Trials@uspto.gov
571.272.7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

GLAXOSMITHKLINE BIOLOGICALS SA,
Patent Owner.

Case IPR2018-01229
Patent No. 8,753,645 B2

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

SMITH, *Administrative Patent Judge*.

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

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–11 of U.S. Patent No. 8,753,645 B2 (the "'645 patent"). Paper 1 ("Pet."). GlaxoSmithKline Biologicals SA ("Patent Owner") filed a Preliminary Response to the Petition. 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. 18–24. 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 the Declaration of John T. Haines ("Haines Declaration," Ex. 1061), and Patent Owner filed its sur-reply (Paper 12, "Sur-Reply"). As discussed below, we conclude that the Petition need not be dismissed based on the real parties-in-interest argument advanced by Patent Owner.

We have authority under 35 U.S.C. § 314(a) to determine whether to institute an *inter partes* review. 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). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '645 patent. Therefore, we institute an *inter partes* review for claims 1–11 of the '645 patent.

A. Related Proceedings

Petitioner concurrently filed (1) another petition for *Inter Partes* Review against the '645 patent on other grounds [IPR2018-01236], and (2) petitions for *Inter Partes* Review of U.S. Patent No. 9,265,839 [IPR2018-01234 and IPR2018-01237]. Pet. xiii. U.S. Patent No. 9,265,839 is a continuation of U.S. Patent Application No. 13/581,824, which issued as the '645 patent. *Id.* Patent Owner indicates that it is unaware of any additional matters involving US Patent Nos. 8,753,645 or 9,265,839. Paper 4, 2.

B. The '645 Patent (Ex. 1001)

The '645 patent "relates to the conjugation of [bacterial] saccharides and proteins using reductive animation." Ex. 1001, 1:16–17. According to the '645 patent, reductive animation involves two steps: "(1) oxidation of the antigen, and (2) reduction of the antigen and a carrier protein to form a conjugate. The oxidation step may involve reaction with periodate, however oxidation by periodate may lead to size reduction." *Id*. at 1:41–45. The '645 patent further explains that "[t]reatment with periodate may lead to a reduction in the size of the bacterial saccharide (sizing effect)." *Id*. at 6:4–5.

The '645 patent states that "[t]he 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 1:49–51. The '645 patent describes an Example 1 with the heading "Oxidation of 23F and 6B Using Periodate." *Id*. at 19:44–20:35. The '645 patent further states that Table 1 and FIG. 1 **"**describe the results of these experiments. These demonstrate that for the 23F saccharide substantial sizing occurs on oxidation using high molar equivalents of periodate in 100 mM phosphate buffer. This sizing effect can be reduced by reducing the

concentration of phosphate buffer or the molar equivalents of periodate used." *Id*. at 19:64–20:2.

C. Illustrative Claims

Petitioner challenges claims 1–11 of the '645 patent. Claim 1 is reproduced below:

> **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 23F.

Ex. 1001, 27:2–16.

Claim 1 is the only independent claim, and claims 2–11 are directly or indirectly dependent on claim 1. *Id*. at 27:17–28:23.

Claims 4 and 5 read as follows:

> **4**. The process of claim **1** wherein the average molecular weight of the bacterial saccharide is between 1-1100 kDa after step a).

Id. at 27:22–24.

> **5**. The process of claim **1** wherein the average molecular weight of the 23F saccharide is between 100-470 kDa after step a).

Id. at 28:1–3.

D. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. §§ 102 and 103 based on the following grounds. Pet. 6.

Reference[s]	**Basis**	**Claims challenged**
WO'376[1]	§ 102(b)	1–11
WO'376, Frasch,[2] and Lees[3]	§ 103	1–11
WO'376, Frasch, Lees, and GSK 2009 PCT[4]	§103	4 and 5
WO'376, Frasch, Lees, and Prevnar[5]	§103	6
WO'376, Frasch, Lees, and GSK 2009 PCT	§103	10

Petitioner also relies on the Declaration of Fikri Avci, Ph.D. ("Avci Declaration" or "Decl."). Ex. 1009.

