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BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner
v.
GLAXOSMITHKLINE BIOLOGICALS S.A.,
Patent Owner

CASE IPR: Unassigned

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 9,265,839

Claims 1-10

UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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TABLE OF ABBREVIATIONS

Board	Patent Trial and Appeal Board
CDAP	1-cyano-4-dimethylaminopyridinium tetrafluroborate
CRM	cross-reacting material
FDA	Food and Drug Administration
GSK	GlaxoSmithKline Biologicals S.A.
Hib	*Haemophilius influenzae* type b
MEq	molar equivalents
mM	millimolar
MW	molecular weight
PBS	phosphate buffered saline
Petitioner	Merck Sharp & Dohme Corp.
Pn	pneumococcal saccharide
POSA	person of ordinary skill in the art
PS	polysaccharide
RU	repeating unit
S. pneumoniae	*Streptococcus pneumoniae*
USPTO	United States Patent and Trademark Office
WHO	World Health Organization

EXHIBIT LIST

Exhibit No.	Description
1001	United States Patent No. 9,265,839 (Biemans, Duvivier & Gavard) ("'839 patent")
1002	Prosecution History of United States Patent No. 9,265,839 (USSN 14/202,119) ("'119 application")
1003	Prosecution History of PCT Patent Application No. PCT/EP2011/053400 (GlaxoSmithKline Biologicals S.A.) ("PCT application")
1004	PCT Patent Application Publication No. WO 2004/043376A2 (Chen, Chiou, Li & Chen) ("WO'376")
1005	Frasch, "Preparation of Bacterial Polysaccharide-Protein Conjugates: Analytical and Manufacturing Challenges," *Vaccine 27*, 6468-70 (2009) ("Frasch")
1006	Lees, et al., "Conjugation Chemistry," *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*, Chap. 11, 163-74 (ASM Press, Washington, D.C., 2008) ("Lees")
1007	PCT Patent Application Publication No. WO 2009/000825A2 (Biemans, Hermand & Poolman) ("GSK 2009 PCT")
1008	PREVNAR®, *2009 Physicians' Desk Reference*, 63rd ed., 3241-47 (Physicians' Desk Reference Inc., Montvale, N.J., 2008) ("Prevnar")
1009	Declaration of Fikri Avci in Support of Petition for *Inter Partes* Review of United States Patent No. 9,265,839 dated May 17, 2018 ("Avci Decl.")
1010	Cada, et al., "Pneumococcal 7-Valent Conjugate Vaccine," *Hosp. Pharm. 35*(7), 750-60 (2000) ("Cada")
1011	Kim, et al., "Determination of Saccharide Content in Pneumococcal Polysaccharides and Conjugate Vaccines by GC-MSD," *Anal. Biochem. 347*, 262-74 (2005) ("Kim 2005")
1012	PREVNAR® 13, *2011 Physicians' Desk Reference*, 3403-09, 65th ed. (PDR Network, LLC, Montvale, N.J., 2010) ("Prevnar 13")
1013	Emerson, "The Preparation of Amines by Reductive Alkylation," *Organic Reactions 4*, Chap. 3, 174-255 (Roger Adams, U.S.A., 1948)

Exhibit No.	Description
1014	Jennings, et al., "Immunochemistry of Groups A, B, and C Meningococcal Polysaccharide-Tetanus Toxoid Conjugates," *J. Immunol. 127*(3), 1011-18 (Sept. 1981)
1015	United States Patent No. 4,902,506 (Anderson & Eby) ("Anderson")
1016	United States Patent No. 5,565,204 (Kuo & Ree) ("Kuo")
1017	PCT Patent Application Publication No. WO 95/08348A1 (Lees) ("WO'348")
1018	World Health Organization, "Recommendations to Assure the Quality, Safety and Efficacy of Pneumococcal Conjugate Vaccines," Expert Comm. on Biological Standardization, Geneva, Switz. (October 19-23, 2009)
1019	Daum, et al., "Infant Immunization with Pneumococcal CRM_{197} Vaccines: Effect of Saccharide Size on Immunogenicity and Interactions with Simultaneously Administered Vaccines," *J. Infectious Diseases 176*, 445-55 (Aug. 1997)
1020	Steinhoff, et al., "A Randomized Comparison of Three Bivalent *Streptococcus Pneumoniae* Glycoprotein Conjugate Vaccines in Young Children: Effect of Polysaccharide Size and Linkage Characteristics," *Pediatr. Infect. Dis. J. 13*(5), 368-72 (1994)
1021	Vicini, et al., "Thermal Analysis and Characterisation of Cellulose Oxidised with Sodium Methaperiodate," *Thermochimica Acta 418*, 123-30 (2004)
1022	Kim, et al., "Monitoring Activation Sites on Polysaccharides by GC-MS," *Anal. Biochem. 358*, 136-42 (2006)
1023	United States Patent Application Publication No. US 2007/0141084 (Lee & Frasch) ("'084 U.S. Pub. Appln.")
1024	Lee, "Quality Control of Polyvalent Pneumococcal Polysaccharide-Protein Conjugate Vaccine by Nephelometry, *Biologicals 30*, 97-103 (2002) ("Lee (2002)")
1025	United States Patent No. 6,472,506 (Moreau & Mistretta) ("Moreau")

Exhibit No.	Description
1026	Great Britain Patent Application No. 1003922.0 (GlaxoSmithKline Biologicals S.A.) ("GB'922 appln.")
1027	United States Patent No. 8,753,645 (Biemans, Duvivier & Gavard) ("'645 patent")
1028	Prosecution History of United States Patent No. 8,753,645 (USSN 13/581,824) ("'824 application")
1029	United States Patent Application Publication No. US 2007/0184071 (Hausdorff, Siber, Paradiso & Prasad) ("Hausdorff")
1030	Higginbotham, et al., "Degradation of a Pneumococcal Type-Specific Polysaccharide with Exposure of Group-Specificity,' *Proc. Nat'l Acad. Sci. 67*(1), 138-42 (Sept. 1, 1970)
1031	Coico, et al., "Immunogens and Antigens," *Immunology, A Short Course*, 6th ed., Chap. 3, 29-39 (John Wiley & Sons, Inc., Hoboken, N.J., 2009)
1032	Kuo, et al., "Characterization of a Recombinant Pneumolysin and Its Use as a Protein Carrier for Pneumococcal Type 18C Conjugate Vaccines," *Infect. Immun. 63*(7), 2706-13 (July 1995)
1033	Sigma Catalog, *Biochemicals and Reagents for Life Science Research (2000-2001)* (Sigma-Aldrich Co., 2000)
1034	Intentionally Not Used
1035	Avci, et al., "Isolation of Carbohydrate-Specific $CD4^+$ T Cell Clones from Mice After Stimulation by Two Model Glycoconjugate Vaccines," *Nature Protocols 7*(12), 2180-92 (2012)
1036	Hakenbeck, et al., "Versatility of Choline Metabolism and Choline-Binding Proteins in *Streptococcus Pneumoniae* and Commensal Streptococci," *FEMS Microbiol. Rev. 33*, 572-86 (2009)
1037	Jones, "Vaccines Based on the Cell Surface Carbohydrates of Pathogenic Bacteria," *Annals Braz. Acad. Sci. 77*(2), 293-324 (2005)
1038	Geno, et al., "Pneumococcal Capsules and Their Types: Past, Present, and Future," *Clin. Microbiology Reviews 28*(3), 871-99 (July 2015)

Exhibit No.	Description
1039	Jennings, "Capsular Polysaccharides as Vaccine Candidates," *Current Topics in Microbiology & Immunology 150*, 97-127 (1990)
1040	Mäkelä, "Capsular Polysaccharide Vaccines Today," *Infection 12*, Suppl. 1, S72-75 (1984)
1041	Bobbitt, "Periodate Oxidation of Carbohydrates," *Advances in Carbohydrate Chemistry*, 1-41 (Academic Press Inc., New York, N.Y., 1956)
1042	Intentionally Not Used
1043	Intentionally Not Used
1044	Hermanson, *Bioconjugate Techniques*, 2nd ed., 129-31 (Elsevier Inc., Amsterdam, Netherlands, 2008)
1045	PNEUMOVAX® 23, *2009 Physicians' Desk Reference*, 63rd ed., 2078-80 (Physicians' Desk Reference Inc., Montvale, N.J., 2008) ("Prevnar")
1046	Lindstedt, "Periodate Oxidation of Sugars in Neutral Phosphate Buffer," *Nature 156*(3963), 448-49 (Oct. 13, 1945)
1047	Christian, "Stoichiometric Calculations," *Analytical Chemistry*, 5th ed., Chap. 3, 65-114 (John Wiley & Sons, Inc., U.S.A., 1994)
1048	Intentionally Not Used
1049	*Hawley's Condensed Chemical Dictionary*, 13th ed. (John Wiley & Sons, Inc., New York, N.Y., 1997)
1050	Zacharyczuk, *FDA Approves Prevnar 13; ACIP Issues Recommendations for Use*, Healio (Feb. 24, 2010), https://www.healio.com/pediatrics/vaccine-preventable-diseases/news/online/%7B65a93c76-5b34-45a8-98a3-54ff7da7ee05%7D/fda-approves-prevnar-13-acip-issues-recommendations-for-use
1051	Wessels, et al., "Structural Properties of Group B Streptococcal Type III Polysaccharide Conjugate Vaccines That Influence Immunogenicity and Efficacy," *Infection & Immunity 66*(5), 2186-92 (May 1998)
1052	Intentionally Not Used
1053	Determination of Regulatory Review Period for Purposes of Patent Extension; PREVNAR-13, 79 Fed. Reg. 18,035 (Mar. 31, 2014)

Exhibit No.	Description
1054	United States Patent No. 5,623,057 (Marburg, Tolman, Kniskern, Miller, Hagopian, Ip. Hennessey, Kubek & Burke)
1055	PCT Patent Application Publication No. WO 02/22168A2 (Hermand, LaFerriere, Lobet & Poolman)
1056	United States Patent Application Publication No. US 2009/0130137 (Hausdorff, Siber & Paradiso)
1057	Kenne, et al., "Structural Studies of the Capsular Antigen from *Streptococcus Pneumoniae* Type 26," *Carbohydrate Research 73*, 175-82 (1979)
1058	Leontein, et al., "Structural Studies of the Capsular Polysaccharide from *Streptococcus Pneumoniae* Type 12F," *Can. J. Chem. 59*, 2081-85 (1981)
1059	Carlson, et al., "Pneumococcal Vaccine: Dose, Revaccination, and Coadminstration with Influenza Vaccine (40596)," *Proc. of Soc. for Experimental Biology & Medicine 161*, 558-63 (1979)
1060	Declaration of Catharina J. Chin Eng dated May 16, 2018

37 C.F.R. § 42.8 MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

a. ***Real Party-In-Interest*** **(37 C.F.R. § 42.8(b)(1))**. The real parties-in-interest are Petitioner Merck Sharp & Dohme Corp., and Merck & Co., Inc. (collectively, "Merck"). Petitioner is not barred by operation of estoppel to submit this petition for *inter partes* review.

b. ***Related Matters*** **(37 C.F.R. § 42.8(b)(2))**. Petitioner is concurrently filing (1) another petition for *Inter Partes* Review against the '839 patent on other grounds, and (2) petitions for *Inter Partes* Review of U.S. Patent No. 8,753,645. The '839 patent is a continuation of U.S. Patent Application No. 13/581,824, which issued as the '645 patent.

c. ***Designation of Lead and Back-Up Counsel and Service Information*** **(37 C.F.R. § 42.8(b)(3)-(4))**. Petitioner identifies the following:

- *Lead counsel*: Anthony M. Insogna (Reg. No. 35,203)
  JONES DAY
  4655 Executive Drive, Suite 1500
  San Diego, CA 92121-3134
  Tel: (858) 314-1200
  Fax: (844) 345-3178
  Email: MerckGSK-IPRs@jonesday.com

- *Back-up counsel*: Nikolaos C. George (Reg. No. 39,201)
  Gasper J. LaRosa (Reg. No. 62,477)
  Lisamarie LoGiudice (Reg. No. 71,047)
  Catharina J. Chin Eng (Reg. No. 42,412)
  JONES DAY

250 Vesey Street
New York, NY 10281-1047
Tel: (212) 326-3939
Fax: (212) 755-7306
Email: MerckGSK-IPRs@jonesday.com

Arlene L. Chow (Reg. No. 47,489)
Ernest Yakob (Reg. No. 45,893)
HOGAN LOVELLS US LLP
875 Third Avenue
New York, NY 10022
Tel: (212) 918-3000
Fax: (212) 918-3100
Email: arlene.chow@hoganlovells.com
Email: ernest.yakob@hoganlovells.com

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") requests *inter partes* review ("Request") of independent claim 1 and dependent claims 2-10 of U.S. Patent No. 9,265,839 (the "'839 patent") (Exh. 1001, 26:31-27:5) as anticipated and/or obvious under 35 U.S.C. §§ 102 or 103.

