

Filed: August 4, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.,
Petitioner,

v.

POGONA, LLC,
Patent Owner.

Case IPR2026-00189
Patent 11,058,757

**PATENT OWNER'S RESPONSE
UNDER 37 C.F.R. § 42.120**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	LEVEL OF ORDINARY SKILL	2
III.	BACKGROUND TECHNOLOGY AND OVERVIEW OF THE '757 INVENTION	3
IV.	CHALLENGED CLAIMS	9
V.	CLAIM CONSTRUCTION	9
VI.	THE CHALLENGED CLAIMS OF THE '757 PATENT ARE VALID	9
A.	Alexander and Gu's Disclosures of Hundreds to Quadrillions of Options for Serotype Selection Do Not Anticipate the '757 Patent	9
1.	The Mathematical Scope of Alexander and Gu's Disclosures Renders Anticipation Impossible	11
a.	Alexander Reference	11
b.	Gu Reference	12
2.	The Claimed Combination of Serotypes is Not Immediately Apparent to a POSA from Alexander's and Gu's Bare Lists of Serotypes.....	13
3.	Alexander and Gu Are Readily Distinguished from Cases Finding Anticipation	19
B.	Alexander's and Gu's Lists Are Also Too Large for Obviousness	22
C.	The Serotype Prevalence References and/or the Vaccine Recommendation References Do Not Save Petitioner's Obviousness Arguments	23
1.	No Reference Directed a POSA to the Serotype Combinations the Challenged Claims Recite	23
2.	A POSA Seeking to Expand Pneumococcal Conjugate Vaccine Coverage Would Have Been Motivated to Conjugate the Remaining PPSV23 Serotypes.....	29

D.	Dependent Claims 12, 13, and 14 Would Not Have Been Obvious to a POSA.....	33
1.	Claim 12’s Additional Serotype Selection Only Compounds an Already-Insurmountable Combinatorial Problem.....	33
2.	Claims 13 and 14 Would Not Have Been Obvious to a POSA.....	34
a.	Serotype 16F	35
b.	Serotype 6C	36
c.	Serotype 15C	38
E.	Alexander and Gu Do Not Enable a POSA to Make the Claimed Immunogenic Compositions	39
1.	Alexander Fails Multiple <i>Wands</i> Factors.....	40
a.	Excessive Experimentation Required (Factor 1).....	40
b.	Insufficient Direction or Guidance (Factor 2).....	41
c.	Complete Absence of Relevant Working Examples (Factor 3)	42
d.	Highly Unpredictable Art (Factor 7)	43
2.	Gu Similarly Fails the <i>Wands</i> Analysis	44
a.	Excessive Experimentation Required (Factor 1).....	44
b.	Insufficient Direction or Guidance (Factor 2).....	45
c.	Complete Absence of Relevant Working Examples (Factor 3)	46
d.	Highly Unpredictable Art (Factor 7)	46
F.	The Petition Fails to Demonstrate a Reasonable Expectation of Success for Its Obviousness Grounds	47

1.	Petitioner’s Reasonable Expectation of Success Analysis for Alexander Is a Single Conclusory Sentence Without Any Supporting Analysis	52
2.	Gu: Petitioner Conflates Motivation with Reasonable Expectation of Success	53
3.	The “Longstanding Trend in the Art” Contradicts Petitioner’s Conclusory Assertion of a Reasonable Expectation of Success	55
4.	Petitioner’s Combination Theories Based on Serotype Prevalence and Vaccine Recommendation References Fail to Demonstrate a Reasonable Expectation of Success	59
5.	No Serotype-Specific Data Existed to Support a Reasonable Expectation That the Claimed Serotypes Would Be Immunogenic	62
G.	Gu Fails to Disclose the Claimed “Plurality of at Least Two Unique Immunogenic Saccharide-Polypeptide Conjugates”	64
1.	Petitioner’s Argument that a POSA Would “At Once Envisage” this Limitation from Gu Is Contrary to Law	64
2.	“Multiple Glycoconjugates” Does Not Inherently Mean Multiple Serotypes	65
3.	Gu’s Disclosure Is Not “Arranged or Combined in the Same Way as Recited in the Claim”	67
VII.	CONCLUSION.....	69

TABLE OF AUTHORITIES

Cases

<i>3form, Inc. v. Lumicor, Inc.</i> , 678 F. App'x 1002 (Fed. Cir. 2017)	19
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023)	43, 46
<i>Bayer Schering Pharma AG v. Barr Lab'ys, Inc.</i> , 575 F.3d 1341 (Fed. Cir. 2009)	23
<i>Crown Operations Int'l, Ltd. v. Solutia Inc.</i> , 289 F.3d 1367 (Fed. Cir. 2002)	66
<i>Eli Lilly & Co. v. Teva Pharms. Int'l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	54
<i>Ex parte Smith</i> , 2011-003337, slip op. (PTAB Feb. 28, 2012)	13, 14
<i>Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.</i> , 799 F. App'x 838 (Fed. Cir. 2020)	64
<i>Impax Lab'ys, Inc. v. Aventis Pharms., Inc.</i> , 545 F.3d 1312 (Fed. Cir. 2008)	18, 42, 46
<i>In re Arkley</i> , 455 F.2d 586 (CCPA 1972)	13
<i>In re Gleave</i> , 560 F.3d 1331 (Fed. Cir. 2009)	21
<i>In re Kahn</i> , 441 F.3d 977 (Fed. Cir. 2006)	53
<i>In re Magnum Oil Tools Int'l, Ltd.</i> , 829 F.3d 1364 (Fed. Cir. 2016)	53
<i>In re O'Farrell</i> , 853 F.2d 894 (Fed. Cir. 1988)	23

<i>In re Petering</i> , 301 F.2d 676 (CCPA 1962)	16
<i>In re Smith</i> , No. 12-1344, slip op. (Fed. Cir. Nov. 20, 2012).....	13
<i>In re Stepan Co.</i> , 868 F.3d 1342 (Fed. Cir. 2017)	47, 53
<i>InTouch Techs., Inc. v. VGo Commc’ns, Inc.</i> , 751 F.3d 1327 (Fed. Cir. 2014)	47
<i>Kennametal, Inc. v. Ingersoll Cutting Tool Co.</i> , 780 F.3d 1376 (Fed. Cir. 2015)	14
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	23, 53
<i>Labs., Inc. v. Aventis Pharms. Inc.</i> , 545 F.3d 1312 (Fed. Cir. 2008)	16
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	22
<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006)	55
<i>Merck Sharp & Dohme Corp. v. Wyeth LLC</i> , IPR2017-00390, Paper 15 (PTAB Sept. 13, 2017).....	58
<i>Merck Sharp & Dohme LLC v. Pogona, LLC</i> , IPR2026-00221, Paper 2 (PTAB Jan. 26, 2026)	2
<i>Merck v. Wyeth</i> , IPR2017-01223, Paper 8 (PTAB Oct. 20, 2017).....	21
<i>Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.</i> , 50 F.4th 147 (Fed. Cir. 2022)	16, 17
<i>Net MoneyIN, Inc. v. VeriSign, Inc.</i> , 545 F.3d 1359 (Fed. Cir. 2008)	10, 67, 69

<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.</i> , 851 F.3d 1270 (Fed. Cir. 2017)	passim
<i>Perricone v. Medicis Pharm. Corp.</i> , 432 F.3d 1368 (Fed. Cir. 2005)	19
<i>Purdue Pharma Prods. L.P. v. Par Pharm., Inc.</i> , 377 F. App'x 978 (Fed. Cir. 2010)	19
<i>Sanofi Pasteur Inc. & SK Chemicals Co. v. Pfizer Inc.</i> , IPR2018-00188, Paper 8 (PTAB Mar. 12, 2018)	58
<i>Therasense, Inc. v. Becton, Dickinson & Co.</i> , 593 F.3d 1325 (Fed. Cir. 2010)	66
<i>Warner Chilcott Co. v. Teva Pharms. USA, Inc.</i> , 89 F. Supp. 3d 641 (D.N.J. 2015), aff'd, 642 F. App'x 996 (Fed. Cir. 2016) 20, 34	
<i>Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.</i> , 853 F.3d 1272 (Fed. Cir. 2017)	10
<i>Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC</i> , 683 F.3d 1356 (Fed. Cir. 2012)	15, 16, 18, 20
Statutes	
35 U.S.C. § 102	14, 21, 67
Regulations	
37 C.F.R. § 42.100(b)	9

I. INTRODUCTION

Petitioner Pfizer Inc.’s (“Petitioner” or “Pfizer”) challenge to all claims (the “Challenged Claims”) of U.S. Patent No. 11,058,757 (the “’757 patent”) is fundamentally flawed. Alexander and Gu disclose only vast, undirected lists of serotypes—quadrillions of possible combinations from Alexander, hundreds from Gu—from which neither reference, nor the broader prior art, ever singled out the claimed combinations. Indeed, a POSA seeking to expand pneumococcal conjugate vaccine coverage would have been motivated to conjugate the serotypes already validated in PPSV23, not the unrelated, non-PPSV23 serotypes the challenged claims require. Gu does not even disclose the required plurality of unique serotypes in the first place. Nor could a POSA have made, or expected success from, the claimed immunogenic compositions. Neither reference supplies the technical guidance the *Wands* factors require, and Petitioner’s own predecessor told the Board in other proceedings that this field is defined by unpredictability and immune interference, not a reasonable expectation of success.

Patent Owner Pogona, LLC (“Patent Owner” or “Pogona”) respectfully requests that the Board find Petitioner has failed to demonstrate that the Challenged Claims are unpatentable.

II. LEVEL OF ORDINARY SKILL

Petitioner defines the POSA as “includ[ing] a research team with one or more researchers with an M.D. or Ph.D. in immunology, virology, biochemistry, chemistry, or a related discipline, and several years of work experience in vaccinology or related fields, and one or more individuals with an advanced degree and experience in drug delivery of vaccines.” (Petition, 12-13.)¹ Pogona does not agree with the underlined portion, as the ’757 patent is directed to “saccharide-polypeptide conjugates,” not drug delivery of vaccines. (EX1001, abstract; EX2018, ¶25.) In a separate petition against the ’757 patent, Merck defines a POSA as “an individual or team with Ph.D. degrees in the biological and chemical sciences and at least 2 years of work experience, or an M.D. degree with at least 6 years of work experience developing conjugate vaccines, including specifically growing sufficient quantities of bacteria, extracting, purifying and analyzing bacterial polysaccharides, conjugating polysaccharides to a carrier.” *Merck Sharp & Dohme LLC v. Pogona, LLC*, IPR2026-00221, Paper 2, 12-13 (PTAB Jan. 26, 2026). Merck’s definition does not require the underlined portion of Petitioner’s definition.

¹ All emphasis added unless otherwise indicated.

III. BACKGROUND TECHNOLOGY AND OVERVIEW OF THE '757 INVENTION

Patent Owner Pogona is a biotechnology company established to create and bring to market an improved, next-generation pneumococcal conjugate vaccine (“PCV”) utilizing the novel composition of serotypes claimed in the '757 patent.

On July 13, 2021, the U.S. Patent and Trademark Office issued the '757 patent, which claims priority to a provisional filed on March 31, 2016, and is entitled “Saccharide-Polypeptide Conjugate Compositions and Methods of Use Thereof,” to Pogona, LLC as assignee of the named inventors Bruce D. Forrest—Pogona’s CSO and Manager—and Jack D. Love—Pogona’s Head of Regulatory. Dr. Forrest was formerly the global clinical team leader for Prevnar® and Dr. Love was formerly the head of global regulatory affairs for Wyeth/Pfizer Vaccines Research & Development. The two led development of, and regulatory submissions for, both Prevnar and Prevnar 13.

“*Streptococcus pneumoniae* (pneumococcus) can cause serious illness, including sepsis, meningitis, and pneumonia with bacteremia (invasive) or pneumonia without bacteremia (noninvasive).” (EX2007, 1.) As of the priority date of the '757 patent, there were two pneumococcal vaccines licensed for use in the United States. (*Id.*) The first was Merck’s Pneumovax 23 pneumococcal polysaccharide vaccine (“PPSV23”), for which the serotype composition was determined from epidemiology developed in the 1970s. PPSV23 is directed to

serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. Since the early 1980s, PPSV23 has been recommended for individuals aged two and older who have certain medical conditions, as well as for all adults aged sixty-five and older. Pneumococcal polysaccharide vaccines—unlike PCVs—are not immunogenic in children under the age of two.