Patent Owner does not submit a declaration with its Preliminary Response. Other than arguing that the phrase "reducing the sizing effect" in the preamble of claim 1 is a limitation and that the term "average molecular

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[1] Chen et al., WO 2004/043376 A2, published May 27, 2004 ("WO'376"). Ex. 1004.
[2] C. Frasch, *Preparation of bacterial polysaccharide-protein conjugates: Analytical and manufacturing challenges*, Vaccine 27, 6468–70 (2009) ("Frasch"). Ex. 1005.
[3] A. Lees et al., *Conjugation Chemistry*, Chap. 11 *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*, 163–74 (2008) ("Lees"). Ex. 1006.
[4] Biemans et al., WO 2009/000825 A2, published Dec. 31, 2008 ("GSK 2009 PCT"). Ex. 1007.
[5] Prevnar®, *2009 Physicians' Desk Reference, 63rd ed.*, (2008) ("Prevnar"). Ex. 1008.

weight" recited in claims 4 and 5 is limiting, as addressed below, Patent Owner's Preliminary Response does not substantively address any of the validity challenges asserted by Petitioner.

II. ANALYSIS

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. xiii.

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. 18–24. 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"[6] that it contends shows that "Pfenex granted Merck an exclusive worldwide license to Pfenex Expression Technology™ *Pseudomonas*-based recombinant

[6] 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).

protein expression technology for the production of specific proteins to be used in the development of Merck's vaccine product." *Id.* at 22.

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.

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[7] states that, even if one were to accept Patent Owner's 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

[7] Both the Reply and Haines Declaration also refer to Petitioner as "Merck." Paper 10, 1; Decl. ¶ 2.

that it did not file the Petition at the behest of Pfenex and that Pfenex has no reason to desire review of the '645 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 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 '645 patent." Reply, 1. Petitioner also submits a journal article[8] 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 claim 6 of the '645 patent. *Id*. Petitioner further argues that

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

"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.

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 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. 22 (citing Ex. 2003, 1). Patent Owner also argues that Merck has paid Pfenex upfront licensing fees and milestone payments, and that Pfenex is entitled to royalty payments "on any product sales derived from the agreement." Prelim. Resp. 23 (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." Prelim. Resp. 20 (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 6 of the '645 patent. Prelim. Resp. 22–23. Patent Owner 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 '645 patent, and argues that both Petitioner and Pfenex "are involved in making the clinical candidate V114 that contains 23F-CRM197" and are "similarly

at risk of infringing" the '645 patent. Prelim. Resp. 24 (citing Ex. 2006 ¶ 18; 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.

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 need not be named as a real party-in-interest under 35 U.S.C. § 312(a)(2).[9]

"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*

[9] 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*).

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 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 6 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 '645 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. 22–23. 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 incomplete 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.[10] Reply 10, 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 '645 patent will result in depriving Pfenex

[10] 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 was not filed at the behest of Pfenex, and that Pfenex does not desire review of the '645 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 having ordinary skill in the art ("POSA"), as of March 9, 2010, "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. 6–7 (citing Ex. 1009 ¶ 21). Patent Owner does not respond to Petitioner's proposed POSA or set forth an alternative description.

For purposes of this Decision, and based on the current record, we adopt Petitioner's assessment, which appears to be consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *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, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

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

1. "reducing the sizing effect"

Petitioner contends that the preamble phrase "reducing the sizing effect on bacterial saccharide" in claim 1 is not limiting. Pet. 1, 23–26. 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 24–25.

Patent Owner contends that "[t]he prosecution history of the '645 patent illustrates that 'reducing the sizing effect' is not merely an intended purpose but an important characteristic of the claimed process." Prelim. Resp. 11. Patent Owner notes that during prosecution of the '645 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 23F saccharide, i.e., 'the saccharide[] [is] ***not reduced in size*** by the activation process.'" *Id.* at 11–12 (citing Ex. 1002, 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–[16], 33, 46, 51, 62 and 67 . . . under 35 USC § 103 . . . is withdrawn.'" *Id.* at 13 (citing Ex. 1002, 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[11]]** of the capsular saccharide by using low 0.001–0.7 molar equivalents of periodate.

Id. at 12–13 (citing Ex. 1002, 520 (emphases added)).

