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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. 8,753,645

Claims 1-11

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
rPL	recombinant pneumolysin
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. 8,753,645 (Biemans, Duvivier & Gavard) ("'645 patent")
1002	Prosecution History of United States Patent No. 8,753,645 (USSN 13/581,824) ("'824 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. 8,753,645 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)
1014	Jennings, et al., "Immunochemistry of Groups A, B, and C Meningococcal Polysaccharide-Tetanus Toxoid Conjugates," *J. Immunol. 127*(3), 1011-18 (Sept. 1981)

Exhibit No.	Description
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 95/08348 (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")
1026	Great Britain Patent Application No. 1003922.0 (GlaxoSmithKline Biologicals S.A.) ("GB '922 appln.")
1027	United States Patent No. 9,265,839 (Biemans, Duvivier & Gavard) ("'839 patent")
1028	Prosecution History of United States Patent No. 9,265,839 (USSN 14/202,119) ("'119 application")
1029	United States Patent Application Publication No. US 2007/0184071 (Hausdorff, Siber, Paradiso & Prasad) ("Hausdorff")

Exhibit No.	Description
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	Intentionally Not Used
1033	Sigma Catalog, *Biochemicals and Reagents for Life Science Research (2000-2001)* (Sigma-Aldrich Co., 2000)
1034	De Velasco, et al., "Epitope Specificity of Rabbit Immunoglobulin G (IgG) Elicited by Pneumococcal Type 23F Synthetic Oligosaccharide - and Native Polysaccharide - Protein Conjugate Vaccines: Comparison with Human Anti-Polysaccharide 23F IgG," *Infection & Immunity 62*(3), 799-808 (Mar. 1994)
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	Intentionally Not Used
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)
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)

Exhibit No.	Description
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	Richards, et al., "Structure of the Specific Capsular Polysaccharide of *Streptococcus Pneumoniae* Type 23F (American Type 23)," *Biochem. Cell Biol. 66*, 758-71 (1988)
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	United States Patent No. 4,242,501 (Cano & Kuo) ("Cano")
1053	Determination of Regulatory Review Period for Purposes of Patent Extension; PREVNAR-13, 79 Fed. Reg. 18,035 (Mar. 31, 2014)
1054	United States Patent No. 5,623,057 (Marburg, Tolman, Kniskern, Miller, Hagopian, Ip. Hennessey, Kubek & Burke)
1055	Intentionally Not Used
1056	United States Patent Application Publication No. US 2009/0130137 (Hausdorff, Siber & Paradiso)
1057	Intentionally Not Used
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 '645 patent on other grounds, and (2) petitions for *Inter Partes* Review of U.S. Patent No. 9,265,839. 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:

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I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") requests *inter partes* review ("Request") of independent claim 1 and dependent claims 2-11 of U.S. Patent No. 8,753,645 (the "'645 patent") (Exh. 1001, 27:2-28:23) as obvious under 35 U.S.C. § 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, 23F. The very same 23F "glycoconjugates" were well-known long before the alleged invention of the '645 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 '645 patent to

[1] Like the '645 patent specification, "the term 'saccharide'" throughout this Petition "may indicate polysaccharide[s]." (Exh. 1001, 4:48-49).

attach *S. pneumoniae* bacterial saccharides – including 23F – to proteins. POSAs 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 '645 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 was disclosed in publications known to POSAs before the earliest filing date of the '645 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 '645 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 '645 patent that the claimed range of periodate provides unexpected results when compared to using periodate

outside of that range. The data in the '645 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 '645 patent never should have been allowed.

Obviousness. The challenged claims of the '645 patent would have been obvious to POSAs at the time of the alleged invention over U.S. Patent No. 4,902,506 to Anderson, et al. ("Anderson") (Exh. 1015) in view of U.S. Patent No. 5,565,204 to Kuo, et al. ("Kuo") (Exh. 1016).[2] The combination of Anderson and Kuo ("Anderson/Kuo") discloses a process to prepare *S. pneumoniae* saccharide-protein conjugates that is identical to the process of claims 1-11.

Anderson explicitly discloses every element of claim 1 with the exception of the buffer. Specifically, Anderson discloses a conjugation method that includes: (a) activating the 23F bacterial saccharide with approximately 0.31 MEq of periodate, (b) mixing the activated bacterial saccharide with a carrier protein, and (c) conjugation of the activated bacterial saccharide to the carrier protein with a reducing agent to form a conjugate. (Exh. 1015, 23:23-55).

Like Anderson, Kuo discloses a method of making *S. pneumoniae* saccharide-protein conjugates that includes: (a) activating a saccharide with

[2] Anderson and Kuo were not before the Examiner during prosecution.

periodate, (b) mixing the activated saccharide with a carrier protein, and (c) reacting the activated saccharide and the carrier protein with a reducing agent to form a conjugate. Kuo also discloses that the saccharide is activated in a buffer having the features recited in claim 1. While Kuo does not provide a specific example of making a 23F conjugate, Kuo discloses that its methods can be used to make 23F conjugates. (Exh. 1016, 1:9-15, 4:40-44, 5:18-22).

POSAs would have been motivated to combine Anderson's teachings with those of Kuo to arrive at the claimed method, with a reasonable expectation of success. This would have been the case since (1) both references disclose very similar methods for making saccharide conjugates, including 23F conjugates, and (2) non-amine containing buffers, at the claimed concentrations, had been routinely used during periodate oxidation of saccharides.

The claim preamble language "reducing the sizing effect" merely expresses the intended purpose of performing the claimed process and is non-limiting. *See 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 obvious because "reducing the sizing effect" is necessarily achieved by practicing the process steps set forth in Anderson/Kuo.

The challenged claims would also have been obvious to POSAs in further 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 Anderson/Kuo.