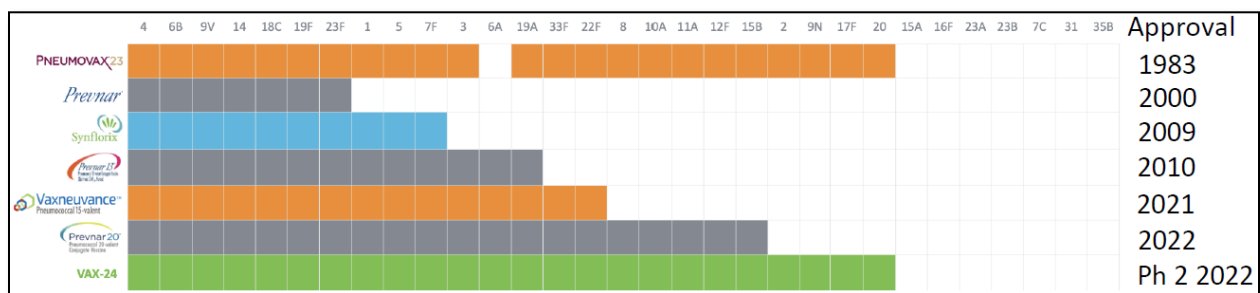
The second was Wyeth/Pfizer’s Prevnar 13 PCV (“PCV13”), which replaced the 7-valent PCV, Prevnar. Prevnar was approved in 2000 and developed by conjugating CRM197 to polysaccharides containing the seven most important serotypes from PPSV23. Prevnar is directed to serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F—all are a subset of the serotypes in PPSV23. When Prevnar was launched, pneumococcus remained the most common cause of severe pneumonia and bacterial meningitis in children.

PCVs overcame the challenge of poor immunogenicity in infants and young children by using conjugation technology. In PCVs, polysaccharides (or their derivatives) are covalently linked to carrier proteins. However, due to the complexity of the conjugation process, PCVs have contained fewer serotypes than the 23 included in PPSV23.

Prevnar 13 (“PCV13”), approved in 2010, was developed by conjugating CRM197 to polysaccharide for what were—at one time—the thirteen most

important serotypes from PPSV23. PCV13 is directed to serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F—all are a subset of the serotypes in PPSV23, minus serotype 6A. Serotype 6A is the only serotype to be added to PCVs beyond the serotypes included in the original PPSV23 before the '757 patent's priority date. PCV13 has been included in the routine pediatric immunization schedule since 2010, and since 2014 has been recommended for all adults aged ≥ 65 in combination with PPSV23.

Since PPSV23 was approved in 1983, pharmaceutical companies have ignored most of the over 100 immunologically distinct serotypes of pneumococcus that have been identified, and have almost exclusively developed new pneumococcal vaccines by conjugating additional serotypes from the original PPSV23 composition backbone:



Pogona took a different approach, focusing not on the PPSV23 composition serotypes, but on aligning vaccine coverage with emerging invasive disease serotypes, based on the '757 patent's inventors' hypothesis that the effectiveness of

PCV13 and its inclusion in routine immunization schedules would increase the importance of non-PCV13 serotypes.

In studying PCVs, Pogona's inventors identified that the marketed and investigational PCVs at the time were likely to provide inadequate coverage against invasive pneumococcal disease ("IPD"), and identified a novel composition of pneumococcal serotypes currently causing IPD that had not previously been included in any pneumococcal vaccine—whether polysaccharide or conjugate.

Pogona's team worked for years on an improved PCV for the prevention of pneumococcal disease not currently covered by Prevnar 13, and developed the novel composition of serotypes described and claimed in the '757 patent, including, for example:

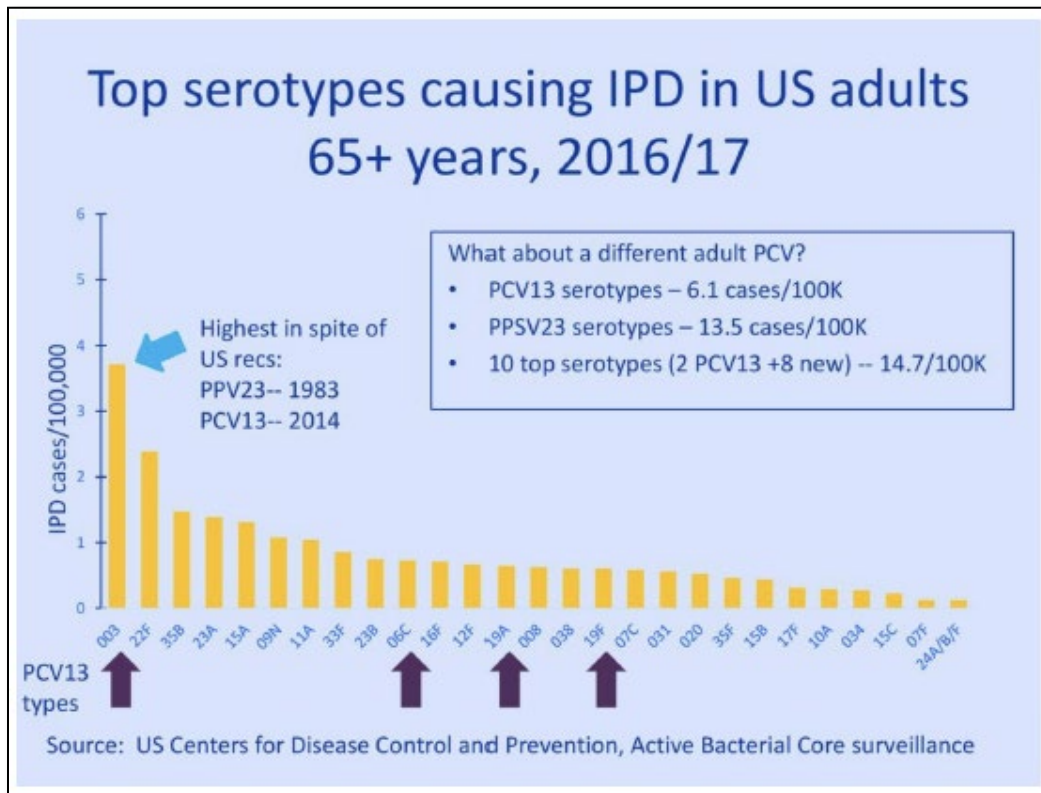
Claim 1: reciting selecting at least two unique serotypes from the group of serotypes 23A, 23B, and 35B—none are serotypes included in PPSV23.

Claim 12: depending from claim 1 and reciting further selecting at least one additional serotype from the group of serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34—of which 6C, 15A, 15C, 16F, 20A, 20B², and 34 are serotypes not included in PPSV23.

² PPSV includes serogroup 20, but does not specify serotypes 20A and 20B.

Claims 13/14: depending from claim 1, wherein the selected serotypes comprise/consist of 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B—of which 6C, 15A, 15C, 16F, 23A, 23B, and 35B are serotypes not included in PPSV23.

Pogona's approach proved to be correct. As Pogona's inventors predicted, the effectiveness of PCV13 resulted in a decrease in disease caused by the 13 PCV13 serotypes, from 75% in the late 1990s to 25% by 2016. Consequently, this decrease in the percentage of disease caused by PCV13 serotypes resulted in an increased rate of disease being caused by non-PCV and non-PPSV23 serotypes as shown in the below chart created in 2018:



(EX2008, 28.)

Over a year after the '757 patent's priority date—on October 26, 2017—the Centers for Disease Control and Prevention's ("CDC") National Center for Immunization & Respiratory Diseases ranked the non-PCV13 serotypes causing invasive pneumococcal disease:

Rank order of non-PCV13 serotypes causing IPD, 2015-2016			
Children < 5 years		Adults ≥ 65 years	
TYPE	Cases/100,000	TYPE	Cases/100,000
23B	0.62	22F	2.57
22F	0.62	23A	1.33
33F	0.57	35B	1.31
15C	0.52	15A	1.16
15A	0.48	33F	0.97
35B	0.43	16F	0.88
10A	0.33	11A	0.82
12F	0.29	9N	0.72
15B	0.29	23B	0.67
38	0.19	12F	0.61
other	1.67	other	4.66

Green denotes serotypes common to both age groups

(EX2009, 9.)

This is what the '757 patent's inventors understood—over a year earlier—when they recited in claim 1 the selection of at least two unique serotypes from the group of serotypes 23A, 35B (top two non-PPSV23 serotypes causing IPD in adults sixty-five and older), and 23B (top non-PPSV23 serotype causing IPD in children under five years). Additionally, claim 12, which depends from claim 1, recites further selecting at least one additional serotype from a group that includes

the following additional serotypes from the CDC's list: serotypes 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, and 22F.

Based on the CDC's data, in a marked departure from decades of pharmaceutical companies developing new pneumococcal vaccines by conjugating additional serotypes from the original PPSV23 composition backbone, CDC advised the pharmaceutical industry in 2018 to update pneumococcal vaccine coverage in adults to include circulating serotypes.

IV. CHALLENGED CLAIMS

Petitioner challenges all claims of the '757 patent.

V. CLAIM CONSTRUCTION

The Challenged Claims of the '757 patent are construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b) (Nov. 13, 2018).

Patent Owner agrees with Petitioner that, for purposes of this Response only, all terms of the '757 patent have their plain and ordinary meaning.

VI. THE CHALLENGED CLAIMS OF THE '757 PATENT ARE VALID

A. Alexander and Gu's Disclosures of Hundreds to Quadrillions of Options for Serotype Selection Do Not Anticipate the '757 Patent

Two fundamental requirements define the anticipation standard. First, anticipation requires that a single reference "describe the claimed invention with

sufficient precision and detail to establish that the subject matter existed in the prior art.” *Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017). Second, the prior art reference must disclose all elements of the claim “arranged or combined in the same way as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

Neither Alexander nor Gu satisfies these fundamental requirements. Neither reference describes the claimed invention with the precision and detail required to show the invention previously “existed in the prior art”—instead, both provide generic lists of serotypes disclosing vast numbers of possible combinations without specifically identifying the claimed invention. (*See* Petition, 24-25, 42.) Moreover, neither reference discloses serotypes “arranged or combined in the same way” as the claims require. The claims, among other requirements, demand a specific combination pattern: glycoconjugates that include at least two serotypes selected from the group consisting of 23A, 23B, and 35B. (EX1001, Claims.) Alexander and Gu merely list serotypes without teaching how to arrange or combine them to satisfy this specific pattern. (*See, id.*) A POSA reviewing these references would find bare lists without any teaching about which serotypes to select, how many to select, or which combination patterns correspond to the claimed invention. (EX2018, ¶63.)

1. The Mathematical Scope of Alexander and Gu's Disclosures Renders Anticipation Impossible

A straightforward mathematical analysis reveals the fundamental problem with Petitioner's anticipation theories: both Alexander and Gu disclose such vast universes of possible vaccine formulations that a POSA could not identify the claimed invention without impermissible "picking and choosing" from extensive possibilities.

a. Alexander Reference

Alexander discloses a list of pneumococcal serotypes that creates an astronomical number of possible vaccine combinations. Alexander "states that 'the compositions of the invention comprise a mixture of conjugates of a separate [polypeptide] of the invention with capsular polysaccharides from 2' up to '30 or more of the following serotypes,' followed by a list of 53 serotypes..." (Petition, 24-25.) Accepting Petitioner's (unavailing) argument that "the POSA would thus understand '35' to encompass 35B" as well as 35A and 35F, then Alexander's list of 53 serotypes—which includes serotype 35—would expand the list to 55 serotypes (converting 35 to 35A, 35B, and 35F). (Petition, 25 n.2)³. Additionally,

³ A POSA would understand, however, that a conjugate comprising "individually a capsular polysaccharide[s] conjugated to a polypeptide," where the conjugated serotype is 35, does not include serotype **35B** individually conjugated to a

because Alexander limits the number of chosen serotypes only by the size of its list—disclosing combinations of up to “30 or more” of its listed serotypes—the number of serotypes that a POSA could choose from Alexander would also be 33 (scenario 1) or 35—under Petitioner’s incorrect serotype 35 argument (scenario 2).

