], in their native forms, are known to be high-molecular-weight polymers, containing well over 1,000 repeat units. While the reduction of size prior to conjugation offers several advantages during conjugate manufacture (e.g., a marked reduction in viscosity and ease of separation of the conjugate from the free carbohydrate), it also entails extra steps and losses and can affect important epitopes.

Ex. 1006, 164. Lees discloses that, in order to form conjugates, "[t]he carbohydrate is first oxidized using sodium periodate to create aldehydes." *Id.* at 167. "[D]epending on where these hydroxyl groups are located on the sugar, oxidation can open up the ring and possibly cleave the polymer," thereby reducing the size reduction of the saccharide. *Id.* at 168. According to Lees, "[v]icinal [cis] hydroxyls are usually cleaved first, and at higher concentrations of periodate, trans hydroxyls are also cleaved." *Id.*

*3. Analysis*

Ground 2 is substantially similar to Ground 1. For this ground, Petitioner additionally relies on the disclosures of Frasch and Lees, summarized above. Pet. 49–59. In particular, Petitioner contends that Frasch discloses saccharide-protein conjugation using periodate as an oxidizing agent and further disclose that "periodate activation changes the saccharide structure and can lead to reduction in its size." *Id.* at 51; Ex. 1005, 6468–69. Petitioner contends "that using higher concentrations of periodate results in the cleavage of more, and different, hydroxyl groups, and thus a greater size reduction of the saccharide." *Id.* at 52 (citing Ex.

1006, 168. Thus, based on the disclosures of Frasch and Lees, Petitioner contends that "POSAs understood that (1) oxidation by periodate can lead to a reduction in the size of the saccharide, and (2) higher concentrations of periodate would lead to a greater reduction in size." *Id.* at 53 (citing Ex. 1009 ¶ 177).

Petitioner contends that Lees teaches that size reduction can affect important epitopes and that "[d]isruption of epitopes on the saccharide interferes with the immunogenicity of the conjugates or the immune system's ability to recognize the conjugates." *Id.* at 53 (citing Ex. 1006, 170 ("excessive modifications to the PS or protein molecules can have an adverse impact on immunogenicity")). Thus, "[c]are must be taken that critical epitopes are not lost or changed by the conjugation process." *Id.* (quoting Ex. 1006, 164).

Having considered the information set forth in the Petition, at this stage of the proceeding, we are persuaded that Petitioner's rationale and evidence establish that there is a reasonable likelihood that Petitioner would prevail in proving that claims 1–10 of the '829 patent are unpatentable over the combination of Anderson, Kuo, Frasch, and Lees.

### *F. Ground 3: Obviousness of Claim 4 over the Combination of Anderson, Kuo, Frasch, Lees, and GSK 2009 PCT*

Petitioner asserts that claim 4 is unpatentable under § 103 as obvious over the combination of Anderson, Kuo, Frasch, Lees, and GSK 2009 PCT. Pet. 59–62. Patent Owner does not substantively address Petitioner's unpatentability contentions.

Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claim 4 is unpatentable over the combination of Anderson, Kuo, Frasch, Lees, and GSK 2009 PCT. We incorporate here our earlier findings and discussion regarding the disclosures of Anderson, Kuo, Frasch, and Lees.

*1. GSK 2009 PCT*

GSK 2009 PCT discloses methods of preparing pneumococcal capsular saccharide-conjugate vaccines, including with periodate activation and reductive amination. Ex. 1007, 17:1–35. GSK 2009 PCT teaches that a carrier protein, such as diphtheria toxoid, is conjugated to pneumococcal saccharides, including 6B. *Id.* at 9:13–14, 10:12–17, 11:34–12:12, 21:28–22:12, 23:15–24:2, 54:28–55:1 (Table 1)).

GSK 2009 PCT discloses that the "present inventors have found that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease . . . In one embodiment, one or more saccharide conjugates of the invention should have an average size of saccharide pre-conjugation of 50–1600, 80–1400, 100–1000, 150–500 or 200–400 kDa." *Id.* at 14:23–33. GSK 2009 PCT discloses that the weight-average molecular weight of the saccharides are measured by MALLS. *Id.* at 15:32–16:6.

*2. Analysis*

Ground 3 is substantially similar to Grounds 1 and 2. For this ground, Petitioner additionally relies on the disclosures of GSK 2009 PCT, summarized above. Pet. 59–62. In particular, Petitioner contends that GSK

2009 PCT discloses that the saccharide that is to be conjugated should have a MW within the range recited in claim 4. *Id.* at 60 (citing Ex. 1007, 14:23–33). For purposes of this Decision, we agree with Petitioner's analysis of claim 4 and adopt it as our own.

At this stage of the proceeding, we are persuaded that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail with respect to claim 4.

## III. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood that it will succeed on at least one of its challenges to patentability. Under the Office's Guidance implementing *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018): "[a]t this time, if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." Guidance on the Impact of *SAS* on AIA Trial Proceedings ("Guidance"), available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial (April 26, 2018). Accordingly, we institute trial as to all claims and all grounds presented in the Petition.

## IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–10 of U.S. Patent No. 9,265,839 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '839 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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