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 '645 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 1-11 of the ’645 patent pursuant to the following statement of precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1-11	103	• **Anderson** • **Kuo**
II	1-11	103	• **Anderson** • **Kuo** • **Frasch** • **Lees**
III	4 and 5	103	• **Anderson** • **Kuo** • **Frasch** • **Lees** • PCT Patent Application Publication No. WO 2009/000825A2 to GSK (“**GSK 2009 PCT**”) (Exh. 1007)

III. A PERSON OF ORDINARY SKILL IN THE ART

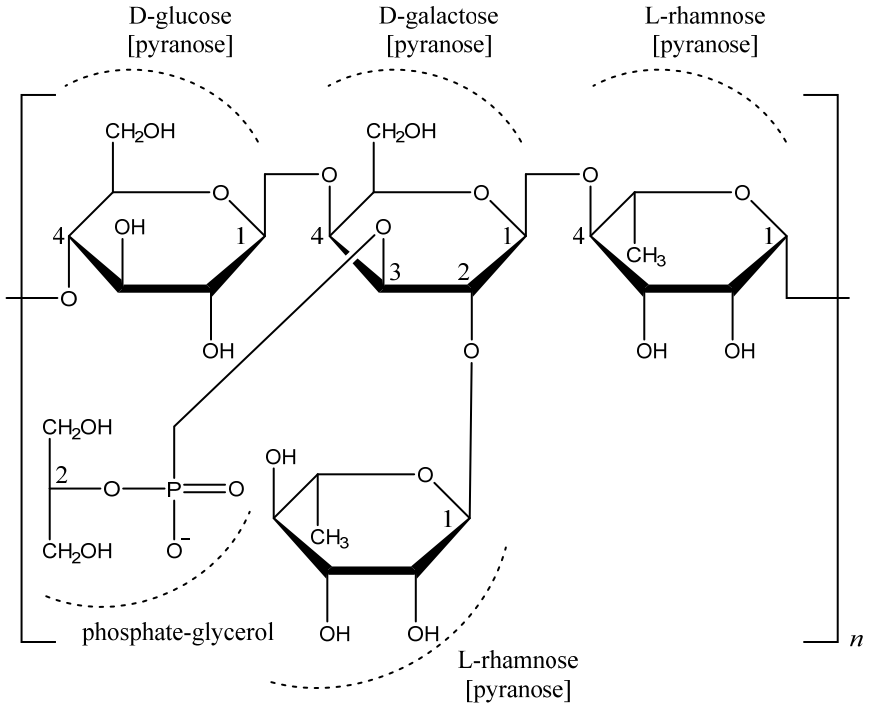
As confirmed by Dr. Avci, a POSA, as of March 9, 2010, would have had a Ph.D. degree in Biochemistry, Chemistry, or a comparable discipline, and at least 2-3 years of research experience focused on carbohydrate chemistry. (Exh. 1009, ¶ 21).

IV. STATE OF THE ART

A. *Streptococcus pneumoniae* "Conjugate" Vaccines

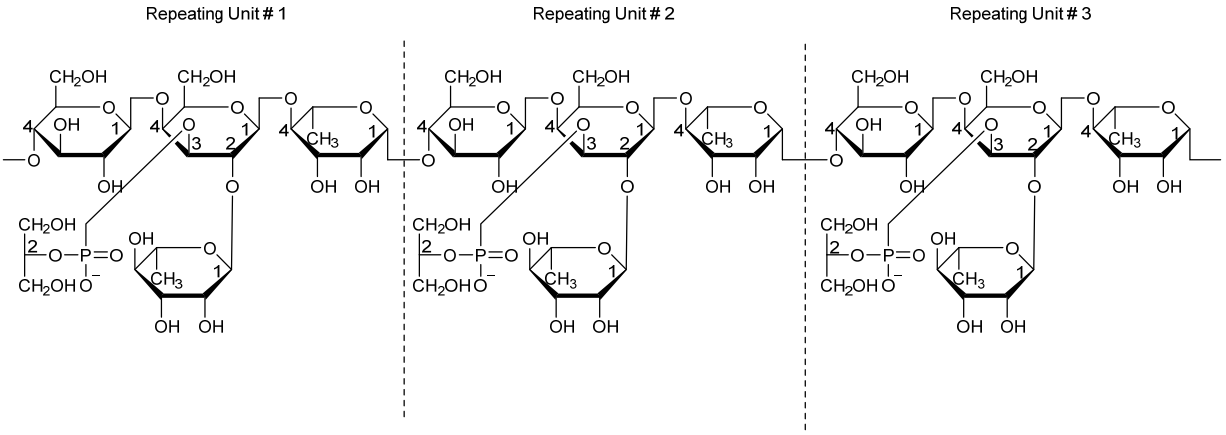
Bacterial saccharides, which form a capsule around the outside of certain bacteria, are made up of polymeric chains of saccharide repeating units ("RU"). (Exh. 1006, 163). These saccharides, including ones covalently linked (*i.e.*, conjugated) to carrier proteins, have long been used successfully in 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, 163-64; 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 23F.



This RU, which has a molecular weight ("MW") of 769.6 g/mol, contains a backbone of three sugar rings (glucose(Glc*p*)--galactose(Gal*p*)--rhamnose(Rha*p*)). (Exh. 1009, ¶¶ 66, 68; Exh. 1047, 66-67). Two branches or side chains, a phosphate-glycerol and a rhamnose, are attached to the galactose. (*Id.*, ¶ 66). The "n" in the figure is the number of RUs in the saccharide. (*Id.*).