Under Scenario 1 (treating Alexander’s disclosure of 53 serotypes as including only 23A and 23B from the required group, not 35B), a POSA could select from over **9 quadrillion** possible combinations from Alexander’s list ($2^{53} - 1 = 9,007,199,254,740,991$). (EX2018, ¶59.) Under Scenario 2 (expanding Alexander’s generic reference to serogroup “35” to include serotypes 35F, 35A, and 35B, resulting in 55 total serotypes), then a POSA could select from over **36 quadrillion combinations** ($2^{55} - 1 = 36,028,797,018,963,967$).

b. Gu Reference

Gu discloses 28 serotypes, including a “narrowed” list of 8 total serotypes (2, 9N, 15A, 17F, 20, 23A, 23B, 35B) with an alleged selection range of 1-8 serotypes per formulation (Pogona disagrees that Gu allows for selecting more than 1 serotype, as discussed in Section VI.G.). (Petition, 42.) A POSA could select

polypeptide because the polypeptide would be conjugated individually to each of 35F, 35A, and 35B. (EX2018, ¶60.)

from **255 distinct possible combinations** from Gu’s list ($2^8 - 1 = 255$). (EX1001, Claim 1; EX2018, ¶62.)

While smaller than Alexander’s quadrillions of possibilities, Gu’s 255 possible combinations still represent a substantial universe of possibilities requiring impermissible selection without guidance—a disclosure that falls well within the range the Board and Federal Circuit have found insufficient for anticipation, as discussed below.

2. The Claimed Combination of Serotypes is Not Immediately Apparent to a POSA from Alexander’s and Gu’s Bare Lists of Serotypes

The prohibition on “picking and choosing” from prior art lists is a foundational principle of anticipation law that explains why references disclosing large numbers of possibilities fail to anticipate specific claimed inventions. As the Board stated in an informative decision in *Ex parte Smith*, for anticipation:

[T]he [prior art] reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures....Such picking and choosing...has no place in the making of a 102, anticipation rejection.

(EX2010 (No. 2011-003337, slip op., 7 (PTAB Feb. 28, 2012) (informative), *aff’d* EX2011 (*In re Smith*, No. 12-1344, slip op. at 2 (Fed. Cir. Nov. 20, 2012)) (quoting *In re Arkley*, 455 F.2d 586, 587-88 (CCPA 1972)) (emphasis in original).)

Applying this principle, the Board in *Ex parte Smith* reversed the prior anticipation finding because “[s]ome picking and choosing of ingredients from the myriad of possible additives listed in [the prior art] depending on the application... is necessary to arrive at” the claimed composition “recited in claims 4 and 5.” *Id.*, 7-8. The Board further linked this principle to the specificity requirement of §102(b). *Id.* at 8.

Federal Circuit precedent has established numerical benchmarks that apply the picking-and-choosing prohibition in practice. These benchmarks demonstrate that even relatively small numbers of combinations can fail to anticipate absent specific directional teaching, while Alexander’s and Gu’s vastly larger universes of possibilities catastrophically exceed any acceptable threshold.

At the lower end of the spectrum, in *Nidec*, the Federal Circuit explained that under a proper interpretation of *Kennametal*—a prior art reference disclosing five binding agents and three coating techniques, creating fifteen possible combinations—the prior art was anticipatory where the reference taught that any of the five binding agents could be used with any of the three coating techniques. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1382-83 (Fed. Cir. 2015)). *Nidec* further explained that in *Kennametal*, “the relevant question was ‘whether the number of categories and components

disclosed in [the prior art reference] is so large that the combination ... would not be immediately apparent to one of ordinary skill in the art.” *Id.* at 1274 (quoting *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012)). Critically, the *Nidec* court held that references cannot use the “at once envisage” standard “to fill in missing limitations simply because a skilled artisan would immediately envision them.” *Id.* at 1274-75. The reference itself must actually teach or disclose the combinations—POSA knowledge cannot supply missing teachings. *Id.*

Moving up the numerical scale, in *Wrigley*, the Shahidi reference disclosed three “particularly preferred” cooling agents (WS-3 and WS-23 were two of the three) and twenty-three flavoring agents (menthol was identified as among the “most suitable” flavoring ingredients). 683 F.3d at 1360-62. This created 69 possible combinations, which the Federal Circuit held anticipatory for two reasons. *Id.* at 1361.

First, this hierarchical, preferential language narrowed the universe of plausible combinations dramatically, directing a POSA to specific components—WS-23 and menthol—rather than requiring selection from equally viable alternatives. *Id.* at 1361. **Second**, the art explicitly “envisions using WS-23 and menthol in a single product,” disclosing “the use of both WS-23 and menthol in chewing gum.” *Id.* at 1361-62. Shahidi did not merely list ingredients—it

affirmatively taught combining them, eliminating the need to pick and choose which combinations to form.

The court then distinguished Shahidi from *Impax*, which involved “hundreds or thousands of compounds” and was found not to be anticipatory. *Id.* at 1362 (citing *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312 (Fed. Cir. 2008)). The *Wrigley* court explained that “[t]he question for purposes of anticipation is therefore whether the number of categories and components in [the prior art] was so large that the combination of WS–23 and menthol would not be immediately apparent to one of ordinary skill in the art.” *Id.* at 1361. Applying this standard while distinguishing *Impax* establishes that sixty-nine combinations approaches the upper limit of what can be “immediately apparent” without further direction, while “hundreds or thousands” clearly exceeds that limit and requires impermissible picking and choosing.

Recently, the Federal Circuit held that *In re Petering*—cited by Petitioner (Petition, 43, 47) stands for the proposition that a skilled artisan may “at once envisage each member of [a] *limited* class, even though the skilled person might not at once define in his mind the formal boundaries of the class.” *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147, 153 (Fed. Cir. 2022) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962) (emphasis in original)). The

Federal Circuit explained, “[t]he key term here is ‘limited.’” *Id.* Specifically, the Federal Circuit noted:

[The prior art’s] list of 33 compounds, with no direction to select [the claimed element] from among them, plus the eight ‘pharmaceutically preferred’ acids and various stoichiometric possibilities, results in 957 salts, some of which may not exist. That is a far cry from the 20 compounds ‘envisaged’ by the narrow genus in *Petering*...[W]e agree...that a class of 957 predicted salts that may result from the 33 disclosed compounds and eight preferred acids, some of which may not even form under experimental conditions, is insufficient to meet the ‘at once envisage’ standard set forth in *Petering*.

Id. at 153-54.

Alexander clearly requires the impermissible “picking and choosing” that Federal Circuit and PTAB precedent explicitly prohibit, because its 53-55 components resulting in quadrillions of possible combinations is so large that the claimed combination of serotypes “would not be immediately apparent to one of ordinary skill in the art.” (EX2018, ¶61.) *Nidec*, 851 F.3d at 1274. Alexander provides bare lists of 53-55 serotypes with no guidance on which combinations to select, no hierarchical preferences, no working examples, and no teaching about the claimed at least 2 serotypes “from a group consisting of 23A, 23B, and 35B.” (Petition, 24-25; EX1001, Claim 1.) Petitioner’s expert agrees. (EX2022, 106:14-108:4.) A POSA must pick and choose among quadrillions of possibilities to arrive

at a combination satisfying this limitation. (EX2018, ¶¶61, 63, 65.) This is not a case where the reference “clearly and unequivocally disclose[s] the claimed [combination]”—it is a case requiring extensive selection from vast alternatives.

Similarly, Gu requires impermissible picking and choosing because its 8 components resulting in 255 possible combinations falls within the “hundreds or thousands” of possible combinations that the Federal Circuit found not to be anticipatory in *Impax. Wrigley*, 683 F.3d at 1362 (citing *Impax*, 545 F.3d 1312). Importantly, Gu lacks all the directional features that made smaller numbers of combinations (sixty-nine) anticipatory in *Wrigley*. *See Wrigley*, 683 F.3d at 1361. Gu does not teach which specific combinations to form, which combinations are preferred, or how to identify combinations satisfying the claimed limitation from among the 255 possibilities. (Petition, 42.) A POSA must pick and choose from 255 possibilities without any directional guidance. Petitioner’s expert agrees. (EX2022, 95:8-16, 96:21-98:18, 106:14-108:4, 108:5-17.) In the absence of these teachings, Gu’s 255 possible combinations is so large that the claimed combination of serotypes “would not be immediately apparent to one of ordinary skill in the art.” (EX2018, ¶¶64-65.) *See Nidec*, 851 F.3d at 1274. Gu requires impermissible picking and choosing, and thus fails anticipation, just as *Impax*’s similarly directionless “hundreds or thousands” of combinations also failed. *See Impax*, 545 F.3d at 1315-16.

3. Alexander and Gu Are Readily Distinguished from Cases Finding Anticipation

Petitioner's cited anticipation cases are either inapposite or involved prior art with far fewer possible combinations and substantially more directional teaching than Alexander or Gu provides. (*See* Petition, 25-26.)

Two of Petitioner's cited cases—*3form* and *Purdue*—are simply irrelevant. (Petition, 25.) In *3form*, the prior art disclosed “more than forty” objects, but only one was “compressible” as the claims required—making the case turn on whether a single named object met that property, not on picking a combination from vast possibilities. *3form, Inc. v. Lumicor, Inc.*, 678 F. App'x 1002, 1009-10 (Fed. Cir. 2017). Unlike *3form*'s single viable option, neither Alexander nor Gu discloses any specific formulation matching the claimed serotype combination(s).

Purdue also misses the mark. It addressed obviousness, not anticipation—applying an inapposite standard—and even there, the Federal Circuit found it obvious to select just one item from a list of fourteen, far fewer options than Alexander's or Gu's. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 981-82 (Fed. Cir. 2010).

Perricone illustrates the simplest anticipation case: a POSA needed only a single, straightforward selection—one specifically-named ingredient from fourteen options—with no combinatorial complexity. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376-77 (Fed. Cir. 2005). Alexander's and Gu's numbers fall far

outside that range, and unlike Perricone’s single ingredient, the claimed invention requires identifying specific combinations from astronomical or substantial alternatives, without guidance.

As discussed above, *Wrigley*’s 69 combinations were anticipatory only because of directional teaching Alexander and Gu lack—the closest numerical analogue is *Impax*’s “hundreds or thousands of compounds,” which was not anticipatory. 683 F.3d at 1361-62.

At the upper limit, a district court in *Warner* found approximately 336 combinations (14 bisphosphonates×4 chelating agents×6 delayed-release mechanisms) a “defined and limited class” where the claimed combination was “immediately apparent,” because the prior art directed a POSA to select one ingredient from each defined list such that it “combine[s] [the elements] in the same way as recited in the claim,” rather than through “random selection from unrelated elements.” *Warner Chilcott Co. v. Teva Pharms. USA, Inc.*, 89 F. Supp. 3d 641, 656-57 (D.N.J. 2015), *aff’d*, 642 F. App’x 996 (Fed. Cir. 2016).

Alexander’s quadrillions present no such “defined and limited class,” and Gu’s 255 combinations lack *Warner Chilcott*’s category-by-category guidance—according to Petitioner’s own expert, Gu allows selecting anywhere from one to all eight listed serotypes with zero guidance. (See EX1002, ¶195; EX2022, 95:8-16, 96:21-98:18, 106:14-108:4, 108:5-17.)

Petitioner’s lone large-number case, *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009), is still dwarfed by Alexander’s numbers and presents distinguishing features Alexander and Gu lack. (Petition, 26-27.) There, the Wraight reference “expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP–2”—more than 1,400 sequences—which the Federal Circuit held anticipatory for two reasons. *Id.* at 1338.

First, *Gleave* conceded enablement, stating “it is well within the skill of an ordinary person in the art to make any oligodeoxynucleotide sequence.” *Id.* at 1336. Here, enablement is both disputed and lacking, as discussed in Section VI.E. **Second**, *Gleave*’s claims required only sequences “of sufficient length to act as an antisense inhibitor” and expressly “do not require antisense activity”—meaning “evidence as to whether particular compounds work for their intended purpose is irrelevant to our § 102(b) analysis.” *Id.* Here, by contrast, the claims require the conjugates to be immunogenic—a functional limitation requiring conjugates to actually elicit immune responses (*see* Petition, 30-31, 41, 45-46), and, as the Board held in *Merck*, that requires data specific to the conjugated serotype. *Merck v. Wyeth*, IPR2017-01223, Paper 8 at 11-14 (PTAB Oct. 20, 2017). Under *Gleave*’s own reasoning, then, “evidence as to whether particular compounds work for their intended purpose” is highly relevant here, and Alexander and Gu provide none. *In re Gleave*, 560 F.3d at 1336; *see* Section VI.E.