Conjugates of bacterial saccharides[1] (sugars) to proteins are commonly-used components of vaccines. The challenged claims are directed to processes for making conjugates of a particular *S. pneumoniae* bacterial saccharide, 6B. The very same 6B "glycoconjugates" were well-known long before the alleged invention of the '839 patent. Indeed, they were featured in Pfizer's well-known, commercial Prevnar® vaccine.

There is nothing new or nonobvious about the claimed process. The claims are directed to the use of lower concentrations of the chemical "periodate" to activate a bacterial saccharide so that it can then be attached to a carrier protein. But persons of ordinary skill in the art ("POSAs") used that same conjugation reaction (known as "reductive amination") for decades before the '839 patent to attach *S. pneumoniae* bacterial saccharides – including 6B – to proteins. POSAs

[1] Like the '839 patent specification, "the term 'saccharide'" throughout this Petition "may indicate polysaccharide[s]." (Exh. 1001, 4:57-59).

also routinely used low concentrations of periodate to activate saccharides. They did so because they understood that using too much periodate can break too many chemical bonds, thereby reducing saccharide size (*i.e.*, sizing effect) and inhibiting the saccharide's ability to trigger an immune response.

The '839 patent claims add nothing to this prior art conjugation process. They merely require: (1) activation of the bacterial saccharide using lower amounts of periodate (in the range of 0.001-0.7 molar equivalents ("MEq")) in commonly-used buffers with concentrations between 1-100 mM; (2) mixing the activated saccharide with a carrier protein; and (3) reacting the activated saccharide and the carrier protein with a reducing agent to produce a conjugate. Each step of that process, arranged as claimed, was disclosed in publications known to POSAs before the earliest filing date of the '839 patent. Also well-known were the results of practicing this conventional process: that using lower periodate concentrations will break fewer bonds in the saccharide structure and reduce the undesirable "sizing effect."

Nevertheless, the Patent Owner ("PO") was granted the '839 patent based on arguments it made to the USPTO that the claimed periodate range of 0.001 to 0.7 MEq was novel and produced unexpected results. As discussed below, neither argument has merit. There is also no evidence in the '839 patent that the claimed range of periodate provides unexpected results when compared to using periodate

outside of that range. The data in the '839 patent merely show what was well-known (and expected) from the prior art: as periodate concentration is lowered, the sizing effect is reduced. Accordingly, the '839 patent never should have been allowed.

Anticipation. PCT Patent Application Publication No. WO 2004/043376A2 ("WO'376") (Exh. 1004), titled "Compositions and Methods for Treating or Preventing Pneumococcal Infection," discloses a process to prepare *S. pneumoniae* saccharide-protein conjugates that is identical to the process of claims 1-10 of the '839 patent.[2] In particular, Example 4 of WO'376 discloses a method for conjugating bacterial saccharides, including 6B, that includes (a) activating the bacterial saccharide with approximately 0.27 MEq of periodate in 100 mM buffer, (b) mixing the activated bacterial saccharide with carrier protein, and (c) reacting the activated 6B bacterial saccharide and the carrier protein to form a conjugate. (Exh. 1004, 23:24-27:25).[3]

The claim preamble language "reducing the sizing effect" merely expresses the intended purpose of performing the claimed process and is non-limiting. *See*

[2] WO'376 was not before the Examiner during prosecution.

[3] All citations herein refer to the exhibits' native page numbers, except IPR page numbers are used where the exhibits do not include native page numbers.

Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1374-75 (Fed. Cir. 2001). Even if that phrase were limiting, the claims are still anticipated because "reducing the sizing effect" is necessarily achieved by practicing the process steps set forth in Example 4 of WO'376.

Obviousness. The challenged claims would also have been obvious to POSAs at the time of the alleged invention over WO'376 in view of Frasch, et al., "Preparation of Bacterial Polysaccharide-Protein Conjugates: Analytical and Manufacturing Challenges," *Vaccine 27*, 6468-70 (2009) ("Frasch") (Exh. 1005) and Lees, et al., "Conjugation Chemistry," *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*, Chap. 11, 163-74 (ASM Press, Washington, D.C., 2008) ("Lees") (Exh. 1006). Frasch and Lees are in the same field of art and are representative of the state of that art at the time of the alleged invention. They not only teach POSAs how to avoid a size reduction, but also to expect a reduction in sizing effect when following the steps of WO'376.

In view of the foregoing, Petitioner respectfully submits there is at least a reasonable likelihood that it will prevail in showing at least one of the challenged claims is unpatentable. In support of the proposed grounds for unpatentability, this Petition is accompanied by the declaration of Dr. Fikri Avci (Exh. 1009), an expert in carbohydrate chemistry, particularly in the area of glycoconjugate vaccines.

II. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

A. Grounds For Standing

Petitioner certifies that: (1) the '839 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting review of any claim on the grounds identified in this Petition. 37 C.F.R. § 42.104(a). The Office is authorized to charge all fees due in connection with this matter to Deposit Account No. 50-3013.

B. Identification Of Challenge

Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-10 of the '839 patent pursuant to the following statement of precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-10	102(b)	• **WO'376**
II	1-10	103	• **WO'376** • **Frasch** • **Lees**
III	4	103	• **WO'376** • **Frasch** • **Lees** • PCT Patent Application Publication No. WO 2009/000825A2 to GSK ("**GSK 2009 PCT**") (Exh. 1007)

Ground	Claims	Basis	Reference(s)
IV	5	103	• **WO'376** • **Frasch** • **Lees** • Prevnar®, *2009 Physicians' Desk Reference*, 63rd ed. (Physicians' Desk Reference Inc., Montvale, N.J., 2008) ("**Prevnar**") (Exh. 1008)
V	9	103	• **WO'376** • **Frasch** • **Lees** • **GSK 2009 PCT**

III. A PERSON OF ORDINARY SKILL IN THE ART

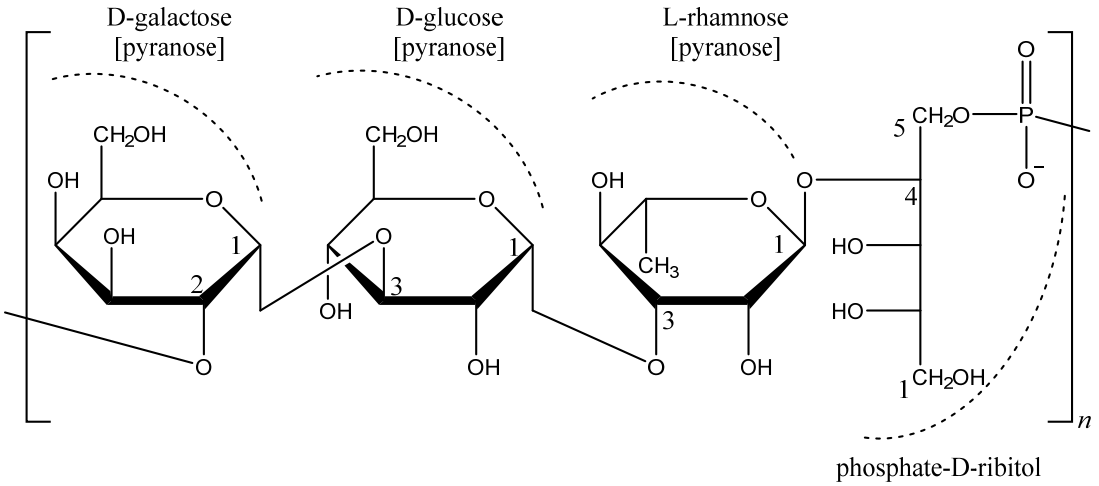
As confirmed by Dr. Avci, a POSA, as of March 9, 2010, would have had a Ph.D. degree in Biochemistry, Chemistry, or a comparable discipline, and at least 2-3 years of research experience focused on carbohydrate chemistry. (Exh. 1009, ¶ 21).

IV. STATE OF THE ART

A. *Streptococcus pneumoniae* "Conjugate" Vaccines

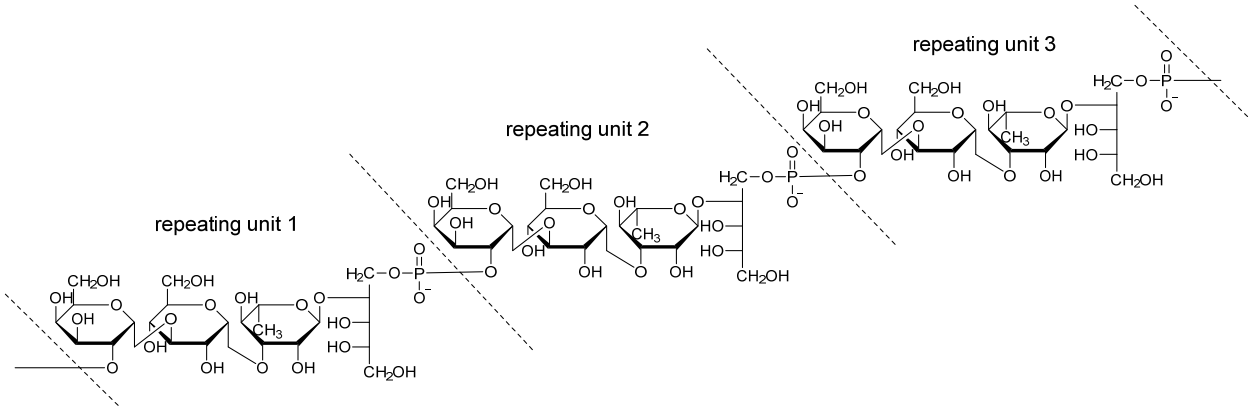
Bacterial saccharides, which form a capsule around the outside of certain bacteria, are made up of polymeric chains of saccharide repeating units ("RU"). (Exh. 1006, 163). These saccharides, including ones covalently linked (*i.e.*, conjugated) to carrier proteins, have long been used successfully in vaccines. (*Id.*; Exh. 1009, ¶¶ 32-35; Exh. 1039, 97; Exh. 1040, S72; Exh. 1045, 2078).

Streptococcus pneumoniae, or pneumococcal bacteria, is a common cause of invasive and respiratory disease. (Exh. 1006, 164; Exh. 1010, 750; Exh. 1008, 3241; Exh. 1037, 293; Exh. 1038, 872). Different pneumococcal strains, or serotypes, are classified according to the particular capsular saccharide structure each exhibits on its cell surface. (Exh. 1010, 750; Exh. 1008, 3242). The figure below (derived from Exh. 1011, 266) depicts the particular saccharide RU for 6B.



This RU, which has a molecular weight ("MW") of 683.5 g/mol, contains a backbone of three sugar rings (galactose(Gal*p*) -- glucose(Glc*p*)--rhamnose(Rha*p*)) and a phosphate-D-ribitol unit that is attached to the rhamnose sugar ring. (Exh. 1009, ¶¶ 66, 68; Exh. 1057, 178; Exh. 1047, 66-67). The "n" in the figure is the number of RUs in the saccharide. (*Id*., ¶ 66).