The 23F RUs are attached to each other in the 23F saccharide as follows (*Id.*, ¶ 67):

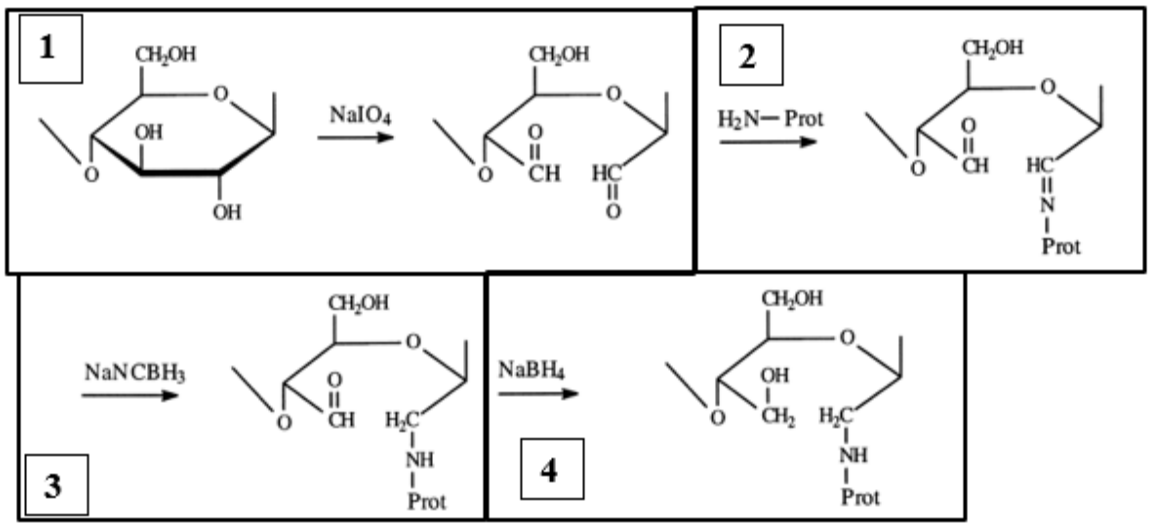


The FDA approved the first commercially available conjugate vaccine against *S. pneumoniae*, Prevnar® ("Prevnar") in 2000. (Exh. 1010, 750). The seven bacterial saccharide-carrier protein conjugates in Prevnar, which included 23F, were produced by periodate activation, *i.e.*, oxidation, followed by 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 23F. (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, ¶ 37). The reductive amination process involves coupling of an aldehyde and an amine to form the final "conjugated" product. (Exh. 1013, 175). Conjugation of oxidized saccharides with proteins through reductive amination was well-documented long before the '645 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, 12:41-60).

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." 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.*).

It was well-known at the time of the alleged invention that significant changes in pH reduce control over reaction conditions or prevent the oxidation of the saccharide (*see* box "1") from occurring under constant conditions. (Exh. 1006, 166-67). A buffer, such as phosphate buffered saline ("PBS"), or sodium acetate buffer, is a solution that resists a change in pH when acid or base is added to the reaction. (Exh. 1049, 169; Exh. 1046, 448). Thus, periodate oxidation reactions were routinely performed under buffered conditions. (Exh. 1044, 131; Exh. 1004, 23:25-33; Exh. 1016, 10:46-48; Exh. 1009, ¶ 44).

POSAs were aware to "[a]void amine-containing buffers . . . because they may interact with the aldehyde groups as they are formed" during oxidation. (Exh. 1044, 131). Moreover, POSAs were aware that the concentration of the buffer can be readily determined, particularly since the prior art disclosed concentrations of non-amine containing buffers for oxidation of saccharides. For example, the prior art used the following buffer conditions for periodate oxidation of pneumococcal saccharides, including 23F: 100 mM PBS[3, 4] and 100 mM acetate buffer.[5] In fact,

[3] (Exh. 1004, 23:25-33).

[4] (Exh. 1024, 98).

[5] (Exh. 1016, 10:47-50, 10:65-67, 12:41-45).

these buffers were used for the activation of saccharides with amounts of periodate within the claimed range. (Exh. 1009, ¶ 45). Therefore, selecting a type and concentration of buffer was merely a matter of routine optimization and well within the ordinary skill in the art.

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[6], 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).

[6] 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 the epitopes present. (*See* Exh. 1031, 37).

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 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, ¶ 53).[7]

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

[7] Emphasis added throughout unless otherwise noted.

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. 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, 14:21-25; 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 '645 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. 1034, 805; Exh. 1048, 762-63).

By the time of the '645 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 '645 PATENT

The '645 patent issued on June 17, 2014 and is assigned on its face to GlaxoSmithKline Biologicals S.A. (Exh. 1001, IPR1). The '645 patent issued from U.S. Patent Application No. 13/581,824 (the "'824 application") (Exh. 1002), which 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.[8] (Exh. 1001, 1:5-11). U.S. Patent No. 9,265,839 (the '839 patent") (Exh. 1027), issued from U.S. Patent Application No. 14/202,119 (the "'119 application") (Exh. 1028), which is a continuation of the '824 application. (Exh. 1027, IPR1). PO filed a terminal disclaimer during prosecution of the '119 application to overcome the Examiner's double patenting rejection over the '645 patent. (Exh. 1028, IPR667). The specifications of the '645 and '839 patents are identical, and the claims are directed to an identical process, except the claims of the '839 patent recite serotype 6B instead of 23F.

Claim 1 of the '645 patent, the only independent claim, is directed to a process for conjugating bacterial saccharide 23F:

> **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,

[8] The '645 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 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.

b) mixing the activated bacterial saccharide with a carrier protein;

c) reacting the activated bacterial saccharide and the carrier protein with a reducing agent to form a conjugate;

wherein step a) occurs in a buffer which does not contain an amine group, and the buffer has a concentration between 1-100 mM and wherein the bacterial saccharide is *S.pneumoniae* capsular saccharide 23F.