B. Alexander’s and Gu’s Lists Are Also Too Large for Obviousness

In Grounds II and IV, Petitioner devotes a single paragraph of each Ground to arguing in conclusory fashion—with no evidence in support of its argument—that if Alexander and/or Gu do “not disclose a composition with saccharide-polypeptide conjugates comprising at least two capsular polysaccharides from serotypes 23A, 23B, and 35B,” they are nonetheless obvious because a “POSA would understand that increasing the number of serotypes in a PCV would broaden its disease coverage.” (Petition, 49, 37 (similar).) However, as Petitioner’s expert admits, neither Alexander nor Gu provides any guidance to a POSA to narrow the possible combinations of serotypes to a POSA can select based on the references’ lists of serotypes. (EX2022, 95:8-16, 96:21-98:18, 106:14-108:4, 108:5-17; EX2018, ¶66.) Without such narrowing, the number of possible combinations for both Alexander and Gu falls well beyond the limit that the Federal Circuit has set for obviousness to try. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (holding that selection from a list of eight additives and a list of ten composition forms, totaling eighty possible combinations, resulted in “numerous combinations indicat[ing] that these disclosures would not have rendered the claimed invention obvious to try.”).

What Petitioner advocates is exactly what the Federal Circuit has held to be outside the bounds of the Supreme Court’s “*KSR* prong requiring the field of

search to be among a ‘finite number of identified’ solutions”: “When ‘what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful’ an invention would not have been obvious.” *Bayer Schering Pharma AG v. Barr Lab’ys, Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007); *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Indeed, Petitioner’s argument is worse than that derided by the Federal Circuit, because a POSA would not be able to stop when it simply found a combination of serotypes from Alexander or Gu that was “successful.” Rather, the POSA would have to continue to try all serotype combinations to ensure it stumbled upon the claimed combination, since the POSA would not know it had done so without the hindsight of the ’757 patent. (EX2018, ¶¶68-69.) The ’757 patent claims therefore cannot be obvious in light of Alexander or Gu. (EX2018, ¶70.)

C. The Serotype Prevalence References and/or the Vaccine Recommendation References Do Not Save Petitioner’s Obviousness Arguments

1. No Reference Directed a POSA to the Serotype Combinations the Challenged Claims Recite

Petitioner claims that “the serotype-selection question before the POSA was

consistently and repeatedly answered by the field with the serotypes Patent Owner claims.” (Petition, 51.) What Petitioner omits is that the serotype-selection question was answered by **many** different serotypes in addition to those the Challenged Claims recite. (EX2018, ¶71.) For this reason, the prior art available to a POSA, which Petitioner argues should be combined with Alexander and/or Gu, does nothing to narrow the number of serotype combinations available to a POSA in Alexander and/or Gu, which remain too numerous to have been obvious to try under Federal Circuit precedent. (EX2018, ¶72.) Indeed, the prior art available to a POSA makes the serotype-selection question even worse than it would be with Alexander or Gu standing alone. (EX2018, ¶73.) Rather than directing a POSA to the claimed serotypes, Petitioner’s “serotype prevalence” and “vaccine recommendation references” collectively address 38 serotypes—either suggesting potential inclusion in a vaccine or noting prevalence:

Legend: D = disclosed | P = disclosed, identified as prevalent | V = disclosed, suggested/included for a vaccine | B = both prevalent and vaccine-suggested

Sero-type	EX1010	EX1011	EX1018	EX1013	EX1014	EX1015	EX1016	EX1017	EX1019
1	V	V	P	V	D	D	V	P	V
2	V						V		D
3	V		P	P		P	P	D	V
4	V	P	B				V	V	V
5	V	V	V	V		D	V	V	V
6A	V		V	V		D	V	V	B
6B	V	P	V			D	V	V	V
6C	B	D	P	P		D	B	D	
6D	B								
7A			D					D	
7F	V		P	D	D	D	P	P	V
8	V		P	P			V	D	D
9A							V		
9N	V		B			D	V		D
9V	V	V	V				V	V	V
10A	V				P	D	V	D	D
11A	B		B	D		P	V		D
11B	B								
11C	B								
11F	B								
12F	V		P			D	V	D	B
13			D	D		D			
14	V	P	P				V	V	V
15A	V	V	P	P		P		D	D
15B	B		D	P	D	P	V	D	D
15C	B		D			P		D	
16F						P			
17F	V					D	V		D
18C	V	P	V		D		V	V	V
19A	V	P	P	P		P	P	D	V
19F	V	P	B	P		D	V	V	V
20	V		D			D	V		B
21						P			D
22F	V		P	D		D	P	V	P
23A	B	V	D	P		P	D		D
23B			D	D		P			B
23F	V	P	B						V
24A			D						
24F			D						
31						P		V	
33A						D			
33F	B				P	D	P	V	D
34						D			
35B	B		D	P		P			
35F						D			
38			D			D			

This art may reduce Alexander’s potential combinations from over 9 quadrillion (a list of 53) to a still incomprehensible over 4 billion ($2^{32} - 1 = 4,294,967,295$, from the 32 serotypes so addressed), but it does nothing to narrow Gu’s list. All 8 of Gu’s serotypes are among the ones Petitioner’s references address in this same limited way.

Even worse, the broader prior art available in this proceeding—rather than the cherry-picked references Petitioner relies on—address 57 serotypes on the same basis:

None of the serotypes recited in the Challenged Claims was among the thirteen covered by PCV13—the conjugate vaccine in routine pediatric use as of March 31, 2016. (EX2018, ¶74.) A POSA seeking to expand vaccine coverage beyond PCV13 therefore faced not a handful of candidates, but a sprawling and constantly shifting field of emerging non-PCV13 serotypes, and nothing in the art singled out the claimed serotypes for selection (either 2 of serotypes 23A, 23B, and/or 35B as in claim 1, or the added serotypes of 6C, 9N, 15A, 15C, and 16F recited in claims 13 and 14). (EX2018, ¶75.)

To the contrary, the surveillance literature available to a POSA as of the priority date showed that emerging non-PCV13 serotypes numbered in the dozens and that which serotypes were “emerging” depended on geography, age, and the type of clinical specimen examined. (EX2018, ¶¶86-87.) Petitioner’s expert agrees. (EX2022, 131:7-133:18.) Global surveillance spanning 32 IPD datasets—including five U.S. systems, Canada, Australia, and multiple European countries—identified non-PCV13 serotypes 2, 8, 9A, 12A, 12F, 15B, 45, and 46 among the most commonly reported worldwide. (EX2023, 5; EX2024.) In England and Wales, IPD in children under five caused by non-PCV13 serotypes 24F, 15B/C, 22F, 8, 38, 11A and 21 increased following PCV13 introduction. (EX1017, 540.) In Germany, meningitis caused by non-PCV13 serotypes 10A, 11A, 12F and 33F increased in children under sixteen post-PCV13, while a different set—11A, 12F and 20—

increased in adults ≥ 16 , even as 10A, 22F and 6C decreased in that older population. (EX2025, 9-10; EX2018, ¶¶87-88.) That divergence between the pediatric and adult data—which Petitioner’s expert has also pointed out—where the serotypes trending upward in one population were trending downward in the other, is itself evidence that no single, predictable set of non-PCV13 serotypes would have presented itself to a POSA as the obvious next composition. (EX2018, ¶¶83, 85, 87; EX2022, 130:12-131:5.)

The same pattern held outside Europe, with each region’s data pointing to a different set of leading candidates: Taiwan’s most prevalent non-PCV13 types were 23A, 15B and 10A, drawn from 53 distinct serotypes across 3,659 isolates; Saudi Arabia’s pediatric IPD data implicated 15, 23A, 24, 12F, 11, 23B, 22 and 8; U.S. meningitis surveillance showed increases in 7C, 10, 11, 15A, 15C, 17, 21, 23A, 23B, 33F, 35B and 37; China’s hospitalized children were infected with 6C, 15B/C, 15F/15A, 23A, 20, 10B, 28F/28A and 34; and U.S. middle ear and mastoid cultures identified 15F, 16, 20, 23B, 33F, 34 and 35F. (EX2026, 3346-47, Figure 1; EX1011, 213; EX2027, 770; EX2028, 1, 6; EX1015, 1341, 1342; EX2018, ¶¶88.)

Taken together, this literature would have presented a POSA with at least the following emerging non-PCV13 serotypes to choose among: 2, 6C, 7C, 8, 10A, 10B, 11, 11A, 12A, 12F, 15, 15A, 15B, 15C, 15F, 16, 17, 20, 21, 22, 22F, 23A, 23B, 24, 24F, 28A, 28F, 33F, 34, 35B, 35F, 37, 38, 45 and 46. (EX2018, ¶¶89.) A

POSA would have faced a field of varying emerging serotypes defined by geography, age, and specimen-dependent variability, not any consistent signal favoring the claimed serotypes—and nothing in the record would have motivated a POSA to select them to the exclusion of the many others the same literature identified. Each Challenged Claim is therefore non-obvious. (EX2018, ¶¶77, 78, 81, 83, 85, 89-92.)

2. A POSA Seeking to Expand Pneumococcal Conjugate Vaccine Coverage Would Have Been Motivated to Conjugate the Remaining PPSV23 Serotypes

Rather than blindly experimenting with every serotype combination available to a POSA in Alexander and Gu, a POSA seeking to increase the serotype coverage of pneumococcal conjugate vaccines would instead have been motivated to develop a conjugate vaccine that incorporated the serotypes already included in PPSV23.⁴ (EX2018, ¶93.) A POSA would have understood that PPSV23 contained serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F, and that it provided the broadest serotype coverage of any licensed pneumococcal vaccine. (EX2018, ¶¶93, 95.) At

⁴ A POSA also would have been motivated to improve PCV13's serotypes or pursue a non-serotype-based PCV, without reaching the claims. (EX2018, ¶¶102-116.)

the same time, the art recognized that PPSV23's polysaccharide formulation elicited only a T-cell independent immune response, resulting in important disadvantages compared to conjugate vaccines. Unlike conjugated vaccines, PPSV23 was not immunogenic in children under two years of age, did not generate immunological memory, and did not induce mucosal immunity capable of reducing nasopharyngeal colonization. (EX2029, 2472; EX2018, ¶¶94.) Consequently, a POSA would have recognized a clear opportunity to combine the broad serotype coverage of PPSV23 with the well-established immunological advantages of conjugate vaccine technology by developing a conjugated version of PPSV23. The natural development path for a POSA was to conjugate the remaining PPSV23 serotypes, in keeping with the development pattern of pneumococcal vaccines since PCV7 in 2000—not to replace them with serotypes outside the PPSV23 formulation, which had only been done for one of PCV13's 13 serotypes. (EX2018, ¶¶99-100.)

The epidemiological evidence available before the priority date reinforced this motivation. Contemporary surveillance demonstrated that PPSV23 provided substantially broader coverage of circulating IPD serotypes than existing conjugate vaccines. The Public Health Agency of Canada (PHAC) reported that PPSV23 covered 70.6% of circulating serotypes, compared to only 35.4% for PCV13. (EX1019, 34.) PHAC further reported that the PPSV23-exclusive serotypes—2, 8,

9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F—were increasing in prevalence across all age groups, rising from 24.7% to 37.6% between 2010 and 2013.

(EX1019, 36; *see* EX1018, 24, 26.) This data would have informed a POSA that the serotypes unique to PPSV23 were becoming increasingly important causes of disease and therefore should be incorporated into future conjugate vaccines.

(EX2018, ¶95.)

Clinical recommendations likewise pointed the POSA toward utilizing—not abandoning—the PPSV23 serotype composition. (EX2018, ¶96.) Based on randomized clinical trials demonstrating approximately 74% efficacy against invasive pneumococcal disease, ACIP recommended PPSV23 for all adults aged 65 years and older and for younger adults with specified high-risk conditions. After PCV13 became available, ACIP continued to recommend routine administration of both vaccines in series. (EX2030, 1103-05.) As ACIP explained:

PPSV23 contains 12 serotypes in common with PCV13 and 11 additional serotypes. In 2013, 38% of IPD among adults aged ≥ 65 years was caused by serotypes unique to PPSV23. Given the high proportion of IPD caused by serotypes unique to PPSV23, broader protection is expected to be provided through use of both PCV13 and PPSV23 in series.

(EX2031, 823.) These recommendations reflected the prevailing understanding that the additional PPSV23 serotypes remained medically important and should continue to be included in vaccination strategies. (EX2018, ¶¶96-98.)