The 6B RUs are attached to each other in the 6B saccharide as follows (*id*., ¶ 67):



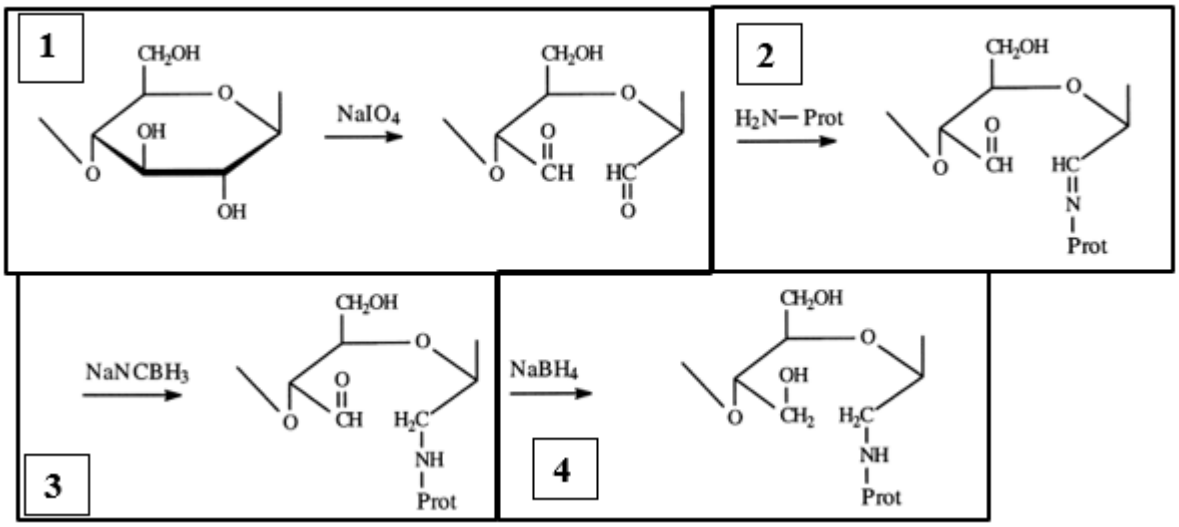
The FDA approved the first commercially available conjugate vaccine against *S. pneumoniae*, Prevnar® ("Prevnar") in 2000. (Exh. 1010, 750). The seven bacterial saccharide-carrier protein conjugates in Prevnar, which included 6B, were produced by periodate activation, *i.e.*, oxidation, followed by reductive amination. (Exh. 1008, 3241; Exh. 1010, 750; ; Exh. 1006, 164, 167-68). In 2010, the FDA approved Prevnar® 13 ("Prevnar 13"), which includes the conjugates of the seven serotypes in Prevnar, and conjugates from six additional serotypes. (*See* Exh. 1012, 3403; Exh. 1009, ¶ 35; Exh. 1050; Exh. 1053). The thirteen bacterial saccharide-carrier protein conjugates in Prevnar 13 were also made using periodate activation and reductive amination, and also included 6B. (Exh. 1009, ¶ 36; Exh. 1056, ¶ [0036]).

B. Reductive Amination And Periodate Oxidation Are Well-Known Standard Chemical Reactions For Making Conjugates

Reductive amination is a standard chemical reaction that has been used routinely since at least the 1940s to conjugate molecules. (Exh. 1009, ¶ 38). The

reductive amination process involves coupling of an aldehyde and an amine to form the final "conjugated" product. (*Id.*, ¶ 38; Exh. 1013, 174). Conjugation of oxidized saccharides with proteins through reductive amination was well-documented long before the '839 patent. (Exh. 1014, 1011). In fact, periodate activation and reductive amination had been used for decades to make bacterial saccharide-protein conjugates. (Exh. 1015, 23:23-55; Exh. 1016, 5:5-9).

The figure below (derived from Exh. 1006, 169) depicts a standard prior art reaction that uses reductive amination to conjugate a saccharide to a protein. The saccharide in the exemplary reaction could be part of a bacterial saccharide RU of a pneumococcal saccharide:



First, as shown in box "1," the saccharide is "activated" by periodate (sodium periodate ($NaIO_4$) in this example) via oxidation of adjacent hydroxyl groups (–OH) known as "vicinal diols" to produce reactive aldehydes (CH=O).

(*Id*., 166-67). This step is performed because native saccharides do not normally contain aldehyde groups. (Exh. 1009, ¶ 38; Exh. 1041, 1-3). In this example, the vicinal diol is on a sugar ring. The oxidation cleaves the carbon-carbon bond between the hydroxyl groups of the vicinal diol, thereby opening the ring structure and forming the reactive aldehydes. (Exh. 1009, ¶ 40). Because this reaction opens the ring, it also destabilizes the saccharide and makes it more susceptible to fragmentation. (*Id*., ¶¶ 40, 48; Exh. 1006, 167-68; Exh. 1021, 123, 125 (oxidation of the diols in the sugar rings, opened the rings, which weakened the bonds between the rings resulting in fragmentation of the saccharide, and therefore a reduction in the size of the saccharide)).

Next, as shown in box "2," the activated saccharide is mixed with a carrier protein to form a saccharide-protein conjugate. (Exh. 1009, ¶ 41). The reaction is made irreversible in the presence of a reducing agent (here, sodium cyanoborohydride ($NaNCBH_3$)) to form the conjugate, as shown in box "3." (*Id.*). Finally, as shown in box "4," a quencher (here, sodium borohydride ($NaBH_4$)) can be added to convert unreacted aldehyde groups to corresponding hydroxyls. (*Id.*).

C. POSAs Knew That Periodate Can Alter Saccharide Size And Immunogenicity

1. POSAs knew to avoid excessive changes to saccharide structures

As explained above, the activation step generates aldehyde groups to allow conjugation of saccharides to carrier proteins. However, care must be taken not to break so many bonds in the saccharide structure during activation as to cause undue saccharide fragmentation, loss of epitopes[4], and creation of unwanted new epitopes, which can adversely affect immunogenicity. (Exh. 1006, 166; Exh. 1005, 6469). The sizing effect occurs because portions of the saccharide, such as a side chain, break off, or because the saccharide backbone breaks. (Exh. 1009, ¶¶ 47-49).

POSAs were well aware of the importance of balancing the need to generate active groups with the need to preserve saccharide structure. (*Id*., ¶ 52). To achieve that balance, POSAs knew to use mild reaction conditions. (*See* Exh. 1006, 166 (reaction "should be mild so that it does not (i) destroy significant

[4] An epitope is a portion of an antigen (here, the saccharide) that is capable of binding an antibody. The immune system mounts an immune response against antigens by producing antibodies or generating cells with specificities to epitopes present. (*See* Exh. 1031, 37).

epitopes on either the protein or the PS, (ii) cause undesired depolymerization of the PS, or (iii) introduce any deleterious epitopes"); Exh. 1017, 2, 4 (reaction "should be sufficiently *gentle* to retain important antigenic sites" and moreover, "sodium periodate may break up carbohydrates into smaller fragments and/or disrupt epitopes, which may be undesirable"); Exh. 1009, ¶¶ 52-53).[5]

2. POSAs considered saccharide size when designing activation conditions

Saccharide size—and the potential for saccharide size reduction—was a criterion POSAs kept in mind when designing the activation step of a saccharide-conjugation process. (Exh. 1009, ¶¶ 46, 54-55). For example, in its recommendations for quality, safety and efficacy of pneumococcal conjugate vaccines, the World Health Organization recommended that pneumococcal saccharide size be measured both before and after activation. (Exh. 1018, 15; *see also* Exh. 1005, 6469 ("The 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 PS.")).

It had also been reported in the prior art that conjugates comprising larger pneumococcal saccharides may produce better immune responses. (*See, e.g.,* Exh.

[5] Emphasis added throughout unless otherwise noted.

1009, ¶ 56; Exh. 1019, 450 (finding that in general conjugates with longer saccharides, including ones with 23F and 6B, were more immunogenic than conjugates with smaller ones); Exh. 1007, 14; Exh. 1051, 2190 ("An effect of molecular size on immunogenicity has been well-known for pure polysaccharide antigens; optimal antibody responses generally require immunogens with M_rs of 90,000 or higher . . . . Results of the present study support, as well, an effect of molecular size on immunogenicity of polysaccharide-protein conjugate vaccines.")).

PO acknowledged the teachings in the prior art that larger saccharides may produce better immune responses. During prosecution of PCT Patent Application No. PCT/EP2011/053400 ("PCT application") (Exh. 1003), to which the '839 patent claims priority, PO cited Steinhoff (Exh. 1020) as showing "that smaller Streptococcal saccharides tend to be less immunogenic than larger Streptococcal saccharides." (Exh. 1003, IPR89-90; Exh. 1060).

3. Greater amounts of periodate increase oxidation, saccharide size reduction and epitope disruption

When more periodate is available in the reaction, a greater number of saccharide moieties are oxidized, leading to a greater sizing effect and epitope disruption. (Exh. 1009, ¶¶ 50, 59). "One important potential problem with use of periodate to activate the PS is altering the physical structure of the PS, with loss of important epitopes." (Exh. 1005, 6469; *see also* Exh. 1017, 4 ("sodium periodate

may break up [bacterial] carbohydrates into smaller fragments and/or disrupt epitopes, which may be undesirable"); Exh. 1022, 137 ("[c]oncurrent with increasing periodate oxidation levels were decreasing levels of periodate-susceptible residues and increasing levels of specific oxidation/reduction products")).

D. Periodate Amounts Were Routinely Optimized

At the time of the alleged invention, POSAs knew how to avoid or limit excessive changes to the saccharide structure while generating sufficient reactive aldehyde groups. (Exh. 1009, ¶¶ 52-53). When oxidizing saccharides with periodate, it was well-known that reaction conditions such as molar ratios of periodate have to be optimized. (Exh. 1006, 168). Not only was the amount of periodate recognized as a variable to optimize when activating saccharides, but as detailed above, saccharide size—and the possibility of saccharide size reduction (*i.e.*, "sizing effect") was a result POSAs would have kept in mind when performing such optimization. (Exh. 1009, ¶ 57). Thus, a wealth of knowledge in the art was available to POSAs that rendered optimization of periodate amounts routine. (*Id.*, ¶ 58; Exh. 1044, 131; Exh. 1046, 448; Exh. 1049,169).

By the time of the '839 patent, it was known that milder oxidization conditions using sufficiently low levels of periodate would avoid undesired alterations of the saccharide structure/size. (Exh. 1009, ¶¶ 53, 60). "Undesirable

fragmentation can be avoided or controlled through selection of the particular oxidizing agent and the concentration of the oxidizing agent employed." (Exh. 1023, ¶ [0074]).

As shown in Table 1, *infra*, it was well-known at the time of the alleged invention that the amount of periodate suitable for oxidizing pneumococcal saccharides was within the range recited in the '839 patent claims. (Exh. 1009, ¶ 42).

V. THE '839 PATENT

The '839 patent issued on February 23, 2016 and is assigned on its face to GlaxoSmithKline Biologicals S.A. (Exh. 1001, IPR1). The '839 patent issued from U.S. Application No. 14/202,119 ("the '119 application") (Exh. 1002), which is a continuation of U.S. Patent Application No. 13/581,824 ("the '824 application") (Exh. 1028), which issued as U.S. Patent No. 8,753,645 ("the '645 patent") (Exh. 1027). The '824 application is a U.S. national phase application of PCT/EP2011/053400 (Exh. 1003), filed on March 7, 2011. (Exh. 1001, IPR1). The PCT application claims priority to Great Britain Patent Application No. 1003922.0 (the "GB'922 appln.") (Exh. 1026) filed on March 9, 2010.[6] (Exh.

[6] The'839 patent claims are not entitled to the March 9, 2010 filing date of the GB'922 appln. because it fails to disclose (1) the range of 0.001-0.7 MEq of

1001, 1:5-12). PO filed a terminal disclaimer during prosecution of the '119 application to overcome the Examiner's double patenting rejection over the '645 patent. (Exh. 1002, IPR667). The specifications of the '839 and '645 patents are identical, and the claims are directed to an identical process, except the claims of the '645 patent recite serotype 23F instead of 6B.

Claim 1 of the '839 patent, the only independent claim, is directed to a process for conjugating bacterial saccharide 6B:

> **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

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periodate, or either end of the recited range, (2) a pH range of 3.5-8.0, as recited in claim 3 and (3) the 1-1100 kDa size range of claim 4.

1-100 mM and wherein the bacterial saccharide is *S. pneumoniae* capsular saccharide 6B.

(Exh. 1001, 26:30-44). As shown, claim 1 includes a preamble setting forth the intended result (*i.e.*, "reducing the sizing effect") of the three subsequently recited steps.

No deference should be given to the Examiner's decision to allow the '839 patent. During prosecution, the Examiner did not consider WO'376, the anticipating reference discussed below. (Exh. 1004). The Examiner also did not consider Frasch, Lees, GSK 2009 PCT or Prevnar in connection with prosecution of the claims.[7] (Exhs. 1005-1008).

Moreover, PO misled the Examiner regarding the alleged unexpected properties conferred by the claimed range of periodate MEqs (*i.e.*, 0.001-0.7) to rebut a *prima facie* showing of obviousness.