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. 26. That is, "'reducing the sizing effect' is a result of using the 0.001–0.7 MEq of

[11] The parties agree that the original language "reducing the size" was a typographical error made by the Examiner. Pet. 26, n.11; Prelim. Resp. 12–13, n.5.

periodate of step a), which was already recited in the body of claim 1 before the addition of this claim term." *Id.* (citing Ex. 1002, 519). "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." Pet. 26.

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.

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. 9–10. 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 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 '645 patent. While the '645 patent discloses that the inventors "surprisingly found" a way to achieve the "retention of size and/or the retention of epitopes," the '645 patent also discloses that this size reduction effect is accomplished by "using lower concentrations of periodate in the presence of low phosphate." Ex. 1001, 1:49–51. 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. 26.

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.). 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, that amendment was not limited to adding language to the preamble, but also deleted text from the body of the claim. Ex. 1002, 518. Second, the Examiner's Reasons for Allowance acknowledges that the purpose of the claimed 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." Pet. 26. The language adds context and purpose, but does not otherwise limit the claim.

2. "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. 27. At this stage of the proceeding, for purposes of this decision, we adopt Petitioner's unopposed construction.

3. "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 depends from claim 1 and further recites that "the average molecular weight of the bacterial saccharide is between 1-1100 kDa after step a)." Ex. 1001, 27:22–24. Claim 5, which also depends from claim 1, further recites that "the average molecular weight of the 23F saccharide is between 100-470 kDa after step a)." *Id.* at 28:1–3. Petitioner contends that the recitations of the molecular weights are non-limiting and merely reflect the "intended results that follow from practicing the claimed method." Pet. 29.

Patent Owner contends that "the only difference between claim 1 and claims 4 and 5 is that claims 4 and 5 further recite different ranges of post-activation and pre-conjugation 'average molecular weight' of 23F," and that "[t]his indicates that the recited molecular weight limitations represent meaningful manipulative differences in the recited steps compared to claim 1." Prelim. Resp. 16–17 (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 the "molecular weight range recited in claims 4 and 5 . . . 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, summarized above, that the wherein clauses of claims 4 and 5 further limit independent claim 1 and adopt it as our own at this stage of the proceeding. We construe the term "average molecular weight," for the purposes of this decision, to have the express definition set forth in the '645 patent, i.e., "the weight-average

molecular weight (Mw) of the bacterial saccharide measured prior to conjugation and is measured by MALLS." Ex. 1001, 5:53–55;[12] *see Sinorgchem Co., Shandong v. Int'l Trade Comm'n*, 511 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.").

4. Other Terms

We determine, for purposes of this Decision, that we need not expressly construe any undisputed terms. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy).

D. Principles of Law

"A single prior art reference that discloses, either expressly or inherently, each limitation of a claim invalidates that claim by anticipation. Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency. . . . Moreover, '[i]nherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics

[12] We note that the terms "average molecular weight" and "weight-average molecular weight" are used synonymously in the '645 patent. *See* Ex. 1001, 5:52–55 ("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.").

or functioning of the prior art.'" *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005) (internal citations omitted).

A patent 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). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

E. Anticipation by WO'376

Petitioner asserts that claims 1–11 of the '645 patent are unpatentable as anticipated by WO'376. Pet. 30–45.

1. WO '376 (Ex. 1004)

WO'376 describes polysaccharide-polypeptide conjugates for treating or preventing pneumococcal infection. Ex. 1004, Abstract. WO'376 describes an Example 4 titled "Preparation of Polysaccharide-Protein Conjugates." *Id.* at 23:22–27:25. Section A of Example 4 is titled "Oxidation of Polysaccharide" and Section D of Example 4 is titled

"Preparation of Polysaccharide-Protein Conjugates." *Id.* at 23:25–33 and 27:13–25.

Section A of Example 4 describes the addition of 1 mL of 0.2 M phosphate buffered saline (PBS) to pneumococcal capsular polysaccharides, such as 6B and 23F, dissolved in distilled water. *Id.* at 23:26–29. Section A further describes the oxidation of the polysaccharide with 2 mM sodium periodate. *Id*. at 23:29–30.