Additionally, the prior art provided no motivation for a POSA to omit medically validated PPSV23 serotypes in favor of serotypes that had never been included in PPSV23. (EX2018, ¶99.) As Dr. Zhanel explains, a POSA would not have designed a new conjugate vaccine using serotypes 23A, 23B, or 35B (or, as is relevant to later claims, 6C, 15A, 16F, or 34) because those serotypes were not part of PPSV23—the vaccine that represented the scientifically accepted benchmark for broad pneumococcal coverage. (EX2018, ¶100.)

The teachings of Alexander and Gu reinforce this conclusion. Rather than directing a POSA toward arbitrary or unrelated serotypes, both references continued to focus on the serotypes already validated in PPSV23 as providing the broadest clinically relevant pneumococcal coverage. (EX2018, ¶101.) Specifically, Alexander expressly discloses every PPSV23 serotype that remained absent from PCV13—namely serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F—thereby identifying the precise serotypes a POSA would have recognized as the logical candidates for expanding conjugate vaccine coverage beyond PCV13. (EX2018, ¶101.) Likewise, Gu specifically identifies serotypes 2, 9N, 17F, and 20, each of which is included in PPSV23 but absent from PCV13, confirming that the

art continued to focus on conjugating the remaining PPSV23 serotypes rather than selecting unrelated serotypes outside the PPSV23 framework. (EX2018, ¶101.)

D. Dependent Claims 12, 13, and 14 Would Not Have Been Obvious to a POSA

1. Claim 12’s Additional Serotype Selection Only Compounds an Already-Insurmountable Combinatorial Problem

Claim 12 depends from claim 1 and requires selection of an additional unique serotype from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34—fourteen further candidates layered on top of the selection claim 1 already requires from the group consisting of 23A, 23B, and 35B. (EX1001, Claims.) As described in Sections VI.A. and V.B., selecting at least two of serotypes 23A, 23B, and/or 35B already required impermissible picking and choosing from Alexander’s quadrillions of possible combinations or Gu’s 255 possible combinations. Requiring a POSA to make a further, independent selection from fourteen additional candidates only compounds the problem as each additional required selection narrows the odds of landing on the claimed composition and moves the claimed combination further still from anything “immediately apparent” to a POSA, or from any “defined and limited class”—the opposite of what Federal Circuit precedent demands for anticipation or “obvious to try.” (EX2018, ¶¶75, 79, 91.) *See Nidec*, 851 F.3d at 1274; *Warner Chilcott*, 89 F.

Supp. 3d at 657. Claim 12 is therefore non-obvious for at least the same, compounded reasons that defeat obviousness of claim 1.

2. Claims 13 and 14 Would Not Have Been Obvious to a POSA

Rather than requiring selection of some subset from a list of candidates, claim 13 requires that the composition comprise, and claim 14 requires that the composition consist of, capsular polysaccharides from all eight of: 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B—fixing the target at a single, specific eight-serotype composition rather than leaving any room for selection among alternatives.

(EX1001, Claims.) This is the narrowest, most specific claim scope at issue in this proceeding, and consequently the target least “immediately apparent” to a POSA and least likely to be the product of anything but impermissible, hindsight-driven selection. As demonstrated in Sections VI.A.-C., none of Alexander, Gu, or the broader surveillance and prevalence literature singled out this precise eight-serotype combination over the dozens of other emerging non-PCV13 serotypes then under study.

Additionally, three of the eight serotypes claims 13 and 14 recite—16F, 6C, and 15C—were each, independently, serotypes a POSA had affirmative reasons *not* to select. (EX2018, ¶118.) Neither Alexander nor Gu mentions 6C, and Gu’s 8-serotype list upon which Petitioner relies also does not include serotypes 15C and 16F. (Petition, 24-25, 42; EX2018, ¶¶61, 64.) But the prior art did not merely fail

to direct a POSA to these serotypes. It affirmatively counseled against their inclusion, whether because the serotype was clinically insignificant, because cross-protection from an already-marketed vaccine component was expected to address it, or both. (EX2018, ¶118.)

a. Serotype 16F

The available surveillance data as of March 31, 2016 showed serotype 16F was neither common nor emerging. (EX2018, ¶124.) Global surveillance spanning 32 IPD datasets did not include 16F among the 21 most common serotypes causing IPD worldwide. (EX2023, 5; EX2024.) In England and Wales, IPD caused by serotype 16F was uncommon and did not significantly increase over time, and cases in children under five decreased as other non-PCV13 serotypes increased during the same period of PCV13 exposure. (EX1017, 540.) The pattern was global: no cases of serotype 16F disease were reported in Germany, among 3,659 isolates in Taiwan, among twenty circulating serotypes in Saudi Arabia, or in hospitalized children in China, and only a single U.S. meningitis case was attributed even to serotype 16 generally—not specifically identified as 16F—even as other non-PCV13 serotypes showed genuine increases. (EX2025, 7-10; EX2026, 3346-47; EX1011, 213; EX2028, 1, 6; EX2027, 770; EX2018, ¶¶121-123.) What little was known about serotype 16F’s biological behavior reinforced this picture. Researchers studying the serotype in Australian aboriginal children

found it associated with nasopharyngeal colonization and capable of causing IPD, but not associated with severe outcomes, genetically diverse, and susceptible to antibiotics. (EX2032, 2434-35; EX2018, ¶125.) A POSA would have considered this the profile of a serotype with no urgency to address, and so would have had no motivation to select serotype 16F for a new formulation. (EX2018, ¶¶120, 124-125.)

b. Serotype 6C

For serotype 6C, a POSA would have expected that no separate targeting was necessary due to cross-protection from serotype 6A (and perhaps 6B) in PCV13. (EX2018, ¶126.) Researchers previously demonstrated that serotypes 6A and 6C displayed extensive structural similarity, with the only difference being a glucose (serotype 6C) versus a galactose (serotype 6A) in carbohydrate composition—a difference so small that anti-sera had historically typed both as serotype 6A. (EX2036, 1231-32.) Consistent with that structural relationship, PCV13 (which contains 6A and 6B) immune sera showed strong opsonophagocytic responses to serotypes 6A (100% responders), 6B (100% responders), and 6C (96% responders). (EX2037, 1.) Researchers had thus concluded that the 6A (perhaps with some help from 6B) conjugate in PCV13 would routinely elicit functional responses to serotype 6C, such that immunization

with PCV13 would protect against serotype 6C disease in a high proportion of humans. (EX2037, 4-5; EX2018, ¶¶127-139.)

Real-world surveillance confirmed this mechanism was working. Serotype 6C, like 16F, was absent from the same 21-most-common-serotype global surveillance discussed above, and was not reported as a common or emerging serotype globally or regionally. (EX2023, 5; EX2024.) U.S. surveillance through the Active Bacterial Core network found no serotype 6C pediatric IPD in 2013, unsurprising given that “the minor paediatric IPD serotype 6C is also predicted to be targeted by PCV13 through cross-protection from the 6A antigen.” (EX2038, 11.) Independent data confirmed the trend: declining prevalence in U.S. pediatric hospital cultures, with none isolated from mastoid cultures in 2012 or 2013; decreased overall prevalence following PCV13 implementation; and reductions in serotype 6C disease across all age groups in England and Wales (EX1015, 1341-42; EX1013, 6486; EX1017, 540; EX2018, ¶¶131-133.).

A POSA weighing this evidence of a demonstrated cross-reactive immune mechanism plus consistent, multi-source epidemiological confirmation that it was working, had every reason to expect PCV13 already addressed serotype 6C, and no reason to add it to a new formulation, particularly in light of the data surrounding other serotypes. (EX2018, ¶134.)

c. Serotype 15C

Serotype 15C presented the same scenario, but with cross-reactivity to PPSV23's serotype 15B. A POSA would have been aware that PPSV23 already contained serotype 15B, and so would not have been motivated to add serotype 15C to a new conjugate vaccine—focusing instead on conjugating 15B itself—on the reasonable assumption that 15B-induced antibodies would provide at least partial immunological cross-protection against 15C. (EX2018, ¶135.) Serotypes 15B and 15C are structurally very similar, can undergo phase variation, and in some cases cannot be distinguished by serotyping methods at all, such that antigenic cross-reactivity between the two would be expected to produce at least partial cross-protection. (EX2034, 1224; EX2018, ¶135.)

The epidemiological record gave no reason to depart from that expectation. Serotype 15C was not reported as a common or emerging serotype in the same 21-most-common-serotype global surveillance discussed above, which specifically distinguished 15B (commonly reported) from 15C (not so). (EX2023, 5; EX2024.) No cases of serotype 15C were reported in Taiwan (where the twelve most prevalent serotypes accounted for 87.0% of all isolates) or in Saudi Arabia (where IPD caused by twenty different serotypes was observed). (EX2026, 3346-47; EX1011, 213; EX2018, ¶¶135-137.) Nothing in this record would have directed a POSA to serotype 15C, and the same cross-reactivity that made 15B-induced

protection a reasonable expectation gave a POSA an affirmative motivation to leave 15C out of new conjugation efforts, particularly in light of the data surrounding other serotypes. (EX2018, ¶138.)

Each of these three serotypes—16F, 6C, and 15C—independently undercuts any suggestion that the eight-serotype combination recited in claims 13 and 14 would have been obvious to a POSA. Far from directing a POSA to include them, the prior art showed 16F to be clinically insignificant, and showed 6C and 15C to be serotypes a POSA already expected to be addressed through cross-protection. This compounds, rather than resolves, the combinatorial and PPSV23-completion problems already discussed, such claims 13 and 14 would not have been obvious to a POSA. (EX2018, ¶¶118, 125, 134, 138.)

E. Alexander and Gu Do Not Enable a POSA to Make the Claimed Immunogenic Compositions

The success of any conjugation reaction depends on a combination of variables that must be evaluated together, not selected independently, for each new starting material—including reactant concentrations, the physical state and surface area of the reactants, and the use of any catalysts. (EX2020, ¶50.) A POSA who must adjust one such variable while holding the others constant, and then test the result, is engaged in precisely the kind of iterative, trial-and-error experimentation the *Wands* factors identify as unreasonable. (EX2020, ¶¶51, 53.) Neither Alexander nor Gu supplies the necessary enablement details to avoid this excessive

experimentation for the claimed serotypes, as detailed below. (EX2020, ¶¶52, 54-55, 73, 88.)

1. Alexander Fails Multiple *Wands* Factors

a. Excessive Experimentation Required (Factor 1)

Alexander provides no specific conjugation protocols, immunogenicity data, or technical guidance for any of the claimed serotypes. (EX2020, ¶56.) While Alexander discloses general concepts for conjugating pan-DR binding peptides to capsular polysaccharides, these generic protocols are not tailored to the claimed serotypes and provide no guidance on which conjugation approach would be appropriate for each. (EX1008, [0087]-[0093]; EX2020, ¶57.) A POSA would need to conduct substantial experimentation to determine, for each claimed serotype: appropriate activation methods for that serotype's polysaccharide structure; optimal conjugation chemistry, linker selection, and solvent system; reactant concentrations, stoichiometric ratios, pH, and ionic strength; agitation method and order of addition; and purification, sterility, and testing protocols to confirm immunogenicity. (EX2020, ¶58.) Alexander's own disclosure confirms, rather than relieves, this burden: it discloses only that reactant concentrations "depend upon numerous factors including reaction conditions such as temperature and pH, and the choice and amount of acceptor saccharides to be glycosylated," without specifying values. (EX1008, [0080]; EX2020, ¶59.). Alexander further

discloses that “[t]he upper limit for the concentrations of reactants that can be used in accordance with the method of the present invention is determined by the solubility of such reactants,” again without providing any serotype-specific guidance. (EX1008, [0080]; EX2020, ¶60.) Alexander’s only disclosed agitation step is likewise tied to a single example, without generalizable guidance on rate or technique, and its sole reference to sterility is a citation to conventional techniques generally, with no serotype-specific protocol. (EX1008, [0117], [0128]-[0129]; EX2020, ¶61-62.) As the Board recognized in *Merck*, “different serotype saccharides follow different pathways for activation (hydrolysis or no hydrolysis prior to [sodium periodate] activation) and conjugation (aqueous or DMSO reactions).” *Merck v. Wyeth*, IPR2017-01223, Paper 8 at 15. Alexander provides no direction for navigating these critical serotype-specific choices for any of the claimed serotypes. Alexander’s only concrete working examples involve serotypes 14, 6B, and 9V, demonstrating that even Alexander’s own inventors required detailed, serotype-specific protocols to achieve successful conjugates. (EX1008, [0127]-[0139]; EX2020, ¶63.) The complete absence of protocols for the claimed serotypes necessitates undue experimentation. (EX2020, ¶64.)

b. Insufficient Direction or Guidance (Factor 2)

Alexander offers only the conclusory statement that compositions contain “an immunogenically effective amount,” without any technical direction on how to

achieve immunogenicity for the claimed serotypes. (EX1008, [0105].) While Alexander describes general pan-DR binding peptide sequences and mentions various conjugation approaches, it provides no guidance on which pan-DR binding peptide sequence or conjugation chemistry is appropriate for each claimed serotype’s structural features, what conjugation efficiency or quality-control targets to aim for, or what immunogenicity testing protocol to follow. (EX1008, [0058]-[0065], [0087]-[0093]; EX2020, ¶65.) As in *Impax*, where “the dosage guidelines are broad and not specific to any of the hundreds of formula I compounds,” Alexander’s generic statements lack the specific direction necessary for enablement of conjugates including any of the claimed serotypes. 545 F.3d at 1315 (quotation omitted). (EX2020, ¶66.)