(Exh. 1001, 27:2-15). 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 '645 patent. During prosecution, the Examiner did not consider Anderson or Kuo, the references discussed below that render the claims obvious. (Exhs. 1015-1016). The Examiner also did not consider Frasch, Lees or GSK 2009 PCT in connection with prosecution of the claims.[9] (Exhs. 1005-1007).

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

[9] 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.

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 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. Patent 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.[10] While the Examiner relied on

[10] The 0.8-1.2 MEq periodate range was used to activate serotype 4, which unlike 23F, 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, ¶¶ 86, 180). POSAs

this disclosure in Hausdorff relating to serotype 4, the Examiner never considered activation conditions for serotype 23F.[11] 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, IPR487-

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would have understood that lower MEq of periodate could be used to oxidize a comparable number of diols in serotype 23F compared to 4. (Exh. 1009, ¶ 86).

[11] In fact, the Examiner did not consider Hausdorff's citation to Anderson, which discloses the use of 0.31 MEq periodate for 23F. (Exh. 1029, ¶ [0039]; Exh. 1009, ¶ 42).

88). 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 routine." (*Id.*). In response, PO argued, as it did during the PCT prosecution, that the claimed periodate range provided unexpected results. (*Id.*, IPR506-09).

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.*, IPR508). 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 '645 patent merely demonstrate a general and continuous trend that was completely expected based on what was known in the art—reducing the amount of periodate reduces the sizing effect. (Exh. 1009, ¶ 90).

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, 1:49-51). 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.*).

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*., 1:52-58). 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 '645 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.[12]

[12] 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.

A. "reducing the sizing effect"

The '645 patent claims a process for conjugating bacterial saccharide 23F and "reducing the sizing effect" of the bacterial saccharide. (Exh. 1001, 27:2-15). The claim term "reducing the sizing effect" is recited only in the preamble of claim 1, the sole independent claim in the '645 patent. (*Id*.). For the reasons discussed 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, ¶ 94; Exh. 1001, 19:65-20:2).

Even if PO argues that "reducing the sizing effect" was added during prosecution 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, 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. 1002, 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 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. 1002, IPR519)[13].

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

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[13] 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. 1002, IPR537).

forth in the body of the claim, *e.g.*, step c) recites the step of "reacting...*to form a conjugate*." (Exh. 1001, 27:10-11).

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, 6:4-5). "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*., 8:1-3). Thus, reducing the sizing effect means to decrease the reduction in size. (Exh. 1009, ¶¶ 95-97).

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, ¶ 100; 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, 20:47-51).. 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, ¶ 101).

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

0.52 mmole sodium periodate = 0.52 mmole periodate[14]

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

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

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. 1001, 27:22-24). Claim 5 recites "[t]he process of claim 1 wherein the average molecular weight of the 23F saccharide is between 100-470 kDa after step a)." (*Id.*, 28:1-3). These recitations of the MWs are statements 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 these recitations of

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

MW are central to patentability or were used to distinguish the claims 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 recitations are limiting, they 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 '645 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, 5:52-56).

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 1-11 Of The '645 Patent Are Obvious Over Anderson In View Of Kuo

Claims 1-11 of the '645 patent are obvious over Anderson, which issued February 20, 1990, in view of Kuo, which issued October 15, 1996. Each of Anderson and Kuo issued more than one year prior to the U.S. filing date of

the ’645 patent (*i.e.*, March 7, 2011) and is prior art.

Anderson discloses a reductive amination method of making conjugates of pneumococcal saccharides, including serotypes 3, 6A, 12, 14 and 23F[15], and a carrier protein. (Exh. 1015, 23:23-55; Exh. 1052, 1:22-40). Anderson’s Example 11 discloses a method for conjugating pneumococcal saccharide 23F (“23F”) by: (a) reacting 23F with 0.31 MEq of periodate (Exh. 1015, 23:44-55), (b) mixing the activated 23F with diphtheria toxoid, a carrier protein (*id*., 23:28-38), and (c) reacting the activated 23F and carrier protein with the reducing agent sodium cyanoborohydride ($NaCNBH_3$) to form a conjugate (*id*.).

Example 11 does not disclose that activation of the saccharide occurs in buffer, as recited in claim 1. However, Anderson discloses the use of buffer in other conjugation reactions. (Exh. 1015, 20:1-8). Moreover, it was well-understood at the time of the alleged invention that changes in pH could affect the oxidation reaction and buffers were commonly used to control the pH of oxidation

[15] There are two nomenclature systems for designating pneumococcal serotypes, Danish and U.S. Because of these two systems, a given serotype may have two interchangeable designations. For example, Type “23” saccharide shown in Table 15, is the U.S. designation, which corresponds to 23F, the Danish designation. (Exh. 1052, 1:22-40; Exh. 1059 559-60).

reactions. (Exh. 1009, ¶ 44). POSAs would have been motivated to perform the reactions disclosed in Anderson in the presence of buffer in view of this common knowledge in the art.

Kuo discloses methods for making conjugates of periodate-activated pneumococcal saccharides and a carrier protein comprising all of the steps of claim 1, including using a buffer having the claimed features. (Exh. 1016, 4:26-56, 5:5-17, 10:43-59, 11:17-39). Kuo exemplifies periodate activation of saccharide Type 14 (Example 3), followed by conjugation to a recombinant pneumolysin carrier protein using sodium cyanoborohydride (Example 5). (*Id.*, 11:20-39).[16] Kuo also disclosed a similar method of periodate activation and conjugation for saccharide Type 18C. (*Id.*, 10:65-11:15, 12:41-60 (Examples 4, 70).