In fact, the claimed range is not critical and does not produce unexpected results—it was chosen only to avoid the prior art. During prosecution of the PCT application, claim 1 originally recited "[a] process for conjugating a bacterial

[7] All prior art relied upon by Petitioner predates the March 9, 2010 filing date of the GB'922 appln (to which PO is not entitled) and predates the March 7, 2011 U.S. (PCT) filing date by more than one year.

saccharide comprising the steps of a) reacting the bacterial saccharide with 0.001-0.7, 0.005-0.5, 0.01-0.5, **0.1-1.2**, 0.1-0.5, 0.1-0.2, **0.5-0.8**, **0.1-0.8**, **0.3-1.0** or **0.4-0.9** molar equivalents of periodate to form an activated bacterial saccharide." (Exh. 1003, IPR37). The Examiner acknowledged that the application concerned periodate oxidation of bacterial saccharides at MEq of periodate from 0.001 to 1.2. (*Id*., IPR58).

The PCT Examiner rejected the application as obvious in view of U.S. Application Publication No. 2007/0184071 ("Hausdorff") (Exh. 1029), which discloses the oxidation and conjugation of pneumococcal capsular saccharide serotype 4 at 0.8-1.2 MEq of periodate.[8] While the Examiner relied on this disclosure in Hausdorff relating to serotype 4, the Examiner never considered

[8] The 0.8-1.2 MEq periodate range was used to activate serotype 4, which unlike 6B, does not have native diols. (Exh. 1029, ¶ [0196]; *see also* Exh. 1011, 265). Consequently, a pre-activation step is used for serotype 4 to create diols. (Exh. 1029, ¶¶ [0194], [0196]; Exh. 1030, 138; Exh. 1009, ¶¶ 83, 157). POSAs would have understood that lower MEq of periodate could be used to oxidize a comparable number of diols in serotype 6B compared to 4. (Exh. 1009, ¶ 83).

activation conditions for serotype 6B.[9] In an effort to avoid that art, PO narrowed the claims to recite 0.001-0.7 MEq periodate (the broadest recited range that does not include 0.8-1.2 MEq), stating that the 0.8-1.2 MEq used in Hausdorff "is significantly higher than the range claimed in the amended claims." (Exh 1003, IPR70).

Despite PO's subsequently proffered arguments that the claimed range produced unexpected results, the claimed range was chosen only to avoid the prior art, not because it is critical or provides unexpected results compared to periodate MEq outside the claimed range. *See In re Gentile*, 11 F.3d 1069 (Table), 1993 WL 393318, at *2 (Fed. Cir. Oct. 5, 1993); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Like the PCT Examiner, the U.S. Examiner also relied on prior art showing the oxidation of serotype 4 using 0.8-1.2 MEq of periodate. (Exh. 1002, IPR555-56). The Examiner rejected the claims, stating that it would have been obvious to use various concentrations of periodate to activate the saccharide based on this prior art teaching since "optimum or workable ranges are performed in the art as

[9] In fact, the Examiner did not consider Hausdorff's citation to Anderson, which discloses the use of 0.27 MEq periodate for 6A, whose RU has virtually the same structure as that of 6B. (Exh. 1029, ¶ [0039]; Exh. 1015, 21:18, 22:53).

routine." (*Id*.). In response, PO argued, as it did during the PCT prosecution, that the claimed periodate range provided unexpected results. (*Id*., IPR587-90).

The intrinsic record demonstrates that the claimed range does not produce any unexpected results. During prosecution, PO argued that the "claimed range of 0.001-0.7 molar equivalents has [produced] unexpected properties for the 23F and 6B saccharides [because they] are not reduced in size by the activation process." (*Id.*, IPR589). Apparent from a review of Table 1 and Figure 1 of the specification, the saccharides are, in fact, reduced in size by the activation process. The results shown in the '839 patent merely demonstrate a general and continuous trend that was completely expected based on what was known in art—reducing the amount of periodate reduces the sizing effect. (Exh. 1009, ¶ 87).

Nothing in the intrinsic record indicates—much less proves—that 0.001-0.7 MEq periodate produces superior or unexpected results compared to periodate MEqs outside the claimed range. To the contrary, the specification teaches that the 0.8-1.2 MEq range disclosed in the prior art would still lead to a reduction in the sizing effect. For example, the specification expressly discloses the same periodate MEq range disclosed in Hausdorff (0.8-1.2) as an embodiment of the purported invention. The Summary of Invention teaches 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."

(Exh. 1001, 1:51-53). In the next sentence, the specification teaches "a process for conjugating a bacterial saccharide(s) comprising the steps of a) reacting the bacterial saccharide with 0.001-0.7, 0.005-0.5, 0.01-0.5, **0.1-1.2**, 0.1-0.5, 0.1-0.2, **0.5-0.8**, **0.1-0.8**, **0.3-1.0** or **0.4-0.9** molar equivalents of periodate to form an activated bacterial saccharide." (*Id.*, 1:54-60).

Thus, the specification discloses that the same concentration ranges disclosed in Hausdorff—0.8-1.2 MEq periodate—would produce the same results as the claimed invention. Moreover, at least one range disclosed, 0.1-1.2 MEq, entirely overlaps the range disclosed in the prior art. (*Id*., 1:54-60). Thus, when the specification discloses that "***lower concentrations of periodate***" "lead to retention of size and/or the retention of epitopes," these concentrations ***include*** the periodate range disclosed in the prior art. Apart from the disclosure set forth above in the Summary of Invention, the claimed range is never once mentioned in the specification.

For at least these reasons, the Board should give no deference to the Examiner's decision to allow the '839 patent.

VI. CLAIM CONSTRUCTION

Claim terms should be construed, as they would by POSAs at the filing date, in light of the intrinsic evidence, *i.e.*, the claim language, specification, and prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313-14 (Fed. Cir.

2005). That construction must be consistent with the ordinary and customary meaning of the term, unless it has been given a special definition by the patentee in the specification. *Id*. at 1316. While less significant than intrinsic evidence, extrinsic evidence, *e.g.*, dictionaries, is also considered. *Id*. at 1317.[10]

A. "reducing the sizing effect"

The '839 patent claims a process for conjugating bacterial saccharide 6B and "reducing the sizing effect" of the bacterial saccharide. (Exh. 1001, 26:32-44). The claim term "reducing the sizing effect" is recited only in the preamble of claim 1, the sole independent claim in the '839 patent. (*Id*.). For the reasons discussed

[10] 37 C.F.R. 42.100(b) states that claims must be given their broadest reasonable construction in light of the specification ("BRC standard"). On May 8, 2018, the USPTO proposed rulemaking that would change the standard for construing claims from BRC to the *Phillips* standard. In anticipation that the rule-change will apply to these proceedings, Petitioner construes the claims based on the standard set forth in *Phillips*. Petitioner is not aware of any difference in how the claims would be construed under the BRC. The scope of the challenged claims could not be broader under the proposed *Phillips* construction than it could be under BRC. Therefore, the challenged claims would also be unpatentable under the BRC standard.

below, this term is not limiting or, alternatively, should be given its plain and ordinary meaning: "decreasing the reduction in the size of the bacterial saccharide."

1. The claim term "reducing the sizing effect" is not limiting

"[A] preamble recitation that merely expresses the purpose of performing the claimed steps is **not a limitation** on the claimed process where the **body of the claim fully sets forth the steps** required to practice the claimed process, and where the preamble recitation **does not affect how the claimed steps are to be performed**." *Ex parte Lorens*, No. 2009-011194, 2010 WL 991519, at *5 (B.P.A.I. Mar. 16, 2010) (citing *Bristol-Myers,* 246 F.3d at 1375-76).

Here, the claim language itself supports a finding that the term is a non-limiting statement of intended outcome—*i.e.*, that the claimed steps reduce the sizing effect—rather than adding an additional limitation. The body of claim 1 fully sets forth the steps in the claimed process. *Bristol-Myers*, 246 F.3d at 1375-76; *see also In re Hirao*, 535 F.2d 67, 70 (C.C.P.A. 1976). And the term "reducing the sizing effect" is not recited in the body of the claim setting forth the process.

Moreover, the "reducing the sizing effect" language does not affect how the claimed steps are to be performed. *Bristol-Myers*, 246 F.3d at 1375. Apart from performing process steps a)-c), neither the claim nor the specification explains how to perform additional steps, or to change the order of the claimed steps, in order to

"reduc[e] the sizing effect." The patent only teaches that performing steps a)-c)—in particular step a)—will lead to a reduction in the sizing effect. (Exh. 1009, ¶ 91).

Even if PO argues that "reducing the sizing effect" was added during prosecution of the related '824 application[11] to overcome a rejection, the Board should reject that argument because the Examiner's remarks demonstrate that this term, like the term "conjugating a bacterial saccharide," merely recites the purpose of the claimed process.

In response to the office action issued for the '824 application, applicants argued that "[a]ssuming, *in arguendo*, that the Office had established a case of *prima facie* obviousness," "Applicants have 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." (Exh. 1028, IPR507-08). Then, in the Notice of Allowance, the Examiner indicated that applicants agreed to the Examiner's amendment adding the term "and reducing the sizing effect on bacterial saccharide" to claim 1. (*Id*., IPR518). The Examiner stated:

> The current process is drawn for not only conjugating *S.pneumoniae* capsular saccharide 23F or 6B by using 0.001-0.7 molar equivalents

[11] This application issued as the '645 patent. (Exh. 1017)

of periodate but also *for reducing the size [sic] of the capsular saccharide by using low 0.001-0.7 molar equivalents of periodate*

(Exh. 1028, IPR519).[12]

The 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. Specifically, as the Examiner noted, "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. Clearly, the phrase "conjugating a bacterial saccharide" was not included as an additional limitation since the steps needed to form the conjugate were set forth in the body of the claim, *e.g.*, step c) recites the step of "reacting . . . *to form a conjugate*." (Exh. 1027, 27:10-11).

[12] The Applicant did not disagree but pointed out that there was a typographical error; "reducing the size" should be "reducing the sizing effect", which appears in the amendment. (Exh. 1028, IPR537).

2. Alternatively, "reducing the sizing effect" should be given its plain and ordinary meaning

Alternatively, if the Board finds that the claim term "reducing the sizing effect" is limiting, Petitioner asserts that it should be construed in accordance with its plain and ordinary meaning, which is, "**decreasing the reduction in the size of the bacterial saccharide**."

The specification teaches that "[t]reatment with periodate may lead to a reduction in the size of the bacterial saccharide (sizing effect)." (Exh. 1001, 6:14-15). "When low concentrations of buffer, in particular phosphate buffer and low amounts of periodate are used, this may reduce the sizing effect described above." (*Id*., 8:11-13). Thus, reducing the sizing effect means to decrease the reduction in size. (Exh. 1009, ¶¶ 92-94).

B. "molar equivalents"

The term "molar equivalents of periodate" should be construed to mean "the ratio of moles of periodate to the moles of saccharide repeating unit." This construction is supported by the intrinsic record and reflects the plain and ordinary meaning of the term.

A "molar equivalent" is the ratio of moles of one substance to the moles of another substance. (Exh. 1009, ¶ 97; Exh. 1035, 2183). In fact, POSAs have considered molar ratios of periodate to be a significant parameter for activation of saccharides. (Exh. 1006, 168). It is clear from the specification that "molar

equivalents of periodate" is the ratio of moles of periodate to the moles of saccharide RU. For instance, in Example 2 of the specification, "111 mg of periodate ($NaIO_4$, **0.4 molar equivalents** of periodate)" was reacted with 1 g of saccharide 23F. (Exh. 1001, 19:46-52). The MW of the periodate used (sodium periodate) is 213.9 g/mol. (Exh. 1033, 904).

The below calculation demonstrates that in order to arrive at 0.4 MEq of periodate, PO must have used the MW of the 23F RU, demonstrating that the specification supports Petitioner's construction of "molar equivalents" of periodate. (Exh. 1009, ¶ 98).

$$111\ mg\ \text{sodium}\ periodate\ \times \frac{mmole}{213.9\ mg} = 0.52\ mmole\ sodium\ periodate$$

0.52 mmole sodium periodate = 0.52 mmole periodate[13]

$$1g\ 23F \times \frac{mole}{769.6\ g} \times \frac{1000\ mmole}{1\ mole} = 1.3\ mmole\ 23F$$

$$0.52\ mmole\ periodate\ /\ 1.3\ mmole\ 23F\ RU = \mathbf{0.4\ MEq}$$

C. "molecular weight"

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)." (Exh.

[13] One mole of sodium periodate ($NaIO_4$) contains one mole of periodate (IO_4^-). (Exh. 1033, 904).