Moreover, as discussed in Sections VI.A.-B., Alexander merely lists some of the claimed serotypes among dozens of possible serotypes, without any technical guidance to further narrow the possible serotype combinations. (EX2020, ¶¶67-68.)

c. Complete Absence of Relevant Working Examples (Factor 3)

Alexander provides no working examples demonstrating actual immunogenic conjugates for any of the claimed serotypes. (EX2020, ¶69.) Alexander’s sole immunogenicity data—antibody responses and opsonophagocytic activity for serotype 6B, and antibody titers for 14 and 9V—cannot enable the

claimed serotypes. (EX1008, [0135]-[0141].) The structural and immunological differences between those serotypes and the claimed ones are unaddressed, no correlation or bridging data suggests what would predict success, and the detailed protocols provided are specific to 6B, 14, and 9V alone. (EX2020, ¶70.) Working examples are particularly important for functional limitations in unpredictable fields. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 612-13 (2023).

d. Highly Unpredictable Art (Factor 7)

As discussed in Section VI.F.3., Petitioner’s predecessor, Wyeth, previously told the Board that pneumococcal conjugate vaccine development was highly unpredictable as of the priority date. *Merck v. Wyeth* also illustrates this unpredictability. Even with established conjugation knowledge, the Board found no reasonable expectation that a serotype 3 conjugate would be immunogenic because “the serological antipolysaccharide antibody correlate of protection against pneumococcal infection is poorly defined.” *Merck v. Wyeth*, IPR2017-01223, Paper 8 at 13.

Alexander’s development approach confirms this unpredictability. (EX2020, ¶71.) Alexander discloses multiple different conjugation approaches, including direct conjugation and various linker-based strategies, and multiple different pan-DR binding peptide sequences, but without guidance on which to select for particular serotypes. (EX1008, [0058]-[0065].) Alexander’s own data shows

variability in immunogenicity across different serotypes, with serotype 14 being “the most immunogenic and serotype 9 the least.” (EX1008, [0137]; EX2020, ¶72.)

2. Gu Similarly Fails the *Wands* Analysis

a. Excessive Experimentation Required (Factor 1)

Gu also provides no specific conjugation protocols, immunogenicity data, or technical guidance for the claimed serotypes (other than claim 12’s 22F). (EX2020, ¶74.) While Gu discloses general activation methods using CDT or periodate oxidation, these generic protocols are not tailored to the claimed serotypes and provide no guidance on which activation pathway would be appropriate for each. (EX1009, 9, 22; EX2020, ¶75.) A POSA would need to conduct substantial experimentation to determine, for each claimed serotype: whether to use CDT or periodate activation, and under what conditions; solvent system, ratios, buffer composition, and pH, ionic strength and reaction parameters; and purification, sterility, and testing protocols to confirm immunogenicity. (EX2020, ¶76.) Gu’s own disclosure confirms, rather than relieves, this burden. Gu reports that “several conjugates [were] obtained...by varying different parameters (e.g. pH, temperature of the reactions and concentration of polysaccharide)” but gives no guidance on how to select those parameters for an untested serotype. (EX1009, 93:1-2; EX2020, ¶77.) Gu also discloses various water-to-solvent ratios without explaining which ratios, or ranges of ratios, would be beneficial in other systems. (EX1009,

48; EX2020, ¶78.). Its only concrete buffer and concentration data are serotype-specific—for example, dissolving the 33F polysaccharide in 100 mM sodium phosphate buffer (pH 6.0) to a final concentration of 2 mg/ml in 25 mM buffer, and its stirring, stability-testing, and diafiltration examples likewise appear only at scattered, serotype-specific points in the disclosure, with no indication that these parameters would translate to an untested serotype. (EX1009, 92:9-93:23; 113:5-114:2; EX2020, ¶79.) Gu’s only concrete working examples involve serotypes 22F and 33F demonstrating that even Gu’s own inventors required detailed, serotype-specific protocols to achieve successful conjugates. (EX1009, 87-88, 112-19.) The complete absence of such protocols for the claimed serotypes necessitates undue experimentation. (EX2020, ¶80.)

b. Insufficient Direction or Guidance (Factor 2)

Gu offers only the conclusory statement that glycoconjugates “can be used in the production of antibodies,” without any technical direction on how to achieve immunogenicity for the claimed serotypes (other than claim 12’s 22F). (EX1009, 31:32-32:2.) While Gu describes general chemical schemes for oxo-linked conjugates (Figures 1-4), it provides no guidance on which conjugation chemistry (oxo-eTAC, oxo-eTAAN, or oxo-eTAAD) or activation conditions are appropriate for each claimed serotype’s structural features, what conjugation efficiency or quality-control targets to aim for, or what immunogenicity testing protocol to

follow. (EX2020, ¶81.) As in *Impax*, Gu’s generic chemical schemes lack the specific direction necessary for enablement of the claimed serotypes. 545 F.3d at 1315.

As discussed in Sections VI.A.-B., Gu merely lists some of the claimed serotypes among other, unclaimed serotypes, without any technical guidance to further narrow the possible serotype combinations. (EX2020, ¶¶82-84.)

c. Complete Absence of Relevant Working Examples (Factor 3)

Gu provides no working examples demonstrating actual immunogenic conjugates for any of the claimed serotypes. (EX2020, ¶85.) Gu’s sole immunogenicity data—OPA titers for serotype 33F conjugates in a murine model—cannot enable the claimed serotypes. (EX1009, 87-88.) The structural and immunological differences between serotype 33F and the claimed serotypes are unaddressed, no correlation or bridging data suggests the results would predict success, and the detailed protocols provided are specific to 33F alone. (EX2020, ¶86.) Working examples are particularly important for functional limitations in unpredictable fields. *Amgen*, 598 U.S. at 612-13.

d. Highly Unpredictable Art (Factor 7)

In addition to the discussion of this factor with respect to Alexander in Section VI.E.2.d., Gu’s own development approach confirms the unpredictability of this art. Gu discloses multiple different activation pathways (CDT, CDI,

periodate oxidation) and conjugation chemistries (oxo-eTAC, oxo-eTAAN, oxo-eTAAD), acknowledging that different approaches may be needed for different serotypes. (EX1009, 9, 22.) Gu provides detailed protocols only for its successfully developed serotypes (22F, 33F), implicitly acknowledging that generic guidance is insufficient and that each serotype requires individual experimental development. (EX2020, ¶87.)

F. The Petition Fails to Demonstrate a Reasonable Expectation of Success for Its Obviousness Grounds

Whether obviousness “is based on combining disclosures from multiple references, combining multiple embodiments from a single reference, or selecting from large lists of elements in a single reference, there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.” *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017).

Petitioner gives short shrift to its burden of demonstrating a reasonable expectation of success in each of its obviousness grounds. Petitioner’s expert also did not opine from a POSA’s perspective as of the priority date, as the law requires. Instead, he testified at deposition that his opinions were informed by “21 years of experience in vaccine research”—June 2001 to June 2022—more than six years after the priority date. (EX2022, 24:21-25:7.) That is impermissible hindsight. In *InTouch Techs., Inc. v. VGo Commc’ns, Inc.*, the court reversed an obviousness finding

because the expert “failed to address why one of ordinary skill in the art at the time of the invention...would be motivated to combine” the references, opining only what a skilled artisan “could accomplish” years later—“that is not the relevant inquiry.” 751 F.3d 1327, 1352 (Fed. Cir. 2014). The same defect infects Petitioner’s expert’s testimony, and his opinions on obviousness should be given no weight.

Throughout the Petition, Petitioner ignores the limitation, recited in every claim, that the claimed conjugates must be immunogenic. For example, Petitioner characterizes the claims as “merely claim[ing] including well-known serotypes in a PCV.” (Petition, 2.) Petitioner also repeatedly references the Examiner’s supposed mistake in finding that the claimed serotypes “appear to be free of prior art” when the art before the Examiner “taught precisely the serotypes” at issue. (*See, e.g.*, Petition, 1, 10-12.) In interpreting the Examiner’s statement as a repeated, blatant, error, Petitioner ignores the fact that the claims do not merely recite specific conjugated serotypes, but also require that these serotypes must be “immunogenic.” This is why the Examiner stated that the claimed immunogenic, conjugated serotypes “appear to be free of prior art.”

There is a good reason that Petitioner tries to hand-wave away the “immunogenic” limitation that the claims recite—neither Alexander nor Gu discloses this element, or even comes close. While both references make generic,

conclusory statements about immunogenicity as a goal of their inventions as a whole—without reference to any pneumococcal vaccine embodiment, much less with respect to any particular serotype or combination of serotypes—neither reference provides the specific, technical disclosure required for a POSA to make and use immunogenic conjugates of the claimed serotypes as anticipation requires.

The Board’s decision in *Merck* is directly on point and establishes that invalidating prior art references must provide actual evidence of immunogenicity, not merely generic statements of intent. *Merck v. Wyeth*, IPR2017-01223, Paper 8 at 11-14 (PTAB Oct. 20, 2017). In *Merck*, Petitioner sought to prove obviousness of a 13-valent pneumococcal conjugate vaccine based on the combination of Prevnar 2001 (a marketed 7-valent vaccine) and Overturf 2002. *Id.*

Overturf 2002 disclosed an 11-valent pneumococcal CRM197 conjugate vaccine containing serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F—an actual vaccine formulation in preclinical development. *Id.* at 13. It included a known serotype (serotype 3) recognized as causing serious disease, a proven carrier protein (CRM197) with established efficacy, and explicit reference to conjugation to that carrier. *Id.* at 11-16.

Despite these favorable factors, the Board denied institution because—just as Petitioner has done here—“Petitioner point[ed] to no evidence that the compositions relied upon by [their expert] were tested for the production of a

functional antibody response.” *Id.* at 16. In *Merck*, the Board held that the use of the prior art compositions, even in a vaccine trial, “do not provide evidence for Petitioner’s assertion that any serotype 3 conjugated to a protein carrier is immunogenic as claimed, i.e., showing higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM₁₉₇.” *Id.* at 16-17. The Board also recognized that “[t]here is no indication in Overturf 2002 of how the individual polysaccharides are attached to the carrier protein, or that the composition had been tested.” *Id.* at 15. The Board emphasized that “**different serotype saccharides follow different pathways for activation** (hydrolysis or no hydrolysis prior to [sodium periodate] activation) **and conjugation** (aqueous or DMSO reactions),” and that “the **same conjugation protocol does not work for every polysaccharide.**” *Id.* In other words, generic statements about conjugation cannot substitute for serotype-specific technical disclosure.

In *Merck*, the Board declined institution where the prior art selected and tested the claimed serotypes in a conjugated vaccine, but had no evidence of immunogenicity (even though the goal, of course, was immunogenicity since the serotype was being tested in a vaccine). *Id.* at 15-17. The Board in *Merck* also rejected conclusory expert opinions—like the one here—that the vaccine “would

be immunogenic” as resting on “unsupported opinions” lacking “any objective proof.” *Id.*

Alexander and Gu are materially weaker than the rejected prior art in *Merck v. Wyeth*. Both references provide even less specific technical guidance than Overturf 2002, offering only generic lists of serotypes with conclusory statements about immunogenicity in general. Neither reference provides any indication of how to conjugate serotypes 23A, 23B, or 35B to achieve immunogenicity or which conjugation pathways are appropriate for these serotypes. (EX2020, ¶89.)