While Kuo does not provide a specific example of making a 23F conjugate, Kuo discloses that 23F saccharide can be used in its conjugation methods. Kuo states that "[t]he capsular polysaccharides of various pneumococcal types used in this invention have been described in commonly-assigned U.S. Pat. Nos. 4,242,501 [Exh. 1052] and 4,686,102 (1,3), which are incorporated by reference." (Exh. 1016, 10:27-35). The '501 patent explicitly discloses Type 23F and 14 saccharides. (Exh. 1052, 1:9-14, 29:34-31:43, 36:12-38:15).

[16] Examples 3 and 5 will collectively be referred to as Examples 3/5.

1. Claim 1 is obvious

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, Anderson/Kuo discloses the preamble of claim 1

With respect to the preamble phrase "**[a] process for conjugating a bacterial saccharide**," Anderson discloses methods for conjugating pneumococcal saccharides to carrier proteins. (Exh. 1015, 23:23-43; Exh. 1009, ¶ 115). Thus, Anderson discloses this element of the preamble.

With respect to the preamble phrase "**reducing the sizing effect**," Anderson/Kuo 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) Anderson/Kuo discloses step a), in addition to every other step in the claimed process. (Exh. 1009, ¶ 116).

Claims are not made patentably new by adding inherent results or benefits of prior art processes to the claims as limitations. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011). 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 Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010).

"Reducing the sizing effect" is the natural result of practicing step a). The '645 patent teaches that treatment with periodate during oxidation[17] leads to a reduction in the size of the bacterial saccharide (sizing effect). (Exh. 1001, 6:4-5, 7:1-2). When low concentrations of buffer and low amounts of periodate are used during oxidation, however, the sizing effect is reduced. (*Id.*, 8:1-3, 19:65-20:2). The specification does not teach any additional steps to "reduce[e] the sizing effect" aside from performing step a) of the claimed process (*i.e.*, low MEq

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

periodate (0.001-0.7) and low buffer concentration (1-100mM)). (Exh. 1009, ¶¶ 119-121).

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, IPR508). 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." (Exh. 1002, IPR508). The Examiner then noted in the Notice of Allowance that the reducing in the sizing effect results from using the periodate amounts of step a). (*Id.*, 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, 3-4; 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).

Anderson/Kuo discloses step a), in addition to every other step in the claimed process. As discussed below, Anderson/Kuo discloses 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 of Anderson/Kuo, which discloses this step and every other element in claim 1, necessarily yields this same result. *Kao*, 639 F.3d at 1070 (the claimed effect, which results from practicing an obvious method, adds nothing patentable). Accordingly, Anderson/Kuo discloses 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"

Anderson's Example 11 is directed to pneumococcal saccharide 23F and discloses activation with periodate in the claimed range. Specifically, Anderson teaches that saccharide 23F was activated with 0.31 MEq of periodate, which is within the claimed range. (Exh. 1015, 23:36-55).

The disclosure in Anderson allows for calculation of MEq. Anderson discloses that 10 mg of the polysaccharide was reacted with 4 micromoles (μmol) of sodium periodate ($NaIO_4$), which is equivalent to 4 μmol of periodate (IO_4^-). (*Id*., 23:45-55). The calculation below demonstrates that Anderson used 0.31 MEq of periodate (the ratio of moles of periodate to moles of saccharide 23F RU), which falls within the claimed range of 0.001-0.7 (Exh. 1009, ¶¶ 122-124):

- **<u>Moles of periodate</u>** = 4 μmol

- **<u>Moles of 23F RU</u>**

= (10 mg)/(769.6 mg/mmol[18]) = 0.01299 mmol = 12.99 μmol

- **<u>MEq of periodate</u>**

= (4 μmol periodate)/(12.99 μmol 23F RU) = **0.31 MEq periodate**

Thus, Anderson discloses step a) 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"

Kuo describes activating pneumococcal saccharides Type 14 and 18C by dissolving the saccharides in 100mM (0.1M) sodium acetate buffer (pH 5.0). (Exh. 1016, 10:47-49, 10:65-11:2, 12:41-45). Sodium acetate buffer does not contain an amine group. (Exh. 1033, 1630).

Accordingly, Kuo discloses this limitation. (Exh. 1009, ¶ 126).

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

Anderson teaches that the activated 23F saccharide is reacted with a carrier protein, diphtheria toxoid, by mixing them together. (Exh. 1015, 23:36-55; Exh. 1009, ¶ 127).

[18] (Exh. 1009, ¶ 66).

Thus, Anderson discloses step b).

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

Anderson states that the activated 23F was reacted with the carrier protein and $NaCNBH_3$ (*i.e.*, sodium cyanoborohydride)[19], a well-known reducing agent (Exh. 1006, 168), to form conjugates. (Exh. 1015, 23:36-38).

Accordingly, Anderson discloses step c). (Exh. 1009, ¶ 129).

f. "and wherein the bacterial saccharide is *S. pneumoniae* capsular saccharide 23F"

Anderson discloses this limitation because it specifically discloses a method of conjugating *S. pneumoniae* capsular saccharide 23F.

For at least the reasons set forth above, Anderson/Kuo discloses every element of claim 1 of the '645 patent.

g. POSAs would have been motivated to combine the teachings of Anderson and Kuo to arrive at the method of claim 1

Both Anderson and Kuo relate to methods of activating pneumococcal saccharides with periodate and conjugating these saccharides to carrier proteins using reductive amination. (Exh. 1015, 23:23-55; Exh. 1016, 5:5-9). Thus,

[19] (Exh. 1033, 901).

POSAs would have been motivated to combine the teachings of Anderson and Kuo to make conjugates. (Exh. 1009, ¶ 133).

Moreover, POSAs would have been motivated to combine Anderson's method with Kuo's buffer. As discussed above, periodate activation reactions were routinely performed under buffered conditions to prevent changes in pH during activation. POSAs were aware that amine-containing buffers should be avoided and used buffers in concentrations within the claimed range of 1-100 mM when activating pneumococcal saccharides. (*Id.*, ¶ 135).