1001, 26:50-52). This recitation of the MWs is a statement of intended result that follow from practicing the claimed method and are thus non-limiting. *In re Copaxone 40 Mg Consolidated Cases*, No. 14-1171-GMS, 2016 WL 873062, at *1 (D. Del. Mar. 7, 2016), citing *Bristol-Myers*, 246 F.3d at 1375-76 (the numbers of lesions recited in the claims were non-limiting because they were statements of intended effect of practicing the claimed method).

Moreover, there is no evidence in the intrinsic record that this recitation of MW is central to patentability or was used to distinguish the claim from the prior art. *Id*. (finding claim recitations non-limiting since there was no evidence they were relied on to establish patentability of the dependent claims).

If the Board finds that the MW recitation is limiting, it should be construed to mean that the saccharide, which has been activated in step a), has a weight-average MW within the recited ranges prior to conjugation with the protein. This construction is supported by the statement in the specification of the '839 patent that 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 [a] technique [that] is well-known in the art." (Exh. 1001, 5:61-65).

The remaining terms of the challenged claims are explicitly defined by the specification or have a well-understood ordinary meaning to POSAs and require no

further construction for the purposes of this Petition.

VII. GROUNDS FOR INSTITUTION

A. Ground I: Claims 1-10 Of The '839 Patent Are Anticipated By WO'376

Claims 1-10 of the '839 patent are anticipated by WO'376, published on May 27, 2004. WO'376 is prior art under pre-AIA Section 102(b) with respect to every claim of the '839 patent.

WO'376 is directed to, *inter alia*, *S. pneumoniae* saccharide-carrier protein conjugates for treating or preventing pneumococcal infection, and methods of making the same. (Exh. 1004, IPR1). WO'376 Example 4 discloses a conjugation process for the identical purpose as claim 1 of the '839 patent— to prepare bacterial saccharide-protein conjugates.

In particular, Example 4 discloses a method for conjugating bacterial saccharides, including serotype 6B (*id*., 23:26), by **(a)** reacting the bacterial saccharide with 0.27 MEq of periodate (*id*., 23:27-30; *see below*), in 100 mM phosphate buffer solution (pH 7.2) (*id.,* 23:27-29), **(b)** mixing the activated bacterial saccharide with a pneumolysin carrier protein (*id.,* 27:18-20), and **(c)** reacting the activated bacterial saccharide and the carrier protein with the reducing agent sodium cyanoborohydride to form a conjugate (*id.*).

As discussed below, WO'376 discloses each and every element, arranged as claimed, of the '839 patent's claims 1-10.

1. Claim 1 is anticipated

a. Preamble: "A process for conjugating a bacterial saccharide and reducing the sizing effect on bacterial saccharide comprising the steps of"

(1) The preamble is not limiting

For the same reasons discussed above with respect to claim construction, the preamble of claim 1 is non-limiting—it merely expresses the purpose of performing the claimed process that is fully set forth in the body of claim 1. *Bristol-Myers*, 246 F.3d at 1375-76. Thus, Petitioner need not demonstrate that the prior art discloses the preamble. (*Id*.).

(2) Even if limiting, WO'376 discloses the preamble of claim 1

With respect to the preamble phrase "**[a] process for conjugating a bacterial saccharide**," Example 4 of WO'376 discloses "[m]ethods for the … conjugation of polysaccharides to polypeptides." (Exh. 1004, 11:23-25; Exh. 1009, ¶ 104). Thus, WO'376 discloses this element of the preamble.

With respect to the preamble phrase "**reducing the sizing effect**," WO'376 inherently discloses this element because: (1) "reducing the sizing effect" is the natural result of practicing step a) (*i.e*., treating the bacterial saccharide with 0.001-0.7 MEq of periodate in 1-100 mM buffer); and (2) WO'376 Example 4 explicitly discloses step a), in addition to every other step in the claimed process. (Exh. 1009, ¶ 105).

Claims are not made patentably new by adding inherent results or benefits of prior art processes to the claims as limitations. *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). This is especially true in a case such as this one, where POSAs understood that using lower amounts of periodate would reduce the sizing effect compared to using higher amounts of periodate (*i.e.*, MEq periodate outside of the claimed range). Even if "reducing the sizing effect" wasn't appreciated, "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. IRECO Inc*., 190 F.3d 1342, 1347 (Fed. Cir. 1999); *see also King*, 616 F.3d at 1275.

"Reducing the sizing effect" is the natural result of practicing step a). The '839 patent teaches that treatment with periodate during oxidation[14] leads to a reduction in the size of the bacterial saccharide (sizing effect). (Exh. 1001, 6:14-15). When low concentrations of buffer and low amounts of periodate are used during oxidation, however, the sizing effect is reduced. (*Id.*, 8:1-3, 19:6-10). The specification does not teach any additional steps to "reduc[e] the sizing effect"

[14] Oxidation is the reaction that occurs during step a) of the claimed process.

aside from performing step a) of the claimed process (*i.e.*, low MEq periodate (0.001-0.7) and low buffer concentration (1-100 mM)). (Exh. 1009, ¶¶ 108-109).

In response to an office action during prosecution, PO argued that use of the recited amounts of periodate in step a) resulted in reducing the sizing effect: "[s]accharides conjugated using Applicants' claimed process are not subject to the same sizing effect as those conjugated with higher periodate concentrations." (Exh. 1002, IPR589). PO also argued that "Example 1 illustrates that the use of higher concentrations of periodate leads to a substantial sizing effect" and that the claimed range of 0.001-0.7 MEq "has previously unexpected properties . . ., the [23F and 6B] saccharides are not reduced in size by the activation process." (*Id.*). The Examiner then noted in the Notice of Allowance for the related '824 application that the reducing in the sizing effect results from using the periodate amounts of step a). (Exh. 1028, IPR519).

And, as discussed above, it was well-known in the art that lowering the concentration of periodate decreases changes to saccharide size and structure. (*See* Exh. 1005, 6469; Exh. 1017, 4; Exh. 1022, 137). Thus, in view of the specification, PO's statements during prosecution and the knowledge in the art, it is inherent, and expected, that performing step a) of the claimed process necessarily results in a reduction in sizing effect. *See Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 680 F. App'x 956, 960 (Fed. Cir. 2017).

Example 4 explicitly discloses step a), in addition to every other step in the claimed process. As discussed below, Example 4 of WO'376 anticipates each and every element of the process set forth in the body of claim 1. Since "reducing the sizing effect" is the natural result of practicing step a), the method disclosed in Example 4, which discloses this step and every other element in claim 1, necessarily yields the same result. *See King,* 616 F.3d at 1276 ("[T]o inherently anticipate, the prior art need only give the same results as the patent, not better.").[15] Accordingly, WO'376 anticipates the preamble of claim 1.

b. <u>Step a)</u>: "reacting the bacterial saccharide with 0.001-0.7 molar equivalents of periodate to form an activated bacterial saccharide"

Example 4 of WO'376 is directed to the bacterial saccharide 6B and discloses activation with periodate in the claimed range. Specifically, Example 4 discloses the "Preparation of Polysaccharide-Protein Conjugates," and part A, discloses the process for "Oxidization of Polysaccharide," to activate the

[15] In *King*, the patent claimed that oral bioavailability of metaxalone increased when administered with food. 616 F.3d at 1271. Though the prior art did not identify "increased bioavailability," the Court held that the increase was a necessary result when the drug was administered with food as disclosed in the prior art. *Id*. at 1275.

saccharide. (Exh. 1004, 23:23-33). Part A teaches that bacterial saccharide 6B[16] was "oxidized by reaction" with 0.27 MEq of periodate, which is within the claimed range. (*Id*., 23:26-30); *see Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art") (emphasis in original) (citing *In re Petering*, 301 F.2d 676, 682 (C.C.P.A. 1962)).

The disclosure in Example 4 of WO'376 allows for calculation of MEq. According to part A, "10 mg of polysaccharide was dissolved in 1 mL of distilled water at 4°C overnight." (Exh. 1004, 23:27-28). "One mL of 0.2 M [200 mM] PBS [phosphate buffered saline] (pH 7.2)" was added to the saccharide solution to obtain a total volume of 2 mL. (*Id.,* 23:28-29; Exh. 1033, 781). Next, the "[p]olysaccharide was oxidized by reaction with 2 mM sodium periodate (MW: 213.9)." (Exh. 1004, 23:29-30; Exh. 1033, 904). The calculation below

[16] The specification indicates that 6B was conjugated to pseudopneumolysin in Example 4. Example 5 states, "[t]he *S. pneumoniae* 14, 18C, 19F, 23F, 4, 6B and 9V polysaccharide-pseudopneumolysin protein conjugates prepared as described in Example 4 were tested for their ability to raise antibodies against polysaccharide and pneumolysin in mice." (Exh. 1004, 27:28-30).

demonstrates that Example 4 discloses 0.27 MEq of periodate (the ratio of moles of periodate to moles of saccharide 6B RU), which falls within the claimed range of 0.001-0.7 (Exh. 1009, ¶¶ 111-113):

- **Moles of periodate**

  = 2 mM sodium periodate x 2 mL = 4 µmol sodium periodate

- 4 µmol sodium periodate = 4 µmol periodate

- **Moles of 6B RU**

  = (10 mg)/(683.5 mg/mmol)[17] = 0.01463 mmol = 14.63 µmol

- **MEq of periodate**

  = (4 µmol periodate)/(14.63 µmol 6B RU) = **0.27 MEq periodate**

Thus, WO'376 discloses step a) of the process of claim 1.

c. "wherein step a) occurs in a buffer which does not contain an amine group, and the buffer has a concentration between 1-100 mM"

Example 4, part A, of WO'376 discloses a buffer without an amine group in the claimed concentration range. The relevant discussion in Example 4 is that "[o]ne mL of 0.2 M PBS (pH 7.2)" was added to the saccharide solution to obtain a total volume of 2 mL. (Exh. 1004, 23:28-29).

[17] The MW of the RU of saccharide 6B is 683.5 g/mol (or mg/mmol). (Exh. 1009, ¶ 66).

First, PBS is phosphate buffered saline, which does not contain an amine group. (*Id.,* 29:1-2; Exh. 1033, 781). Second, 1 mL of 0.2 M PBS is added to a 1 mL solution of saccharide in water to obtain a volume of 2 mL. Since the volume doubles, the initial buffer concentration of 0.2 M (200 mM) is reduced by half to 0.1 M (100 mM). (Exh. 1009, ¶¶ 115-116).

Accordingly, WO'376 discloses this limitation.

d. <u>Step b)</u>: "mixing the activated bacterial saccharide with a carrier protein"

Example 4, part D of WO'376, describes the "Preparation of Polysaccharide-Protein Conjugates." (Exh. 1004, 27:13). Part D discloses that "10 mg of pseudopneumolysin in 0.1 M PBS was added to the oxidized [*i.e*., activated] polysaccharide reaction mix and incubated at room temperature with gentle stirring for 30 min." (*Id*., 27:16-18).[18] The specification also teaches that pseudopneumolysin is "useful [as a] carrier[] of polysaccharides." (*Id*., 10:18). Thus, WO'376 discloses mixing the activated bacterial saccharide with a carrier protein and discloses step b) of the claimed process. (Exh. 1009, ¶¶ 117-119).

[18] While saccharide 18C is specifically identified in part D of Example 4, Example 5 states that "*S. pneumoniae* 14, 18C, 19F, 23F, 4, 6B and 9V polysaccharide–pseudopneumolysin protein conjugates [were] prepared as described in Example 4." (Exh. 1004, 27:28-29).

e. Step c): "reacting the activated bacterial saccharide and the carrier protein with a reducing agent to form a conjugate"

Example 4, part D, of WO'376 states that sodium cyanoborohydride, a well-known reducing agent (Exh. 1006, 168), "was added" to the "oxidized polysaccharide and pseudopneumolysin mixture." (Exh. 1004, 27:18-20). As discussed above, the "oxidized polysaccharide" corresponds to the activated bacterial saccharide and pseudopneumolysin is the carrier protein.[19]

Accordingly, WO'376 discloses step c) of the claimed process. (Exh. 1009, ¶ 120).

f. "and wherein the bacterial saccharide is *S. pneumoniae* capsular saccharide 6B"

WO'376 discloses this limitation because it specifically discloses a method of conjugating *S. pneumoniae* capsular saccharide 6B. WO'376 teaches that "[i]n some embodiments, the capsular saccharide is selected from the group consisting of serotype 4, **6B**, 9V, 14, 18C, 19F, and 23F." (Exh. 1004, 2:17-18, 11:11-15). Moreover, Example 4, Part A, of WO'376 states that for the purpose of preparing "Polysaccharide-Protein Conjugates," "Pneumococcal capsular polysaccharides,

[19] Again, Example 5 states that "*S. pneumoniae* 14, 18C, 19F, 23F, 4, 6B and 9V polysaccharide-pseudopneumolysin protein conjugates [were] prepared as described in Example 4." (Exh. 1004, 27:28-29).

such as 4, **6B**, 9V, 14, 18, 19F, and 23F, were purchased from American Type Culture Collection (Manassas, VA)." (*Id*., 23:23-27). Further, Example 5 states that "[t]he *S. pneumoniae* 14, 18C, 19F, 23F, 4, **6B** and 9V polysaccharide-pseudopneumolysin protein conjugates ***prepared as described in Example 4*** were tested for their ability to raise antibodies against polysaccharide and pneumolysin in mice." (*Id.,* 27:28-30). Moreover, Figure 11 of WO'376 shows "a graph depicting anti-pneumolysin IgG antibody production elicited in mice following immunization with a serotype 6B polysaccharide-pseudopneumolysin conjugate." (*Id.,* 7:27-29).