Alexander states only that “[t]he present invention is directed to vaccines which contain as an active ingredient an immunogenically effective amount of a composition comprising at least one conjugate of the present invention.” (EX1008, ¶105.) This conclusory statement provides no level of immune response that constitutes “immunogenically effective” or how to achieve it for any the claimed serotypes. (EX2020, ¶90.) Alexander’s immunogenicity data is limited to ELISA and opsonophagocytic results for serotypes 6B, 14, and 9V, with no immunogenicity data for the claimed serotypes. (EX1008, ¶¶134-41) Alexander provides no correlation data suggesting that results for the exemplified serotypes would predict success for the claimed serotypes. (*See, id.*)

Similarly, Gu discloses “immunogenic compositions” in its title and abstract, and states that “[g]lycoconjugates of the invention comprising a bacterial capsular

polysaccharide can be used in the production of antibodies against such a bacterial capsular polysaccharide.” (EX1009, Cover, (54), (57), 30:32-31:2.) Like Alexander, Gu’s disclosure provides no technical direction toward achieving immunogenicity for the claimed serotypes. (EX2020, ¶¶91.) Gu’s immunogenicity data is limited to OPA titers for serotype 33F, with no immunogenicity data for serotypes 23A, 23B, or 35B. (EX1009, 86:23-87:14) Like Alexander, Gu provides no framework for determining what immune response level would enable the immunogenicity limitation for untested serotypes. (*See, id.*)

1. Petitioner’s Reasonable Expectation of Success Analysis for Alexander Is a Single Conclusory Sentence Without Any Supporting Analysis

Petitioner argues that it would have been obvious for a POSA to select the claimed serotypes considering Alexander. (Petition, 37.) But Petitioner’s entire showing on reasonable expectation of success is the second half of one sentence appearing at the end of a paragraph otherwise focused entirely on motivation to combine: “The POSA...would have reasonably expected to succeed in making such a composition.” (*Id.* (citing EX1002, ¶¶143-144).) Petitioner’s expert declaration does not help—it too focuses almost entirely on motivation, and on reasonable expectation of success merely repeats the Petition’s language nearly verbatim: “The POSA would also have reasonably expected, based on Alexander, to succeed in making such a composition.” (EX1002, ¶144.) Full stop. Even

though “selecting from large lists of elements in a single reference” requires “a reasonable expectation that such a [selection] would be successful,” that is the entirety of the reasonable expectation to combine analysis Petitioner and its expert set forth. *See In re Stepan*, 868 F.3d at 1346 n.1.

The law is clear: “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements.”). Because Petitioner has not provided this required “articulated reasoning with some rational underpinning,” Petitioner’s obviousness ground based on Alexander must fail. *See id.*

2. Gu: Petitioner Conflates Motivation with Reasonable Expectation of Success

Petitioner’s argument that a POSA would select the claimed serotypes in light of Gu is similarly deficient. The entirety of the Petition’s reasonable expectation of success analysis reads: “The POSA also would have reasonably expected, based on this reference and the longstanding trend in the art toward including more serotypes, to succeed in making such a composition.” (Petition, 49 (citing EX1002, ¶195).) Petitioner’s supporting expert declaration elaborates only

slightly, adding without explanation or citation that including all eight serotypes disclosed in Gu—when the currently-available vaccine only targeted thirteen serotypes, “would have been manageable to do”:

Indeed, it would have been obvious to include all eight of the serotypes disclosed in one list in Gu, as the skilled artisan would have recognized as of the priority date that adding eight serotypes to prior art pneumococcal conjugate vaccines would have been manageable to do...

(EX1002, ¶195.)

In addition to failing as conclusory, for the reasons discussed with respect to Alexander in Section VI.F.1., this assertion wrongly conflates *motivation* with *reasonable expectation of success*—two distinct legal requirements that Petitioner must independently satisfy. *See Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021) (“[W]e must first emphasize the clear distinction in our case law between a patent challenger’s burden to prove that a skilled artisan would have been motivated to combine prior art references and the additional requirement that the patent challenger also prove that the skilled artisan would have had a reasonable expectation of successfully achieving the claimed invention from the combination.”).

The “longstanding trend in the art toward including more serotypes” is evidence of *motivation*—it explains *why* a POSA would *want* to add more

serotypes (to broaden disease coverage), not the technical feasibility of achieving it. But motivation and reasonable expectation of success are separate requirements. (Petition, 49 (citing EX1002, ¶195).) *See id.* The Federal Circuit has held that “to have a reasonable expectation of success, one must be motivated to **do more than** merely to ‘vary all parameters or **try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave** either no indication of which parameters were critical or **no direction as to which of many possible choices is likely to be successful.**” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). That researchers *wanted* to include more serotypes in a pneumococcal vaccine says nothing about whether they could *successfully* select and conjugate the claimed serotypes and achieve immunogenicity. (EX2018, ¶139; EX2020, ¶92.) Petitioner has not explained—much less provided evidence showing—why a POSA would have expected to successfully add the claimed serotypes from among the 255 possible choices in Gu to a vaccine formulation.

3. The “Longstanding Trend in the Art” Contradicts Petitioner’s Conclusory Assertion of a Reasonable Expectation of Success

Far from supporting a reasonable expectation of success, the “longstanding trend in the art,” including the pace of pneumococcal conjugate vaccine development itself, demonstrates the substantial technical challenges inherent in

increasing valency. From Prevnar’s 2000 licensure with 7 serotypes to PCV13’s 2010 licensure with 13, only 6 additional serotypes were successfully added in a decade (Petition, 6-7)—an average of less than one serotype every two years. (EX2018, ¶140.)

One reason for this slow pace—and a reason that the POSA would be limited in how many serotypes they could add to the existing PCV13 vaccine in March of 2016—is the concern over immune interference. (EX2018, ¶141.) Because multivalent conjugate vaccines expose the immune system to increasing numbers of antigens simultaneously, adding serotype-specific polysaccharide conjugates to an existing vaccine risks immune interference (also called antigenic interference) that can reduce the immune response to serotypes already in the formulation, through mechanisms including carrier-specific T-helper cell interactions, T-cell bystander interferences, or carrier induced epitopic suppression. (EX2035, 226; EX2018, ¶¶142-144.) As researchers explained, “[h]igher valency PCVs are not likely to be developed due to the high costs of development and the complexity of ensuring adequate immunogenicity for each serotype,” and that “there may be a reduction in the ability of some children to respond to certain common serotypes when vaccinated with PCV13 compared vaccination with PCV7.” (EX1040, 1015; EX2018, ¶143.)

That concern was borne out by clinical data comparing PCV13 to its 7-valent predecessor. In a randomized, double-blind, non-inferiority trial in healthy US infants, three of PCV13's serotypes—6B, 9V, and 3—failed to meet the pre-defined non-inferiority criterion for serum IgG response after the primary infant series. (EX1024, 497-98.) Across all seven serotypes shared between PCV7 and PCV13, antipolysaccharide IgG GMC ratios were higher for PCV7 than for PCV13, and PCV7 elicited higher functional (OPA) responses for five of the shared serotypes. (EX1024, 498.) The same pattern persisted after the toddler booster dose. PCV7 produced superior IgG responses for every shared serotype except 19F, and higher OPA responses for six of the seven shared serotypes (EX1024, 500-01; EX2018, ¶145.) In other words, the immune response to PCV13's own shared serotypes measurably suffered simply from adding six more antigens to a 7-valent formulation—precisely the interference mechanism a POSA would have expected to worsen, not improve, with each further serotype added, particularly in older or immunocompromised populations less able to mount a robust immune response to begin with. (EX2018, ¶146.)

Petitioner's own predecessor made exactly this point to the Board while opposing patent claims covering the PCV13 formulation Petitioner now treats as a mere steppingstone. Wyeth, acquired by Petitioner in 2009 (Petition, 1), told the Board that “[a] POSA would have had significant concerns expanding the

formulation of Prevnar 2005 because of the possible loss of immunogenicity due to ‘immune interference’ when developing a 13-valent conjugate vaccine, especially considering the highest valency present in a licensed conjugate vaccine was the 7-valent Prevnar® vaccine.” (EX2016, ¶26 (*Merck Sharp & Dohme Corp. v. Wyeth LLC*, IPR2017-00390, EX2118, 11-12) (citations omitted).) Wyeth went further, telling the Board that “[c]onjugate vaccine development, especially multivalent conjugate development, was an unpredictable field characterized more by failures than successes,” and that manufacturers “encountered numerous problems regarding efficacy and stability in developing conjugate vaccines, often resulting in failure.” *Merck Sharp & Dohme Corp. v. Wyeth LLC*, IPR2017-00390, Paper 15 at 5 (PTAB Sept. 13, 2017) (citations omitted). Pfizer made the same admission in a different IPR, explaining that “[d]ifferent serotypes have varying chemical and immunological properties and these differences make the development of multivalent vaccines a challenge,” including “immune interference between protein conjugates of serotypes and carrier induced epitopic suppression.” (*Sanofi Pasteur Inc. & SK Chemicals Co. v. Pfizer Inc.*, IPR2018-00188, Paper 8 at 3 (PTAB Mar. 12, 2018).)

These admissions directly refute Petitioner’s present, unsupported assertion that a “longstanding trend” toward higher-valency vaccines gave a POSA a reasonable expectation of success. The Board’s decision in *Merck*, discussed in

Section VI.F., reinforces the same point with respect to the unpredictability of the art generally. If Wyeth/Pfizer itself warned the Board that a POSA would have had “significant concerns” about immune interference at the 13-valent stage, a POSA would have expected even greater interference from the higher-valency vaccine the challenged claims require (since Petitioner’s expert acknowledged that a POSA would want to build a vaccine on top of the serotypes already included in PCV13, and not omit any of the already-included serotypes). (EX2018, ¶148; EX2022, 77:4-78:1.) This concern would be magnified in adults ≥ 65 and immunocompromised patients least able to compensate for a reduced immune response. (EX2018, ¶148.) Petitioner’s obviousness arguments therefore fail.

4. Petitioner’s Combination Theories Based on Serotype Prevalence and Vaccine Recommendation References Fail to Demonstrate a Reasonable Expectation of Success

Petitioner attempts to salvage its obviousness case by combining either Alexander or Gu with “Serotype Prevalence References” and “Vaccine Recommendation References.” (Petition, 50-54.) This combination theory fails for the same fundamental reason that dooms Petitioner’s other obviousness theories: complete absence of evidence supporting a reasonable expectation of success. Petitioner’s combination theory rests on a demonstrable falsehood—the claim that there are “multiple teachings of PCVs that included these serotypes.” (Petition,

54.) As shown below, Petitioner has identified *zero* PCVs that included any of the claim 1 serotypes.

First, Petitioner’s entire showing on reasonable expectation of success once again consists of the second half of a single sentence, asserting that “the POSA would have had a reasonable expectation of success, as illustrated by the *multiple teachings of PCVs that included these serotypes*.” (Petition, 54 (citing EX1002, ¶204).) This assertion is demonstrably false. Petitioner has identified **zero** prior art references disclosing actual PCVs that included any of the claim 1 serotypes—23A, 23B, or 35B. (See Petition, 52-54.) The Vaccine Recommendation References cited by Petitioner do not disclose or teach any such vaccines. At best, they *suggest* that these serotypes *might be considered* for *future* inclusion in vaccines. Speculation about future possibilities provides no basis whatsoever for a reasonable expectation that such vaccines would be successful.

Petitioner’s supporting expert declaration, while omitting the Petition’s false statement, elaborates only slightly, adding without explanation or citation an argument similar to the one he proffered with respect to Gu:

[G]iven the maturity of pneumococcal saccharide-polypeptide conjugate vaccine technology, the widespread recommendations to include additional serotypes, and the clear trend in the industry towards inclusion of additional serotypes, the POSA would have had a reasonable expectation of success in being able to do so.

(EX1002, ¶204.) Once again, Petitioner’s expert opinion is “conclusory and unsupported, [and so] adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight.” *See Xerox*, IPR2022-00624, Paper 9 at 16.