In view of the knowledge in the art, POSAs would have been motivated to use the buffer in Kuo (100mM) to prevent pH changes during periodate activation in Anderson's method. (*Id.*, ¶ 136).

h. Reasonable expectation of success

POSAs would have had a reasonable expectation of success in combining the teachings of Anderson and Kuo to achieve the claimed process. As discussed above, Anderson discloses a method involving periodate activation for making 23F-protein conjugates that meet all the limitations of the claimed process except the recited buffer. (Exh. 1015, 23:36-55). Kuo's method, which according to Kuo can be used to make 23F conjugates, involves periodate activation of saccharides in the recited buffer. (Exh. 1016, 10:42-51, 11:17-40). Both references use periodate in the claimed range during activation. (Exh. 1009, ¶ 137).

In addition, POSAs were aware of the benefit of using non-amine containing buffers, such as an acetate buffer, as used in Kuo, when performing periodate activation. (*Id.*, ¶ 139). Therefore, POSAs would have reasonably expected that a non-amine containing buffer could be successfully used with Anderson's method. (*Id.*). Also, non-amine containing buffers at a concentration of 100 mM, such as those in Kuo, had been used to activate saccharides with periodate in amounts within the claimed range. (*Id.*). Thus, POSAs would have had a reasonable expectation of success in using Kuo's buffer, which had the features of the buffer of claim 1, in Anderson's method to achieve the claimed process. (*Id.*, ¶¶ 139-140).

Furthermore, although claim 1 does not require that the conjugates exhibit an immune response effect, Anderson and Kuo each discloses that its respective methods successfully produced conjugates exhibiting such activity. (Exh. 1015, 23:40-43; Exh. 1016, 14:12-37, Tables 1-3).

2. Claim 2 is obvious

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, 27:16-18). Kuo discloses that during periodate activation the pneumococcal saccharides were dissolved in 0.1M or 100mM sodium acetate buffer. (Exh. 1016, 10:46-48).

Thus, Anderson/Kuo renders obvious claim 2. (Exh. 1009, ¶ 142).

3. Claim 3 is obvious

Claim 3 recites "[t]he process of claim 1 wherein the pH in step a) is pH 3.5-8.0." (Exh. 1001, 27:20-21). Kuo discloses that during periodate activation the saccharide was dissolved in 0.1M, or 100mM, "sodium acetate buffer (pH 5.0)." (Exh. 1016, 10:46-48). A buffer with pH 5.0 falls within the scope of the claimed pH range 3.5-8.0. Thus, Anderson/Kuo renders obvious claim 3. (Exh. 1009, ¶ 143).

4. Claims 4 and 5 are obvious

As discussed above with respect to claim construction, the claims 4 and 5 recitations of the MWs are non-limiting.

Even if they are limiting, however, Kuo discloses average MW ranges that render obvious the ranges recited in claims 4 and 5. Claims 4 and 5 require the bacterial saccharide, which has been activated in step a), have weight-average MW within the recited ranges prior to conjugation with the protein. (Exh. 1001, 5:52-56).

Kuo discloses that its activated saccharides have a "chain length of about 15-800 monomeric units," prior to conjugation with the protein. (Exh. 1016, 4:55-56). Since saccharide chains are made up of RUs, POSAs would have understood that the term "monomeric unit" meant a saccharide RU. Based on Kuo's

disclosure of the number of RUs in the saccharide chains, the average MW of the saccharide chains could have been determined since the MWs of pneumococcal RUs are known. (Exh. 1009, ¶ 146).

For 23F, the average MWs that correspond to the chain lengths disclosed in Kuo are from 11.5 to 615.7 kDa.[20] (*Id.*, ¶ 147). This range overlaps with, and in fact falls completely within, claim 4's recited range of 1-1100 kDa, and entirely overlaps claim 5's recited range of 100-470 kDa. Also, techniques for adjusting saccharide sizes prior to conjugation and measuring such sizes were well-known. In view of this knowledge and Kuo's disclosed MW range, POSAs would have been motivated and had a reasonable expectation of success in obtaining the MW of claims 4 and 5. Thus, Anderson/Kuo renders these claims obvious. (*Id.*, ¶ 148).

[20] 15-800 monomeric units = 15-800 RUs

MW of the 23F RU = 769.6 g/mol

769.6 g/mol = 769.6 Da = 0.7696 kDa

15 RUs x 0.7696 kDa = 11.5 kDa

800 RUs x 0.7696 kDa = 615.7 kDa

5. Claim 6 is obvious

Claim 6 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, 28:4-7). Anderson teaches that its saccharides are conjugated to diphtheria toxoid. (Exh. 1015, 23:23-55).

Thus, Anderson/Kuo renders obvious claim 6. (Exh. 1009, ¶ 150).

6. Claim 7 is obvious

Claim 7 recites "[t]he process of claim 1 wherein the reducing agent comprises sodium cyanoborohydride or sodium triacetoxyborohydride." (Exh. 1001, 28:8-10). Anderson discloses that sodium cyanoborohydride ($NaCNBH_3$) was added to the activated saccharides and carrier protein. (Exh. 1015, 23:36-38; Exh. 1006, 168).

Thus, Anderson/Kuo renders obvious claim 7. (Exh. 1009, Exh. 151).