Section D of Example 4 describes the conjugation of *S. pneumoniae* polysaccharide to pseudopneumolysin protein by direct conjugation using a reductive animation assay. *Id.* at 27:14–18. Section D further describes that sodium cyanoborohydride was added to the oxidized polysaccharide and pseudopneumolysin mixture. *Id*. at 27:18–20. WO'376 further describes that polysaccharide-pseudopneumolysin protein conjugates, such as 23F and 6B, were prepared as described in Example 4 and tested for their ability to raise antibodies against polysaccharide and pneumolysin in mice. *Id.* at 27:28–30.

2. Analysis

Anticipation – claim 1

The Petition includes a limitation-by-limitation comparison of the disclosure of WO'376 to independent claim 1, including citations to the Avci Declaration as support. Pet. 30–40.

Petitioner argues that Example 4 of WO'376 discloses a conjugation process to prepare bacterial saccharide-protein conjugates, and that the preamble of claim 1 is non-limiting. *Id.* at 30–31. Petitioner further argues that, even if limiting, WO'376 inherently discloses "reducing the sizing effect" because it is the natural result of practicing step a) of claim 1, which Example 4 explicitly discloses. *Id.* at 31–34. As discussed above, we do not

find, at this stage of the proceeding, that the phrase "reducing the sizing effect" is a limitation of claim 1.

Petitioner explains that WO'376 discloses "that bacterial saccharide 23F was 'oxidized by reaction' with 0.31 MEq of periodate,[13] which is within the claimed range." *Id*. at 35. In particular, Petitioner shows how the disclosure in Example 4 allows for the calculation of MEq, and specifically the calculation that Example 4 discloses use 0.31 MEq of periodate. *Id.* at 35–36. Moreover, in addition to disclosing step a) of the process of claim 1, Petitioner explains that Example 4 discloses "wherein step a) occurs in a buffer which does not contain an amine group, and the buffer has a concentration between 1–100 mM." *Id*. at 37. In particular, Petitioner explains that PBS does not contain an amine group and that the amount of buffer used in Example 4 is calculated to be 0.1 M (100 mM). *Id*.

Regarding claim step b), Petitioner refers to section D of Example 4 as disclosing that pseudopneumolysin was added to the oxidized (activated) polysaccharide reaction mix, and the teaching of WO'376 that pseudopneumolysin is useful as a carrier of polysaccharides. *Id.* at 37–38 (citing Ex. 1004, 10:18).

Regarding claim step c), Petitioner points to the disclosure in Example 4 of the addition of sodium cyanoborohydride (a reducing agent as indicated in Ex. 1006, 168) to the oxidized polysaccharide (i.e. the activated bacterial saccharide) and pseudopneumolysin (i.e. carrier protein) mixture. *Id.* at 38–39. Petitioner also explains that the limitation "and wherein the bacterial

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[13] Petitioner construes the term "molar equivalents of periodate" as meaning "the ratio of moles of periodate to the moles of saccharide repeating unit." Pet. 27–28. Patent Owner does not contest this construction in its Preliminary Response.

saccharide is *S. pneumoniae* capsular saccharide 23 F" is disclosed by WO'376 because it specifically discloses a method of conjugating *S. pneumoniae* capsular saccharide 23F. *Id.* at 39–40.

At this stage of the proceeding, we have not made a final determination with respect to the patentability of claim 1 or the construction of any claim term. However, for the reasons articulated by Petitioner, and in light of the evidence currently of record, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claim 1 is anticipated by WO'376.

Anticipation – dependent claims

The Petition includes a limitation-by-limitation comparison of the disclosure of WO'376 to dependent claims 2, 3, and 6–11, including citations to the Avci Declaration as support. Pet. 40–45. As for claims 4 and 5, Petitioner relies on its contention that the recitations of the molecular weights are non-limiting. *Id.* at 40.

The Preliminary Response does not substantively address Petitioner's citations and arguments regarding dependent claims 2–11 beyond its claim construction arguments concerning claim 1 and dependent claims 4 and 5. Accordingly, based on our review of the parties' positions, the evidence of record, and our discussion of claim 1 above, we determine that at this stage of the proceeding the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that one or more of claims 2–11 are anticipated by WO'376.