As discussed in Section VI.C., the “widespread recommendations to include additional serotypes and the clear trend in the industry towards inclusion of additional serotypes” go to motivation to combine but say nothing about a reasonable expectation of success. And as shown in Section VI.F.3., Petitioner’s own predecessor called this field “unpredictable...characterized by more failures than successes”—yet Petitioner’s expert never explains what makes it “mature” instead. This does not indicate a reasonable expectation of success, particularly in light of the absence of any explanation for Petitioner’s expert’s unsupported conclusion.

Second, the Serotype Prevalence References at best establish that some claimed serotypes were known and prevalent—but knowledge of a serotype’s existence is not a reasonable expectation that its immunogenic conjugate can be successfully made. (EX2018, ¶149.) Roughly 100 pneumococcal serotypes were known as of the priority date, yet by 2016 only 13 had been successfully incorporated into a conjugate vaccine. (*See* Petition, 7.) Had mere knowledge and prevalence sufficed, all roughly 100 would have been included; that they were not,

despite known need, decades of research, and commercial incentive, shows that technical feasibility—not knowledge or desire—is the rate-limiting factor.

(EX2018, ¶150.) As described in Sections VI.E. and VI.F.3., that gap reflects serotype-specific conjugation chemistry, unpredictable immunogenicity, potential interference, and formulation stability.

5. No Serotype-Specific Data Existed to Support a Reasonable Expectation That the Claimed Serotypes Would Be Immunogenic

The unpredictability of the immune response discussed in Sections VI.E. and VI.F.3., is borne out by the very correlate of protection used to license PCVs.

(EX2018, ¶151.) A POSA was aware that licensure of a conjugate pneumococcal vaccine required demonstrating a threshold serum concentration of 0.35µg/ml of anti-capsular antibody, aggregated across all serotypes within the vaccine.

(EX2033, 839; EX2018, ¶152.) This correlate of protection has been used to license vaccines containing additional serotypes, including PCV13, without the need for formal efficacy studies. (Choi 2016, 165; EX2018, ¶152.)

That aggregate correlate, however, masked enormous serotype-to-serotype variability. (EX2018, ¶153.) PCV13 vaccine effectiveness ranged from 26% for serotype 3 to 98% for serotype 6A, corresponding to calculated protective serum concentrations of 2.83µg/ml for serotype 3 and just 0.16µg/ml for serotype 6A.

(EX2033, 843.) This data has been interpreted as showing the 0.35µg/ml threshold

to be an underestimate for some serotypes and an overestimate for others. (EX2033, 842-843.) Recalculating the correlate of protection for the PCV7 serotypes using post-PCV13 IgG data yielded 0.59µg/ml, leading researchers to conclude that “this finding suggests that the 0.35ug/ml correlate for PCV7 serotypes is too low and does not predict vaccine performance with much precision,” that “serotype-specific correlates of protection vary widely,” and that “[t]his finding shows that the notion of a threshold concentration of circulating serotype-specific IgG that is protective is overly simplistic.” (EX2033, 839, 844-845; EX2018, ¶153.)

Functional antibody data were even more concerning. (EX2018, ¶154.) Researchers found that opsonophagocytic antibody titres of 1 in 8 or higher did not predict vaccine protection. (EX2033, 839.) The researchers explained that “[w]ith such wide variation between the correlates for different serotypes, a single aggregate correlate would be unlikely to have any biological plausibility, thus we made no attempt to derive one for functional antibody,” and that “[t]he results of our study suggest that no single threshold can be applied for all PCV13 serotypes, because the performance of each individual serotype-specific functional assay varies.” (EX2033 843, 845; EX2018, ¶154.)

No such data—for either serum IgG concentration or OPA titer—existed for any of the serotypes recited in the Challenged Claims. (EX2018, ¶157.) A POSA

therefore had no basis to predict, and could not have reasonably expected, that conjugates of the claimed serotypes would be immunogenic without individually testing each one. (EX2018, ¶¶155-156, 158; EX2020, ¶93.)

For each of these reasons, a POSA would not have had a reasonable expectation of success in achieving the immunogenic compositions claimed in the '757 patent. (EX2018, ¶159.)

G. Gu Fails to Disclose the Claimed “Plurality of at Least Two Unique Immunogenic Saccharide-Polypeptide Conjugates”

1. Petitioner’s Argument that a POSA Would “At Once Envisage” this Limitation from Gu Is Contrary to Law

Petitioner acknowledges that Gu does not literally disclose the “plurality of at least two unique immunogenic saccharide-polypeptide conjugates” that all Challenged Claims recite, arguing instead that “the POSA would understand that Gu discloses compositions which comprise glycoconjugates with at least two of the three serotypes listed in limitation 1.c, and the POSA would at once envisage a vaccine composition involving glycoconjugates with at least two of the required serotypes.” (Petition, 42-43.) This is directly contrary to Federal Circuit precedent, which has “previously rejected the proposition that ‘a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would ‘at once envisage’ the missing limitation.’” *Galderma Lab’ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App’x 838, 845 (Fed. Cir. 2020) (quoting *Nidec*, 851 F.3d at

1274-75). A court is “not permitted ‘to fill in missing limitations simply because a skilled artisan would immediately envision them.’” *Id.* Because controlling precedent forecloses anticipation based on what a POSA “would at once envisage,” Petitioner’s anticipation challenge as to Gu fails.

2. “Multiple Glycoconjugates” Does Not Inherently Mean Multiple Serotypes

Because Petitioner acknowledges that Gu does not literally disclose the recited “plurality of at least two unique immunogenic saccharide-polypeptide conjugates,” Petitioner relies on an inherency argument based on Gu’s claim reciting “[a]n immunogenic composition comprising *at least one* glycoconjugate.” (Petition, 41 (emphasis in Petition).) Petitioner argues that “[b]y saying ‘at least’ Gu conveys to the POSA compositions that have multiple glycoconjugates....[T]he POSA would understand that a composition where all the glycoconjugates are the same serotype would not be described as having multiple glycoconjugates.” (Petition, 41 (citing EX1002, ¶153).) Not so. A composition with multiple glycoconjugates can refer to at least three different formulation approaches—(1) multiple serotypes conjugated to multiple carrier proteins; (2) multiple serotypes conjugated to a single carrier protein; or (3) a single serotype conjugated to multiple carrier proteins—as Petitioner’s own expert agrees. (EX2018, ¶¶162-163; EX2022, 116:21-117:21.) The Santiesteban-Lores study demonstrates this third

approach, using multiple glycoconjugates wherein a single serotype (6B) is conjugated to two different carrier proteins, PspA1 and PspA3. (EX2015, 1-5.)

Notably, “[i]nherency, however, may not be established by probabilities or possibilities.” *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (cleaned up). Because having multiple glycoconjugates does not necessarily mean having glycoconjugates with at least two unique serotypes, Petitioner’s inherency argument fails.

Despite carrying the burden of establishing that this limitation is necessarily present in Gu, Petitioner cites no evidence beyond its expert’s declaration, which for this proposition quotes the Petition verbatim. (Petition, 41 (citing EX1002, ¶153).) *See Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377-78 (Fed. Cir. 2002) (“[Petitioner] bears an evidentiary burden to establish that the limitation was necessarily present.”). Under the Board’s precedential decision in *Xerox*, expert testimony that “merely repeats, verbatim, the conclusory assertion for which it is offered to support” without citing “any additional supporting evidence or provid[ing] any technical reasoning” is “entitled to little weight”—and is “particularly problematic” where, as here, it is “offered not simply to provide a motivation to combine prior-art teachings, but rather to supply a limitation missing from the prior art.” *Xerox*, IPR2022-00624, Paper 9 at 16 (precedential). That is exactly what Petitioner’s expert’s unsupported opinion does here—supply the

missing disclosure of a “plurality of at least two unique immunogenic saccharide-polypeptide conjugates” that Gu itself lacks. (Petition, 40-41.)

3. Gu’s Disclosure Is Not “Arranged or Combined in the Same Way as Recited in the Claim”

Petitioner additionally argues that Gu discloses the recited “plurality of at least two unique immunogenic saccharide-polypeptide conjugates” by combining three passages—concerning preservatives, dosage amounts, and a dependent claim reciting “at least one glycoconjugate”—with Gu’s disclosure of a single pneumococcal glycoconjugate on page 22 of this 137-page document. (Petition, 40-43.) As discussed in Section VI.G.2., none of these disclosures necessarily indicate multiple serotypes, and combining them with Gu’s page 22 disclosure is forbidden under Federal Circuit precedent.

The Federal Circuit has held that “unless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.” *Net MoneyIN*, 545 F.3d at 1371. For these reasons, “it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.” *Id.*

Contrary to Petitioner’s characterization, Gu’s disclosure of pneumococcal conjugates consistently uses singular language when describing serotype selection: “In specific embodiments, the Pn capsular polysaccharide is selected from the group consisting of Pn-serotype 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F capsular polysaccharides.” (EX1009, 22:25-23:1.) Gu’s specific embodiments confirm this: “In one such embodiment, the capsular polysaccharide is a Pn-33F capsular polysaccharide. In another such embodiment, the capsular polysaccharide is a Pn-22F capsular polysaccharide.” (EX1009, 23:3-7.) Every specific embodiment in Gu related to pneumococcal glycoconjugates describes selecting one serotype, not multiple.

Nor does anything in Gu suggest combining the three passages Petitioner relies on with that serotype-selection disclosure. **First**, Gu’s page 57 disclosure that “[t]he immunogenic compositions of the invention may further comprise one or more preservatives in addition to a plurality of capsular polysaccharide-protein conjugates” appears in a paragraph about preservatives—not the selection of multiple serotypes. (EX1009, 57:12-20; EX2018, ¶164.) **Second**, Gu’s disclosure that “[t]he immunogenic amount of a conjugate or immunogenic composition may vary depending upon the bacterial serotype...The immunogenic amount of the different polysaccharide components in an immunogenic composition may diverge and each comprise 1 ug...or about 100 ug of any particular polysaccharide

antigen” addresses the weight of a component, not the number of serotypes selected. (EX1009, 63:6-12; EX2018, ¶165.) **Third**, Gu’s claim 25 recites “[a]n immunogenic composition comprising at least one glycoconjugate as defined in anyone [sic] of claims 1 to 24 and a pharmaceutically acceptable excipient, carrier, or diluents.” (EX1009, 123:9-11.) As explained in Section VI.G.2., “at least one glycoconjugate” does not inherently include multiple serotypes. (EX2018, ¶¶162-163.) Further, only claims 17 and 18 among claims 1–24 claim a pneumococcal glycoconjugate, and both use the same singular construction as the rest of Gu’s disclosure: “[t]he glycoconjugate of anyone [sic] of claims 1 to 16, wherein the saccharide is a capsular polysaccharide derive from *S. pneumoniae*.” (*Id.*, Claim 17.)

These disclosures therefore do not disclose the use of multiple glycoconjugates—but even if they did, they are far removed from Gu’s disclosure of a group of serotypes on page 22, and thus are not “arranged or combined in the same way as recited in the claim” as anticipation requires. *Net MoneyIN*, 545 F.3d at 1371. Petitioner’s anticipation argument must therefore fail with respect to Gu.

VII. CONCLUSION

Patent Owner respectfully requests the Board confirm all claims of the ’757 patent are patentable.

Dated: August 4, 2026

Respectfully Submitted,

/Sarah E. Spires/

Counsel for Patent Owner

Reg. No. 61,501

SKIERMONT DERBY LLP

1601 Elm Street, Suite 4400

Dallas, Texas 75201

P: 214-978-6600/F: 214-978-6601

CERTIFICATE OF WORD COUNT

Under the provisions of 37 CFR § 42.24, the undersigned hereby certifies that the Microsoft Office word count for the foregoing **PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120**, excluding the table of contents, table of authorities, listing of challenged claims, certificate of word count, and certificate of service, totals 14,000 words, which is the total word count allowed under 37 C.F.R. § 42.24(b)(2):

Dated: August 4, 2026

/Sarah E. Spires/

Sarah E. Spires (Reg. No. 61,501)
Counsel for Patent Owner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that a true and correct copy of the foregoing **PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.120** was served on August 4, 2026, by delivering a copy via electronic mail to the attorneys of record for Petitioner as follows:

David Krinsky (Reg. No. 72,339)

dkrinsky@wc.com

Julie Tavares (Reg. No. 77,398)

jtavares@wc.com

Yujung Rho (*pro hac vice* requested)

yrho@wc.com

WILLIAMS & CONNOLLY LLP

Dated: August 4, 2026

/Sarah E. Spires/

Sarah E. Spires (Reg. No. 61,501)

Counsel for Patent Owner