For at least the reasons set forth above, WO'376 discloses each and every element of claim 1 of the '839 patent, in the order recited in the claim. As such, WO '376 anticipates claim 1 of the '839 patent. (Exh. 1009, ¶¶ 122-123).

2. Claim 2 is anticipated

Claim 2 recites "[t]he process of claim 1 wherein the buffer is selected from the group consisting of phosphate buffer, borate buffer, acetate buffer, carbonate buffer and citrate buffer." (Exh. 1001, 26:45-47). Example 4 of WO'376 discloses that during the oxidation step, "[o]ne mL of 0.2 M PBS (pH 7.2) was added." (Exh. 1004, 23:28-29). "PBS" is phosphate buffered saline. (*Id*., 29:1-2). Thus, WO'376 anticipates claim 2. (Exh. 1009, ¶ 124).

3. Claim 3 is anticipated

Claim 3 recites "[t]he process of claim 1 wherein the pH in step a) is pH 3.5-8.0." (Exh. 1001, 26:48-49). Example 4 of WO'376 discloses that during the oxidation step, "[o]ne mL of 0.2 M PBS (pH 7.2) was added." (Exh. 1004, 23:28-29). A buffer with pH 7.2 falls within the scope of the claimed pH range 3.5-8.0. Thus, WO'376 anticipates claim 3. (Exh. 1009, ¶ 125).

4. Claim 4 is anticipated

As discussed above with respect to claim construction, the claim 4 recitation of the MWs are non-limiting. Thus, the WO'376 anticipates claim 4.

5. Claim 5 is anticipated

Claim 5 recites "[t]he process of claim 1 wherein the carrier protein is selected from the group consisting of tetanus toxoid, fragment C of tetanus toxoid, diphtheria toxoid, CRM197, Pneumolysin, protein D, PhtD, PhtDE and N19." (Exh. 1001, 26:53-56).

WO'376 discloses conjugation with the carrier protein pneumolysin. WO'376 teaches that "the invention features a composition containing a polypeptide conjugated to a *S. pneumoniae* capsular saccharide, wherein the polypeptide contains a fragment of at least 400 contiguous amino acids of a *S. pneumoniae* pneumolysin protein." (Exh. 1004, 1:28-30). WO'376 discloses the use of pneumolysin proteins with up to 470 of the 471 amino acids present in wild type pneumolysin. (*Id.*, 3:8, 10:2-4). And WO'376 teaches that the pneumolysin

protein utilized for Examples 4 and 5 consists of "amino acids 1-464 of the pneumolysin protein of SEQ ID NO:1." (*Id*., 19:2-3).

Nothing in the '839 patent specification or prosecution history limits the term "Pneumolysin" solely to a single 471 amino acid form of the protein. To the contrary, the specification teaches that "[t]he term 'carrier protein'" includes "pneumococcal pneumolysin (Kuo et al (1995) Infect Immun 63; 2706-13)." (Exh. 1001, 6:28, 6:51-52). The reference cited in the '839 patent, Kuo, et al. (Exh. 1032), uses a recombinant variant of pneumolysin that actually differs from the native form of the protein by at least two amino acids. (*See* Exh. 1001, 6:51-52; Exh. 1032, 2708-09).

Thus, WO'376 anticipates claim 5. (Exh. 1009, ¶¶ 127-130).

6. Claim 6 is anticipated

Claim 6 recites "[t]he process of claim 1 wherein the reducing agent comprises sodium cyanoborohydride or sodium triacetoxyborohydride." (Exh. 1001, 26:57-59). Example 4 of WO'376, states that sodium cyanoborohydride "was added" to the "oxidized polysaccharide and pseudopneumolysin mixture." (Exh. 1004, 27:19-20).

Thus, WO'376 anticipates claim 6. (Exh. 1009, ¶ 131).

7. Claim 7 is anticipated

Claim 7 recites "the process of claim 1 comprising a further step e) of

purifying the conjugate." (Exh. 1001, 26:60-61). Example 4, part D, of WO'376 teaches that once the saccharide-protein conjugate was prepared, the conjugate was purified using size exclusion chromatography. (Exh. 1004, 27:13-25). Example 4 teaches that "[t]he mixture was chromatographed on Sepharose CL-4B column (1.5 x 100 cm) equilibrated with 1 x PBS, pH 7.2. (*Id*., 27:22-23). "The fractions containing both protein and saccharide were pooled and concentrated by an Amicon Centricon-30 (molecular weight cutoff 30,000) and then assayed for protein and polysaccharide content." (*Id*., 27:23-25). Sepharose CL-4B is a well-known agarose-based size exclusion chromatography base matrix. (*See, e.g*., Exh. 1033, 1903).

The '839 patent contemplated such size exclusion chromatography as within the scope of the invention with respect to step e). (Exh. 1001, 12:45-50 (step e)…may comprise size exclusion chromatography.")).

Thus, WO'376 anticipates claim 7. (Exh. 1009, ¶¶ 132-133).

8. Claim 8 is anticipated

Claim 8 recites "[t]he process of claim 1 containing a further step of mixing the conjugate with further antigens." (Exh. 1001, 26:62-63). According to the '839 patent, "further antigens" can comprise other saccharides that are "optionally conjugated to a carrier protein." (*Id*., 12:53-13:20). WO'376 teaches that the conjugate can be mixed with additional antigens, such as other conjugates,

to form "multivalent vaccines which elicit an immune response against a plurality of infectious agents." (Exh. 1004, 11:28-12:6, 27:27-28:7). It further teaches that "[o]ne or more of different capsular polysaccharides can be conjugated to a single polypeptide or a plurality of polypeptides." (*Id.*, 11:16-19).

Thus, WO'376 anticipates claim 8. (Exh. 1009, ¶ 134).

9. Claim 9 is anticipated

Claim 9 recites "[t]he process of claim 8 wherein the further antigens comprise one or more *S. pneumoniae* proteins selected from the group consisting of the Poly Histidine Triad family (PhtX), Choline Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins (or fusions), pneumolysin (Ply), PspA, PsaA, Sp128, Sp101, Sp130, Sp125 and Sp133." (Exh. 1001, 26:64-27:3).

WO'376 teaches that "[o]ne or more of different capsular polysaccharides can be conjugated to a single polypeptide or a plurality of polypeptides" to form a "multivalent conjugate" or "multivalent vaccines." (Exh. 1004, 11:16-19, 12:5). WO'376 teaches that "[i]n general, the polypeptide component of the conjugate: contains either a portion of a *S. pneumoniae* pneumolysin [Ply] protein or a mutated *S. pneumoniae* pneumolysin protein." (*Id*., 9:21-23).

Moreover, WO'376 teaches that the pneumolysin proteins can be expressed fused to "other pneumococcal proteins, such as…choline binding protein A." (*Id*.,

10:12-17). Choline binding protein A is a *S. pneumoniae* protein that belongs to the "Choline Binding Protein family (Cbpx)." (Exh. 1001, 26:67; Exh. 1036, 576, 578; Exh. 1055, 5:14-30).

Accordingly, WO'376 anticipates claim 9. (Exh. 1009, ¶¶ 135-137).

10. Claim 10 is anticipated

Claim 10 recites "[t]he process of claim 1 wherein the conjugate is mixed with an adjuvant or a pharmaceutically acceptable excipient." (Exh. 1001, 27:4-5). WO'376 teaches that "[a]dditives customary in vaccines may also be present, for example stabilizers such as lactose or sorbitol, and adjuvants to enhance the immunogenic response." (Exh. 1004, 12:2-3). Moreover, Example 5 of WO'376 teaches mixing the conjugates "with aluminum hydroxide adjuvant." (*Id*., 27:30-28:1).

Thus, WO'376 anticipates claim 10. (Exh. 1009, ¶ 138).

B. Ground II: Claims 1-10 Would Have Been Obvious Over WO'376 In View Of Frasch And Lees

At the time of the alleged invention, POSAs had a deep well of knowledge regarding the process of conjugating bacterial saccharides to carrier proteins. That knowledge included an appreciation of the advantages and drawbacks of oxidation with periodate, which was one of "the most common activation methods" used in saccharide-protein conjugation at the time. (Exh. 1006, 166-67; Exh. 1005, 6469).

The claims of the ’839 patent add nothing new to what was known in the art. Rather, the ’839 patent claims the process of reductive amination for saccharide-protein conjugation, which was conventional at the time of the alleged invention, and the established scientific principle that lowering the concentration of periodate during oxidation reduces the sizing effect on the saccharide.

1. Claim 1 would have been obvious over WO’376 in view of Frasch and Lees

As discussed above, WO’376 anticipates every limitation of the claims. Accordingly, POSAs following the teachings of WO’376 would have successfully achieve what was claimed in the ’839 patent.

The 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. However, given a POSA’s knowledge that periodate oxidation can decrease the size of the saccharide (*see* Section IV.C), “reducing the sizing effect” would have been obvious.

Frasch and Lees are each representative of the state of the art at the time of the alleged invention, including what was known regarding the effects of periodate on pneumococcal saccharide size and loss of epitopes. (Exh. 1009, ¶ 144). Like WO’376, each of Frasch and Lees discloses saccharide-protein conjugation using periodate as an oxidizing agent. (*Id.*). Frasch and Lees teach POSAs to expect a

reduction in sizing effect when following the steps of Example 4 of WO'376. (*Id.*, ¶ 145). Based on these references, it would have been obvious to POSAs that using lower concentrations of periodate (such as the 0.27 MEq periodate disclosed in WO'376) would reduce the sizing effect. (*Id.*). Each of Frasch and Lees also motivates POSAs to reduce the sizing effect in order to preserve important epitopes for immunogenicity. (*Id.*).

a. Using lower concentrations of periodate to "reduc[e] the sizing effect" would have been obvious

At the time of the alleged invention, it was well-known in the art that the mechanism by which periodate activates saccharides—by oxidizing adjacent hydroxyls—necessarily results in cleavage of the carbon-carbon bonds between the adjacent hydroxyls. This cleavage changes and destabilizes the saccharide structure and ultimately leads to a reduction in the MW of the saccharide (*i.e.*, sizing effect) and loss of important epitopes—effects that POSAs would have been motivated to avoid. The size reduction occurs because portions of the saccharide, such as a side chain portion, break off, or because the saccharide backbone fragments. (*Id.*, ¶ 146).

Frasch and Lees each teaches that periodate activation changes the saccharide structure and can lead to reduction in its size. Frasch, which reviews the "[a]nalytical and manufacturing challenges" associated with the preparation of bacterial saccharide-protein conjugates, teaches that "[o]ne *important potential*

problem with use of periodate to activate the PS is altering the physical structure of the PS, with loss of important epitopes." (Exh. 1005, 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*., 6469, *see also* Exh. 1006, 167; Exh. 1009, ¶ 147).

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*." (Exh. 1005, 6469). In fact, Frasch 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.*; *see also* Exh. 1006, 168*;* Exh. 1017, 4 ("sodium periodate may break up [bacterial] carbohydrates into smaller fragments and/or disrupt epitopes, which may be undesirable")).

Moreover, Lees teaches 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. According to Lees, "[v]icinal [*cis*] hydroxyls are usually cleaved first, *and at higher concentrations of periodate*, *trans* hydroxyls are *also* cleaved." (Exh. 1006, 168).