F. Obviousness Challenges – Secondary Considerations

In connection with the following obviousness challenges, Petitioner argues that "[t]here is no probative evidence of secondary considerations."

Pet. 61–68. Patent Owner does not address this argument in its Preliminary Response.

Petitioner specifically argues that in view of the prior art disclosure of 0.8–1.2 MEq of periodate, Patent Owner erroneously argued that it had "discovered a new range of periodate with unexpected properties." *Id.* at 61 (citing Ex. 1002, IPR507). Petitioner challenges Patent Owner's assertion that Specification Example 1 "established that their claimed range of 0.001-0.7 molar equivalents has previously unexpected properties for the 23F and 6B saccharides, the saccharides are not reduced in size by the activation process." *Id.* (citing Ex. 1002, IPR507–508). Petitioner also challenges Patent Owner's argument that the saccharides conjugated with the claimed process unexpectedly "have been demonstrated to be highly immunogenic." *Id.* (citing Ex. 1002, IPR508).

Petitioner supports these contentions by arguing that the results set forth in Example 1 (1) do not cover the claimed range (i.e. are not commensurate in scope), and (2) are not "unexpected" and the claimed range is not critical. Pet. 61–64. Petitioner also argues that the experiments in Example 1 were not designed to show unexpected results and the allegedly "unexpected" results based on immunogenicity lack nexus. Pet. 64–68.

The issue of secondary considerations is highly fact-specific. At this stage of the proceeding, the record regarding such secondary considerations is incomplete. Our final decision will consider the parties' full record of secondary considerations evidence developed during trial as part of our obviousness analysis.

G. Obviousness in view of WO'376, Frasch, and Lees

Petitioner asserts that claims 1–11 of the '645 patent are unpatentable as obvious in view of WO'376, Frasch, and Lees, including citations to the Avci Declaration as support. Pet. 45–55.

Obviousness – Claim 1

Petitioner repeats its argument that WO'376 anticipates every limitation of claim 1. Pet. 45. Petitioner further asserts that "[t]he only recited language of claim 1 that WO'376 does not explicitly discuss is 'reducing the sizing effect' of the saccharide, which is not even a limitation, but that is the natural result of practicing the claimed process." *Id.* at 46. Petitioner further argues that "given a POSA's knowledge that periodate oxidation can decrease the size of the saccharide . . . 'reducing the sizing effect' would have been obvious." *Id.*

Petitioner asserts that Frasch and Lees teach persons of skill in the art to expect a reduction in sizing effect when following the steps of Example 4 of WO'376, that based on Frasch and Lees "it would have been obvious to POSAs that using lower concentrations of periodate . . . would reduce the sizing effect," and that Frasch and Lees "motivate[s] POSAs to reduce the sizing effect in order to preserve important epitopes for immunogenicity." *Id.* (citing Ex. 1009 ¶ 146); *see also id.* 47–53. Petitioner further argues that Frasch and Lees teach that persons of skill in the art would have a reasonable expectation of success in reducing the sizing effect by following the steps of WO'376 Example 4. *Id.* at 53–54.

Obviousness – Dependent claims

Petitioner argues that the limitations of claims 2–11 are anticipated by WO'376, and that "POSAs would have combined the teaching of WO'376 with Frasch and Lees with a reasonable expectation of success for the same

reasons set forth above with respect to claim 1. *Id.* at 54–55. Thus, as asserted by Petitioner, "claims 2–11 would also have been obvious over WO'376 in view of Frasch and Lees." *Id.* at 55.

Accordingly, for the reasons articulated by Petitioner, and in light of the evidence currently of record, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that one or more of claims 1–11 would have been obvious based on WO'376, Frasch, and Lees.

H. Obviousness in view of WO'376, Frasch, Lees, and GSK 2009 PCT

Petitioner asserts in Grounds III and V that claims 4, 5, and 10 of the '645 patent are unpatentable as obvious in view of WO'376, Frasch, Lees, and GSK 2009 PCT. Pet. 55–58 and 59–61.

Claims 4 and 5

Petitioner contends that claims 4 and 5 would have been obvious based on WO'376, Frasch, and Lees, and further in view of GSK 2009 PCT. Pet. 55–58.