7. Claim 8 is obvious

Claim 8 recites "the process of claim 1 comprising a further step e) of purifying the conjugate." (Exh. 1001, 28:11-12). Anderson discloses that after the conjugates were made, they were purified: "[t]he protein fraction was recovered by precipitation and washing with 90% saturated ammonium sulfate." (Exh. 1015, 23:38-40). Kuo discloses that after its conjugates were prepared, they were

purified using chromatography. (Exh. 1016, 11:29-32). Specifically, the mixtures containing the conjugates were "chromatographed on a column of Sepharose™ CL-4B." (*Id*.). Peak fractions containing the conjugates were identified, pooled and characterized. (*Id*., 11:33-36). Sepharose™ CL-4B is a well-known agarose based size exclusion chromatography base matrix. (*See, e.g*., Exh. 1033, 1903).

The '645 patent contemplated such size exclusion chromatography as within the scope of the invention with respect to step e). (Exh. 1001, 13:39-44 ("step e) . . . may comprise size exclusion chromatography.")).

Thus, Anderson/Kuo renders obvious claim 8. (Exh. 1009, ¶¶ 152-155).

8. Claim 9 is obvious

Claim 9 recites "[t]he process of claim 1 containing a further step of mixing the conjugate with further antigens." (Exh. 1001, 28:13-14). According to the '645 patent, "further antigens" can comprise other saccharides that are "optionally conjugated to a carrier protein." (*Id*., 13:47-14:11). Kuo teaches that saccharide conjugates can be mixed with other antigens, *e.g*., other pneumococcal saccharide-carrier protein conjugates. (Exh. 1016, 5:53-58; *see also id*., 2:23-26). In view of this teaching in Kuo, POSAs would have been motivated to mix the saccharide conjugates made by the method of Anderson/Kuo with other antigens, and would have had a reasonable expectation in doing so.

Thus, Anderson/Kuo renders obvious claim 9. (Exh. 1009, ¶¶ 156-157).

9. Claim 10 is obvious

Claim 10 recites "[t]he process of claim 9 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, 28:15-21).

As discussed above in connection with claim 9, Anderson/Kuo discloses mixing other antigens with its saccharide conjugates. Kuo further teaches that such other antigens can be conjugates of other pneumococcal saccharides and recombinant pneumolysin ("rPL") carrier protein. (Exh. 1016, 5:53-58). In view of this teaching in Kuo, POSAs would have been motivated to mix the saccharide conjugates of Anderson/Kuo with other antigens comprising pneumolysin, with a reasonable expectation of success.

Thus, Anderson/Kuo renders obvious claim 10. (Exh. 1009, ¶¶ 158-159).

10. Claim 11 is obvious

Claim 11 recites "[t]he process of claim 1 wherein the conjugate is mixed with an adjuvant or a pharmaceutically acceptable excipient." (Exh. 1001, 28:22-23). Anderson discloses that its conjugates can be formulated with a pharmaceutically acceptable carrier to produce a vaccine and that such carriers

include aluminum phosphate gel adjuvant suspended in sodium phosphate-buffered saline. (Exh. 1015, 3:4-6, 6:42-46).

Kuo teaches that the "conjugates may be bound to aluminum hydroxide, aluminum phosphate (alum) or other pharmaceutically acceptable adjuvants." (Exh. 1016, 5:46-52, 22:18-20). In addition, Kuo's Example 9 discloses that the conjugates prepared by Example 3/5 were adsorbed onto aluminum phosphate as an adjuvant before they were administered to mice. (*Id*., 14:15-30). Adjuvants, according to the '645 patent, include aluminum hydroxide and aluminum phosphate. (Exh. 1001, 15:35-43).

Based on these teachings, POSAs would have been motivated to mix the saccharide conjugates of Anderson/Kuo with an adjuvant or a pharmaceutically acceptable excipient, with a reasonable expectation of success. Thus, Anderson/Kuo renders obvious claim 11. (Exh. 1009, ¶¶ 160-162).

B. Ground II: Claims 1-11 Would Have Been Obvious Over Anderson/Kuo 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 ’645 patent add nothing new to what was known in the art. Rather, the ’645 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 Anderson/Kuo in view of Frasch and Lees

As discussed above, Anderson/Kuo discloses every limitation of the claims. Accordingly, POSAs following the teachings of Anderson/Kuo would successfully achieve what was claimed in the ’645 patent.

The only recited language of claim 1 that Anderson/Kuo 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, ¶ 167). Like Anderson and Kuo, each of Frasch and Lees discloses saccharide-protein

conjugation using periodate as an oxidizing agent. Frasch and Lees teach POSAs to expect a reduction in sizing effect when following the steps of Anderson/Kuo. Based on these references, it would have been obvious to POSAs that using lower concentrations of periodate (such as the 0.31 MEq periodate disclosed in Anderson) would reduce the sizing effect. Each of Frasch and Lees also motivates POSAs to reduce the sizing effect in order to preserve important epitopes for immunogenicity. (*Id.*, ¶ 168).

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. (*Id.*, ¶ 169). 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. (*Id.*). The size reduction occurs because portions of the saccharide, such as a side chain portion, break off, or because the saccharide backbone fragments. (*Id.*).

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, ¶ 170).

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, ¶ 172).

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 0.31 MEq taught in Anderson, in an effort to preserve immunogenicity. (*Id.*, ¶ 173).

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."[21] (Exh. 1003, IPR90; Exh. 1009, ¶ 175).

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. (Exh. 1009, ¶ 176). For example, Lees discloses that "[t]he

[21] 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).

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).

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, ¶ 177). 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 Anderson/Kuo 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 0.31 MEq of 23F disclosed in Anderson, 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 Anderson—and still remain within the claimed ranged—to optimize the immunogenicity of the saccharide conjugate. (Exh. 1009, ¶ 178).