Based on Frasch and Lees—amongst other available prior art—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. (Exh. 1009, ¶ 149).

b. POSAs would have been motivated to reduce the sizing effect and preserve immunogenicity

POSAs were aware that the sizing effect of periodate can negatively influence immunogenicity. Thus POSAs would have been motivated to use mild periodate conditions, such as 0.27 MEq taught in WO'376, in an effort to preserve immunogenicity. (*Id.*, ¶ 150).

Lees teaches that size reduction can affect important epitopes. Lees discloses that "[w]hile 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." (Exh. 1006, 164). Disruption of epitopes on the saccharide interferes with the immunogenicity of the conjugates or the immune system's ability to recognize the conjugates. (*Id*., 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*., 164). And, as admitted by PO during prosecution of the PCT application, POSAs could "conclude[]" from reading the prior art "that smaller *Streptococcal* polysaccharides tend to be **less immunogenic** than larger *Streptococcal* polysaccharides."[20] (Exh. 1003, IPR90; Exh. 1009, ¶¶ 151-152).

Based on the state of the art at the time, POSAs sought conjugation protocols that would reduce the detrimental effects of the process while preserving immunogenicity. For example, Lees discloses that "[t]he conjugation protocol should be mild so that it does not (i) destroy significant epitopes on either the protein or the PS, (ii) *cause undesired depolymerization of the PS*, or (iii) introduce any deleterious epitopes." (Exh. 1006, 166; *see also* Exh. 1017, 2; Exh. 1009, ¶ 153).

[20] Applicant stated with respect to Steinhoff (Exh. 1020), that "[t]he serotype 23F polysaccharide conjugated (PS-CRM) was significantly more immunogenic than the 23F oligosaccharide similarly directly linked to the carrier protein (OS-CRM). This finding suggests that CPS size influences the immunogenicity of type 23F conjugates and confirms previous reports." (Exh. 1003, IPR90).

Based on the above, it would have been obvious to POSAs that using lower concentrations of periodate during the oxidation step would reduce the sizing effect, and POSAs would be motivated to do so. (Exh. 1009, ¶ 154). Moreover, as discussed further below, there would be a reasonable expectation of success.

c. The claimed range of 0.001-0.7 MEq of periodate would have been obvious

As discussed above, no modification of the reaction conditions disclosed in Example 4 of WO'376 would be required to practice claim 1. Nevertheless, Frasch and Lees confirm that using low concentrations of periodate during the activation step, such as the 0.27 MEq of 6B disclosed in Example 4, would reduce the sizing effect compared to using higher concentrations of periodate. (Exh. 1005, 6469; Exh. 1006, 167-68).

If it were necessary to do so, it would take no more than routine experimentation to adjust the MEq of periodate taught in WO'376—and still remain within the claimed ranged—to optimize the immunogenicity of the saccharide conjugate. (Exh. 1009, ¶ 155).

As shown in the table below, numerous other prior art publications disclosed the use of periodate at concentrations within the claimed range to activate pneumococcal saccharides.

Table 1[21]

Saccharide	Molar Equivalents ("MEq") Periodate Used to Activate Pneumococcal Saccharide ("Pn")	Reference
Pn 4	0.33 MEq 0.17 MEq	WO'376[22] Lee (2002)[23]
Pn 6A	0.27 MEq	Anderson[24]
Pn 6B	0.27 MEq 0.14 MEq	WO'376 Lee (2002)
Pn 9V	0.40 MEq 0.20 MEq	WO'376 Lee (2002)
Pn 12	0.44 MEq	Anderson
Pn 14	0.28 MEq 0.41 MEq 0.14 MEq 0.13 MEq	WO'376 Anderson Lee (2002) Kuo[25]
Pn 18C	0.40 MEq 0.20 MEq 0.19 MEq, 0.37 MEq	WO'376 Lee (2002) Kuo
Pn 19F	0.24 MEq 0.12 MEq	WO'376 Lee (2002)
Pn 23F	0.31 MEq 0.31 MEq 0.15 MEq	WO'376 Anderson Lee (2002)

[21] (Exh. 1009, ¶ 42 and Appendix C; Exh. 1058, 2081; Exh. 1059, 559-60).

[22] (Exh. 1004, 23:23-33 (Example 4A)).

[23] (Exh. 1024, 98, 101-02).

[24] (Exh. 1015, 23:23-55).

[25] (Exh. 1016, 10:42-11:15, 12:23-13:2 (Examples 3, 4, 7)).

In fact, as indicated in the table, the prior art disclosed that amounts within the claimed range were used to activate 6B saccharide. Thus, the prior art at the time of the alleged invention disclosed numerous examples of periodate concentrations that are within the claimed range for activating pneumococcal saccharides, including 6B. *See Titanium Metals*, 778 F.2d at 781 (prior art, which taught an amount falling within the claimed range, disclosed the claimed range).

d. POSAs would have been motivated to combine WO'376 with Frasch and Lees with a reasonable expectation of success

As discussed above, WO'376 is directed to the same technology as the '839 patent, and it teaches every limitation set forth in claim 1. Accordingly, POSAs following Example 4 of WO'376 would successfully achieve what was recited in claim 1 of the '839 patent. While WO'376 does not explicitly discuss that "reducing the sizing effect" is the result of following Example 4, Frasch and Lees teach POSAs that following the steps of Example 4 of WO'376, POSAs would have a reasonable expectation of success in reducing the sizing effect. (Exh. 1009, ¶ 159).

POSAs following Example 4 would be motivated to look to Frasch and Lees, which are directed to the same exact technology at issue in WO'376 (and the '839 patent). Each is representative of the state of the art at the time of the alleged invention, including what was known regarding the effects of periodate on

pneumococcal saccharide size and loss of epitopes. Each discusses conjugation of proteins to pneumococcal saccharides, including 6B—and all three of the references discuss the use of periodate as an activation agent. (*Id.*, ¶ 160; Exh. 1004, 23:23-33, 27:13-30; Exh. 1005, 6469; Exh. 1006, 164-67).

Thus, POSAs considering the method of Example 4 of WO'376 would logically look to Frasch and Lees to ascertain more about the process of activation/conjugation and the effects of that process on the structure and size of saccharides and immunogenicity. (Exh. 1009, ¶ 161). As evidenced by Frasch and Lees, POSAs would know that: (1) periodate activation changes the structure and can lead to decreases in the size of the saccharides, (2) higher concentrations of periodate lead to even more changes, (3) size reduction can lead to loss of important epitopes, and (4) periodate conditions should be mild enough to minimize saccharide structure changes. (*Id.*). Thus, POSAs would be motivated to combine these references and have a reasonable expectation that the process in WO'376's Example 4 would reduce the sizing effect. (*Id.*). In other words, armed with Frasch and Lees, in conjunction with the detailed process set forth in WO'376, POSAs would have a reasonable expectation of success in achieving the claimed method. (Exh. 1009, ¶ 162).

2. Claims 2-10 would have been obvious over WO'376 in view of Frasch and Lees

Claims 2-10, each depend from claim 1. The limitations of claims 2-10 are anticipated by WO'376 for the reasons discussed above, and 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. Accordingly, claims 2-10 would also have been obvious over WO'376 in view of Frasch and Lees.

C. Ground III: Claim 4 Would Have Been Obvious In Further View Of The GSK 2009 PCT

Claim 4 recites "[t]he process of claim 1 wherein the average molecular weight of the bacterial saccharide is between 1-1100 kDa" after the saccharide has been activated in step a). (Exh. 1001, 26:50-52). As discussed above, the MW recitation in this claim, if found to be limiting, should be construed to mean that the bacterial saccharide, which has been activated in step a), has a weight-average MW within the recited ranges prior to conjugation with the protein.

As discussed above, claim 4 would have been obvious over WO'376 in view of Lees and Frasch. Claim 4 would have also been obvious based on these

references and further in view of PO's own prior art, GSK 2009 PCT.[26]GSK 2009 PCT, like WO'376, discloses methods of preparing pneumococcal capsular saccharide-conjugate vaccines, including with periodate activation and reductive amination. (Exh. 1007, IPR1, 17:1-35). GSK 2009 PCT teaches that a carrier protein, such as pneumolysin, is conjugated to pneumococcal saccharides, including 6B. (*Id*., 9:13-14, 10:12-17, 11:34-12:12, 21:28-22:12, 23:15-24:2).

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*., 14:30-33).[27] Therefore, this reference discloses that the saccharide that is to be conjugated should have a MW within the range recited in claim 4 (*i.e.,* 1-1100 kDa). (*See also* Exh. 1054, 13:66-14:7, 16:9-15 (saccharides to be conjugated should have certain sizes prior to conjugation to improve conjugation

[26] GSK 2009 PCT was published on December 31, 2008, more than one year prior to the '839 patent's U.S. filing date of March 7, 2011, and is thus Section 102(b) prior art.

[27] These MW are measured by MALLS. (*Id*., 15:32-16:6)

efficiency; prior to conjugation, 23F saccharides are "about 400-500 KD" and 6B saccharides are "about 300 KD" and "reduction of Pn-Ps size to about 500 plus-minus about 300 kilodaltons is an appropriate target for this phase of the process for each Pn-Ps subtype"); Exh. 1025, 6:14-17 (saccharides used for conjugation have a preferred MW in the "average range of 10,000 to 500,000 [daltons, *i.e.*, 10-500 kilodaltons]")).

Furthermore, the prior art, including GSK 2009 PCT, taught POSAs ways to obtain the pre-conjugation saccharide sizes recited in the claims. (Exh. 1007, 16:11-15). Thus, 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. (Exh. 1009, ¶ 168).

Because (1) both WO'376 and GSK 2009 PCT disclose methods for preparing pneumococcal-protein conjugates, involving periodate activation and reductive amination, and (2) GSK 2009 PCT teaches that pre-conjugation MWs within the claimed ranges improved immune responses, POSAs would have been motivated to combine GSK 2009 PCT's teachings with WO'376's method to arrive at claim 4. Since the references are directed to similar methods, and GSK 2009 PCT and other prior art disclose MWs within the claimed range, POSAs would also have a reasonable expectation of success in doing so. (Exh. 1009, ¶¶ 166-

170).

Accordingly, claim 4 would have been obvious over WO'376, in view of Lees, Frasch, and the GSK 2009 PCT.

D. Ground IV: Claim 5 Is Obvious In Further View Of Prevnar

Claim 5 recites "[t]he process of claim 1 wherein the carrier protein is selected from the group consisting of tetanus toxoid, fragment C of tetanus toxoid, diphtheria toxoid, **CRM197**, Pneumolysin, protein D, PhtD, PhtDE and N19." (Exh. 1001, 26:53-56). As discussed above, claim 5 is obvious based on WO'376 in view of Lees and Frasch. This claim is also obvious based on these references and further in view of Prevnar.[28] (Exh. 1008, 3241-47).

The prior art disclosed using the recited carrier proteins for pneumococcal conjugates. (Exh. 1015, col. 23:23-55 (diphtheria toxoid); (Exh. 1016 (pneumolysin); (Exh. 1008, 3241 (CRM197); (Exh. 1007, 10:12-29, 11:34-12:22 (tetanus toxoid, fragment C of tetanus toxoid, diphtheria toxoid, CRM197, pneumolysin, protein D, PhtD, PhtDE and N19)).

Specifically, Prevnar discloses an FDA-licensed, commercially available vaccine that includes pneumococcal conjugates prepared by reductive amination

[28] Prevnar was published in 2008, more than one year prior to the '839 patent's U.S. filing date of March 7, 2011, and is thus Section 102(b) prior art.

(like those of WO'376). (Exh. 1008, 3241). Prevnar teaches that a carrier protein, *e.g.*, CRM_{197}, is conjugated to its saccharides, including serotype 6B. (*Id.*). Therefore, Prevnar discloses "CRM_{197}" as recited in claim 5.

Since both WO'376 and Prevnar disclose the use of reductive amination to make pneumococcal conjugates, POSAs would have been motivated to use Prevnar's CRM_{197} as the protein in WO'376's method for making 6B-protein conjugates. GSK 2009 PCT's disclosure that both CRM197 and pneumolysin can be used to make pneumococcal conjugates would have motivated POSAs to use CRM197 as the carrier protein for the pneumolysin in WO'376's example to make the conjugates. (Exh. 1007, 10:12-17).

Also, in view of Prevnar's teaching that CRM_{197} was successfully conjugated to pneumococcal saccharides by reductive amination, which were included in a commercially-available vaccine, 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 6B-protein conjugates. Accordingly, claim 5 would have been obvious over WO'376, in view of Lees, Frasch, and Prevnar. (Exh. 1009, ¶¶ 171-175).