Petitioner cites to the statement in GSK 2009 PCT that "[i]n 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 56 (citing Ex 1007, 14:30–32 (Petitioner's emphasis omitted)). Based on that statement, Petitioner contends that GSK 2009 PCT discloses that the saccharide that is to be conjugated should have a molecular weight within the ranges recited in claims 4 and 5. *Id.* at 56. Moreover, Petitioner contends that "the prior art, including GSK 2009 PCT, taught POSAs ways to obtain the pre-conjugation saccharide sizes recited in the claims," and that "based on the prior art, such as GSK 2009 PCT, POSAs knew of and would have been motivated to use

routine ways to obtain the pre-conjugation saccharide sizes recited in the claims with a reasonable expectation of success." *Id.* at 57 (citing Ex. 1009 ¶ 170).

Claim 10

Petitioner asserts that claim 10 is obvious over WO'376 in view of Lees and Frasch, and "is also obvious based on these references and further in view of GSK 2009 PCT." Pet. 60. Petitioner further asserts that GSK 2009 PCT states that its compositions containing the conjugates may also contain *S. pneumoniae* proteins as free or unconjugated proteins," and that "[t]hese proteins can be the ones recited in claim 10, *e.g.*, pneumolysin." *Id.* (citing Ex. 1007, 21:28–31 and 22:8–12). Petitioner further asserts that "POSAs would have been motivated to combine GSK 2009 PCT's *S. pneumoniae* proteins with the conjugates prepared by WO'376's method to arrive at claim 10 of the '645 patent, with a reasonable expectation of success in doing so." *Id.*

Accordingly, for the reasons articulated by Petitioner, and in light of the evidence currently of record, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that one or more of claims 4, 5, and 10 would have been obvious based on WO'376, Frasch, Lees, and GSK 2009 PCT.

I. Obviousness in view of WO'376, Frasch, Lees, and Prevnar

Petitioner asserts that claim 6 of the '645 patent is unpatentable as obvious in view of WO'376, Frasch, Lees, and Prevnar. Pet. 58–59.

Petitioner asserts that, in addition to being obvious based on WO'376 in view of Lees and Frasch, claim 6 is also obvious based on those references and further in view of Prevnar. Pet. 58. Petitioner further asserts

that "Prevnar discloses an FDA-licensed, commercially available vaccine that includes pneumococcal conjugates prepared by reductive amination (like those of WO'376)," and that Prevnar discloses "CRM197" as recited in claim 6 because "Prevnar teaches that a carrier protein, *e.g.*, CRM_{197}, is conjugated to its saccharides, including serotype 23F." Pet. 58–59 (citing Ex. 1008, 3241).

Petitioner also argues that a person of ordinary skill in the art would have been motivated "to use CRM_{197} as the carrier protein for the pneumolysin in WO'376's example to make the conjugates," and that "POSAs would have had a reasonable expectation of success in using CRM_{197} as the carrier protein in WO'376's method for making the 23-F protein conjugates." *Id.* at 59.

Accordingly, for the reasons articulated by Petitioner, and in light of the evidence currently of record, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claim 6 would have been obvious based on WO'376, Frasch, Lees, and Prevnar.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim of the '645 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–11 of the ’645 patent 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 ’645 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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PETITIONER:

Anthony Insogna
Nikolaos George
Gasper LaRosa
Lisamarie LoGiudice
Catharina Chin Eng
JONES DAY
aminsogna@jonesday.com
ncgeorge@jonesday.com
gjlarosa@jonesday.com
llogiudice@jonesday.com
cjchineng@jonesday.com

Arlene Chow
Ernest Yakob
HOGAN LOVELLS US LLP
arlene.chow@hoganlovells.com
ernest.yakob@hoganlovells.com

PATENT OWNER:

Charles E. Lipsey
Rich B. Racine
Joann M. Neth
Amanda Murphy
Yieyie Yang
Trenton Ward
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
charles.lipsey@finnegan.com
rich.racine@finnegan.com
joann.neth@finnegan.com
amanda.murphy@finnegan.com
yieyie.yang@finnegan.com
trenton.ward@finnegan.com