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[22]

Saccharide	Molar Equivalents ("MEq") Periodate Used to Activate Pneumococcal Saccharide ("Pn")	Reference
Pn 4	0.33 MEq 0.17 MEq	WO'376[23] Lee (2002)[24]
Pn 6A	0.27 MEq	Anderson[25]
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[26]
Pn 18C	0.40 MEq 0.20 MEq 0.19 MEq, 0.37 MEq	WO'376 Lee (2002) Kuo

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

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

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

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

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

Saccharide	Molar Equivalents ("MEq") Periodate Used to Activate Pneumococcal Saccharide ("Pn")	Reference
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)

In fact, as indicated in the table, the prior art disclosed that amounts within the claimed range were used to activate 23F 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 23F. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985) (prior art, which taught an amount falling within the claimed range, disclosed the claimed range).

d. POSAs would have been motivated to combine Anderson/Kuo with Frasch and Lees with a reasonable expectation of success

As discussed above, Anderson and Kuo are directed to the same exact technology as the '645 patent, and teach every limitation set forth in claim 1. Accordingly, POSAs following the teaching of Anderson/Kuo would successfully achieve what was recited in claim 1 of the '645 patent. While Anderson/Kuo does not explicitly discuss that "reducing the sizing effect" is the result of following its method, Frasch and Lees teach POSAs that following the steps of the method of

Anderson/Kuo, POSAs would have a reasonable expectation of success in reducing the sizing effect. (Exh. 1009, ¶ 182).

POSAs following Anderson/Kuo would be motivated to look to Frasch and Lees, which are directed to the same exact technology at issue in Anderson/Kuo (and the '645 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 23F—and all four of the references discuss the use of periodate as an activation agent. (Exh. 1009, ¶ 183; Exh. 1015, 23:23-55; Exh. 1016, 4:27-34; Exh. 1005, 6469; Exh. 1006, 164-67).

Thus, POSAs considering the method of Anderson/Kuo 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, ¶ 184). 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 Anderson/Kuo's method would reduce the

sizing effect. (*Id.*). In other words, armed with Frasch and Lees, in conjunction with the detailed process set forth in Anderson/Kuo, POSAs would have a reasonable expectation of success in achieving the claimed method. (*Id.*, ¶ 185).

2. Claims 2-11 would have been obvious over Anderson/Kuo in view of Frasch and Lees

Claims 2-11, each depend from claim 1. The limitations of claims 2-11 are disclosed by Anderson/Kuo for the reasons discussed above in Sections VII.A.2 to VII.A.10, and POSAs would have combined the teaching of Anderson/Kuo with Frasch and Lees with a reasonable expectation of success for the same reasons set forth above with respect to claim 1. Accordingly, claims 2-11 would also have been obvious over Anderson/Kuo in view of Frasch and Lees.

C. Ground III: Claims 4 And 5 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, 27:21-23). Claim 5 recites "[t]he process of claim 1 wherein the average molecular weight of the 23F saccharide is between 100-470 kDa" after the saccharide has been activated in step a). (*Id*., 28:1-3). As discussed above, the MW recitations in these claims, 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, claims 4 and 5 would have been obvious over Anderson/Kuo in view of Lees and Frasch. Claims 4 and 5 would also have been obvious based on these references and further in view of PO's own prior art, GSK 2009 PCT.[27] GSK 2009 PCT, like Anderson and Kuo, 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 diphtheria toxoid, is conjugated to pneumococcal saccharides, including 23F. (*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*

[27] GSK 2009 PCT was published on December 31, 2008, more than one year prior to the '645 patent's U.S. filing date of March 7, 2011, and is thus Section 102(b) prior art.

kDa." (*Id*., 14:23-33).[28] 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), and claim 5 (*i.e*., 100-470 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 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. 1009, ¶ 192; 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, ¶ 192).

Because (1) Anderson, Kuo and GSK 2009 PCT disclose methods for preparing pneumococcal-protein conjugates, involving periodate activation and

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

reductive amination, and (2) GSK 2009 PCT teaches that pre-conjugation MWs within the claimed ranges provide improved immune response, POSAs would have been motivated to combine GSK 2009 PCT's teachings with Anderson/Kuo's method to arrive at the process of claims 4 and 5. 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. (*Id.*, ¶¶ 189-194).

Accordingly, claims 4 and 5 would have been obvious over Anderson/Kuo, in view of Lees, Frasch, and the GSK 2009 PCT.

D. 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, IPR507). 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*., IPR507-8). Moreover, PO argued that the saccharides conjugated with the claimed process "have been demonstrated to be highly immunogenic" unexpectedly. (*Id*., IPR508). 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 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); 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) (Exh. 1001, 20:5-35 (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, ¶ 196).

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

Example 1 of the '645 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, ¶ 197).

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.*, ¶ 198); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739

[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, 19:64-20:2).

(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. (S*ee also* Exh. 1009, ¶ 199).

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.*, ¶ 200).

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, IPR508; Exh. 1009, ¶ 201). 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 27), 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.

(*Id*.). Below is a table summarizing PO's results as presented to the Examiner.

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, 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. (Exh. 1009, ¶ 202).

Second, 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.*, ¶ 203).

Likewise, 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). The table below 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. Again, the criticality of the claimed range cannot be tested against one data point outside of the claimed range. (*Id.*, ¶¶ 204-205).

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

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, IPR508).

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 '645 patent reports the saccharide size for either the conjugate made by reductive amination or by 1-CDAP. Accordingly, no conclusions can be drawn about immunogenicity based on the size of the saccharide prior to conjugation. (Exh. 1009, ¶ 208).

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, IPR508; Exh. 1001, 20:37-22:43). Unlike, the claimed process, CDAP does not involve activation of saccharides with periodate. (Exh. 1001, 21:1-23). 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, ¶ 208). 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).

VIII. CONCLUSION

Based on the foregoing, the Board should institute *inter partes* review and cancel claims 1-11 of the '645 patent as unpatentable.

Respectfully Submitted,

Date: June 11, 2018

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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 13,550 words as counted by the word count function of Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,753,645, 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:

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