E. Ground V: Claim 9 Would Have Been Obvious In Further View Of The GSK 2009 PCT

Claim 9 depends on claim 8, which recites the "process of claim 1 containing a further step of mixing the conjugate with further antigens." (Exh.

1001, 26:62-63). Claim 9 recites the "process of claim 8 wherein the further antigens comprise one or more *S. pneumoniae* proteins selected from the group consisting of the Poly Histidine Triad family (PhtX), Choline Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins (or fusions), pneumolysin (Ply), PspA, PsaA, Sp128, Spl0l, Sp130, Sp125 and Sp133." (*Id*., 26:64-27:3). Claim 9 is obvious over WO'376 in view of Lees and Frasch, as discussed above. Claim 9 is also obvious based on these references and further in view of GSK 2009 PCT.

GSK 2009 PCT states that its compositions containing the conjugates may also contain *S. pneumoniae* proteins as free or unconjugated proteins. (Exh. 1007, 21:28-31). These proteins can be the ones recited in claim 9, *e.g.*, pneumolysin. (*Id*., 22:8-12). Therefore, GSK 2009 PCT discloses mixing the further antigens recited in claim 9 with pneumococcal capsular saccharide conjugates, such as those in WO'376.

Both WO'376 and GSK 2009 PCT relate to pneumococcal-protein conjugates and they disclose similar conjugation methods for preparing them. In view of this common disclosure, 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 9 of the '839 patent, with a reasonable expectation of success in doing so. Therefore, claim 9 would have been obvious

over WO'376, in view of Lees, Frasch, and GSK 2009 PCT. (Exh. 1009, ¶¶ 176-177).

F. There Is No Probative Evidence Of Secondary Considerations

To rebut the examiner's *prima facie* finding that the claims were obvious in view of the prior art disclosure of 0.8-1.2 MEq of periodate, PO argued, erroneously, that it had "discovered a new range of periodate with unexpected properties." (Exh. 1002, IPR588). PO asserted that Example 1 in the specification "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*., IPR589). Moreover, PO argued that the saccharides conjugated with the claimed process "have been demonstrated to be highly immunogenic" unexpectedly. (*Id*., IPR589). For the reasons discussed below, these arguments lack merit and are insufficient to overcome a *prima facie* showing of obviousness.

1. The results set forth in Example 1 do not cover the claimed range

Example 1 does not show that any allegedly unexpected results occurred over the entire claimed range of periodate and is thus insufficient. MPEP 716.02(d); *In re Peterson*, 315 F.3d 1325, 1329-31 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium). The

broadly claimed range of 0.001-0.7 MEq of periodate covers nearly three orders of magnitude. Further, each of the claims is completely silent regarding such parameters as time, temperature, and concentration of reaction. Moreover, the majority of the claims are silent regarding buffer identity (all but claim 2), and pH (all but claim 3).

Example 1, however, only provides data points that are limited to a small portion of this extensive range—for 6B: 0.1-0.3 MEq performed for a single length of time (17 hours), temperature (room temperature), pH (6.0), and buffer (10mM phosphate buffer); for 23F: 0.1-0.5 MEq performed for a single length of time (17 hours), temperature (room temperature), pH (6.0), and buffer (phosphate buffer, either 10mM or 100mM); (Exh. 1001, 19:12-38 (Table 1)). Therefore, even if Example 1 demonstrated unexpected results—which it clearly does not for the reasons discussed below—such a showing would not be commensurate with the scope of the claims and is thus insufficient to rebut a *prima facie* showing of obviousness.[29] (MPEP 716.02(d); *Peterson*, 315 F.3d at 1329-31; Exh. 1009, ¶ 179).

[29] Notably, Example 1 does not state that the results are surprising—in fact, like the prior art, it acknowledges that the sizing effect can be reduced by, for example, reducing the MEq of periodate used. (Exh. 1001, 19:6-10).

2. The results set forth in Example 1 are not "unexpected" and the claimed range is not critical

Example 1 of the '839 patent gives absolutely no indication that the claimed range provides unexpectedly better results than using periodate outside the claimed range, or that it is critical. (Exh. 1009, ¶ 180).

In Example 1, saccharides 23F and 6B were each oxidized using a small number of varying MEq of periodate and concentrations of buffer. After oxidation, the molecular size distributions of the saccharides were measured. The data in Example 1 merely shows that reducing the amount of periodate reduced the sizing effect of the saccharide. That result is precisely what POSAs would have expected. (*Id.*, ¶ 181); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (test results, showing the continuation of a trend already known in the prior art, only establish a difference in degree, not a difference in kind needed to demonstrate unexpected results that are probative of nonobviousness).

The claimed range is also not critical, as higher amounts of periodate (indisputably disclosed in the prior art) also reduce the sizing effect. As discussed above, the original claims in the PCT application recited a range of periodate up to 1.2 MEq but were amended during prosecution to overcome Hausdorff. Based on these facts, inclusion of Example 1 (which discloses results from 0-1.2 MEq of periodate) was designed to show that reducing periodate across the range recited in the specification (*i.e.*, 0.001-1.2 MEq) reduces the sizing effect. Example 1 does

not demonstrate that the claimed periodate range of 0.001-0.7 MEq as amended was somehow critical, or provided any unexpected results compared to the prior art range of 0.8-1.2 MEq. (*See also* Exh. 1009, ¶ 182).

3. The experiments in Example 1 were not designed to show unexpected results

The experimental design of Example 1 fails to support a finding of unexpected results for several reasons. First, there is no evidence that the experiments include sufficient data points or are statistically significant. More importantly, however, the buffer conditions are not held constant. In order to fairly assess the sizing effect of periodate across the claimed range of periodate concentrations, relative to periodate concentrations outside the claimed range, it is critical that the other conditions (*i.e.*, buffer concentration) in Example 1 remain constant. The only variable in the experiment should be the MEq of periodate used. There is no evidence in the intrinsic record that these types of properly controlled tests were conducted. (*Id.*, ¶ 183).

Notwithstanding, PO argued during prosecution that Example 1 showed unexpected results because "[s]accharides conjugated using Applicants' claimed process are not subject to the same sizing effect as those conjugated with higher periodate concentrations." (Exh. 1002, IPR589; Exh. 1009, ¶ 184). In support of that argument, Applicant's asserted the following:

> Example 1 illustrates that the use of higher

> concentrations of periodate leads to a substantial sizing effect.… In Table 1 (page 31), if 1 molar equivalents of periodate is used to oxidize the 23F saccharide, the size of the 23F saccharide is reduced to 36kDa. However when 0.5 molar equivalents of periodate is used, the 23F saccharide maintains a size of 179.1kDa. When 0.2 molar equivalents of periodate is used the 23F saccharide retains a size of 336kDa. When 0.15 molar equivalents of periodate is used a size of 398.5kDa is retained, and when 0.1 molar equivalents of periodate is used a size of 466.9kDa is retained. A similar effect is seen for the 6B saccharide. Here a reduction of size to 868kDa is seen when 0.75 molar equivalents of periodate is used, whereas a size of 975kDa is retained when 0.1 molar equivalents of periodate is used.

(*Id*.). Below are tables summarizing PO's results as presented to the Examiner.

Table A

Periodate (MEq)	Phosphate Buffer (mM)	Size of 6B (kDa)
0.75	10	868
0.3	10	961
0.2	10	990
0.1	10	975

Table B

Periodate (MEq)	Buffer	Size of 23F (kDa)
1.0	**Water**	36
0.5	10 mM PBS	179.1
0.2	10 mM PBS	336
0.15	10 mM PBS	398.5
0.1	10 mM PBS	466.9

As shown above, PO's argument that "[s]accharides conjugated using Applicants' claimed process **are not subject to the same sizing effect** as those conjugated with higher periodate concentrations" is completely erroneous. First, with respect to 6B, PO only compared one condition where the concentration of periodate was outside the upper end of the claimed range (*i.e.*, 0.75 MEq. of periodate). Table A above summarizes the results reported in Table 1 for 6B. As shown, there is only one data point measuring the size of the saccharide when the amount of periodate used was outside of the claimed range. The criticality of the claimed range cannot be tested against one data point outside of the claimed range. (Exh. 1009, ¶ 185).

Likewise, PO ***never tested*** 23F with periodate MEq outside the claimed range (*i.e.*, > 0.7) in 10 mM PBS. The results of samples oxidized in 10 mM PBS cannot be compared to samples oxidized in water. PO's conclusion from these data is a scientifically unsound, and clearly an *ad hoc* comparison manufactured by PO in an attempt to traverse the prior art. (*Id.*, ¶ 186).

Even if one could compare samples oxidized in water and buffer, there is **only one instance** where the periodate MEq falls outside of the claimed range, which is insignificant. The criticality of the claimed range cannot be tested against one data point outside of the claimed range. (*Id.*, ¶ 187).

4. The allegedly "unexpected" results based on immunogenicity lack nexus

Relying on Examples 2 and 3 of the specification, PO also argued during prosecution that the saccharides conjugated with the claimed process "have been demonstrated to be highly immunogenic," compared to other conjugates. (Exh. 1002, IPR589).

The results reported are unrelated to the claims at issue, and thus lack the necessary nexus to overcome a *prima facie* case of obviousness. *In re GPAC Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("for objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention"); *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994) (Even "impressive" evidence of secondary considerations is not "entitled to weight" unless "it is relevant to the claims at issue.").

First, the claims do not require that the conjugates be more immunogenic than those made using 1-cyano-4-dimethylaminopyridinium tetrafluroborate (CDAP). Second, neither Example 2 nor 3 of the '839 patent reports the saccharide size for either the conjugate made by reductive amination or by CDAP.

Accordingly, no conclusions can be drawn about immunogenicity based on the size of the saccharide prior to conjugation. (Exh. 1009, ¶ 190).

Also, PO compared the immunogenicity of the conjugates prepared by oxidation with 0.4 MEq of periodate to that of conjugates made by CDAP. (Exh. 1002, IPR590; Exh. 1001, 19:40-22:7). Unlike, the claimed process, CDAP does not involve activation of saccharides with periodate. (Exh. 1001, 20:1-52). Therefore, the PO's allegedly "unexpected" results are not even based on a comparison with conjugates prepared by a process that used periodate. The results fail to demonstrate that conjugates made with MEq of periodate within the claimed range have better immunogenicity than those made with MEq of periodate outside this range. (Exh. 1009, ¶ 190). Thus, the alleged "unexpected" results were not based on a comparison with the closest prior art, which would have at least used reductive amination, and therefore fail to establish that the claims are not obvious. MPEP 716.02(e); *Bristol-Myers Squibb Co. v. Teva Pharm. USA*, *Inc*., 752 F.3d 967, 977 (Fed. Cir. 2014) (to be probative, results must be unexpected compared with the closest prior art).

Finally, although the claims do not require that the conjugates be immunogenic, based on the prior art presented here, POSAs would have had a reasonable expectation of success in achieving an immunogenic conjugate prepared by activation with the claimed periodate amounts. According to

WO'376, which tested the "ability to raise antibodies against polysaccharide and pneumolysin in mice," "[t]he serum of the conjugate-administered mice," including the 6B conjugate, "exhibited unexpectedly high titers of anti-pneumolysin and anti-polysaccharide antibodies." (Exh. 1004, 27:28-30, 29:9-11). Thus, it was understood that following the process set forth in WO'376 (*i.e.*, 0.27 MEq periodate) yields an immunogenic 6B-pseudopneumolysin protein conjugate. (Exh. 1009, ¶ 191).

VIII. CONCLUSION

Based on the foregoing, the Board should institute *inter partes* review and cancel claims 1–10 of the '839 patent as unpatentable.

Respectfully Submitted,

Date: June 11, 2018

/*Anthony M. Insogna*/

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp.

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Petition complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Petition, including footnotes, contains 13,744 words as counted by the word count function of Microsoft Word.

Dated: June 11, 2018

/*Anthony M. Insogna*/

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,265,839, along with all exhibits supporting and filed with the Petition, were served on June 11, 2018, via UPS overnight courier delivery directed to the attorneys of record for the patents at the following addresses:

GlaxoSmithKline
Global Patents UP4110
1250 South Collegeville Road
Collegeville, PA 19426

GlaxoSmithKline
Global Patents
Five Moore Drive
Mail Stop: 5.5A
Research Triangle Park, NC 27709-3398

Date: June 11, 2018

/*Anthony M. Insogna*/

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel: (858) 314-1200
Fax: (844) 345-3178
Email: MerckGSK-IPRs@jonesday.com

Attorney for Petitioner
Merck Sharp & Dohme Corp.