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

_____

DECLARATION OF DR. GEORGE G. ZHANEL IN SUPPORT OF PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND AND QUALIFICATIONS 2

III. LEGAL PRINCIPLES 10

IV. OVERVIEW OF THE '757 PATENT AND TECHNOLOGY BACKGROUND 17

V. CLAIM CONSTRUCTION 22

VI. THE CHALLENGED CLAIMS OF THE '757 PATENT ARE VALID 23

A. Alexander and Gu's Disclosures of Hundreds to Quadrillions of Options for Serotype Selection Do Not Anticipate the '757 Patent 23

B. Alexander's and Gu's Lists Are Also Too Large for Obviousness 25

C. The Serotype Prevalence References and/or the Vaccine Recommendation References Do Not Save Petitioner's Obviousness Arguments 26

1. No Reference Directed a POSA to the Serotype Combinations the Challenged Claims Recite 26

2. A POSA Seeking to Expand Pneumococcal Conjugate Vaccine Coverage Would Have Been Motivated to Conjugate the Remaining PPSV23 Serotypes—Not Select Unrelated Serotypes Outside PPSV23 33

3. A POSA Would Have Been Motivated to Make a Non-Serotype Based PCV (i.e. a conserved SPN antigen associated with the cell membrane) 39

4. A POSA Would Have Been Motivated to Improve Existing PCVs 46

5. Claims 13 and 14 Would Not Have Been Obvious to a POSA 49

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 2 of 77

a. **Serotype 16F** 50

b. **Serotype 6C**.....54

c. **Serotype 15C**.....59

D. The Petition Fails to Demonstrate a Reasonable Expectation of Success for Its Obviousness Grounds 62

E. Gu Fails to Disclose the Claimed "Plurality of at Least Two Unique Immunogenic Saccharide-Polypeptide Conjugates".....71

I, Dr. George G. Zhanel, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) years and otherwise competent to make this declaration.

2. I have been retained as an expert witness on behalf of Pogona, LLC for the above-captioned *inter partes* review ("IPR"). I understand that the petition for *inter partes* review involves U.S. Patent No. 11,058,757 (the "'757 patent"), which was filed on March 31, 2017. The '757 patent names Bruce D. Forrest and Jack D. Love as the inventors.

3. I make this declaration based on my personal knowledge, educational background and training, consideration of the materials I discuss herein, and my expert opinions.

4. I am being compensated at a rate of $700 per hour for my time in this matter. My compensation does not depend on the outcome of this proceeding and I have no financial interest in its outcome.

5. In preparing this Declaration, I have reviewed and considered the '757 patent, the '757 patent prosecution history, and each of the documents cited herein, and I have considered them in light of general knowledge in the art in the time frame of March 31, 2016—which I understand is the earliest priority date of the '757 patent. In formulating my opinions, I have relied upon my experience,

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 4 of 77

education and knowledge as they relate to the relevant art. I also have considered the viewpoint of a person of ordinary skill in the art in the time frame of the filing date of the ’757 patent.

II. BACKGROUND AND QUALIFICATIONS

6. A copy of my curriculum vitae, which includes further details of my educational background and career, is attached as Exhibit 2019.

7. I currently serve as Professor and Associate Head in the Department of Medical Microbiology and Infectious Diseases, Max Rady College of Medicine, Rady Faculty of Health Sciences, at the University of Manitoba and as Research Director of the Canadian Antimicrobial Resistance Alliance (“CARA”) based in Winnipeg, Canada.

8. I received a B.Sc. in Pharmacy and Pharmaceutical Sciences from the University of Manitoba in Winnipeg, Canada in 1984, a Doctor of Clinical Pharmacy from the University of Minnesota in Minneapolis in 1986, and a Ph.D. in Medical Microbiology from the University of Manitoba in Winnipeg, Canada in 1994. The subject of my doctoral thesis (1994) in Medical Microbiology was “Cellular and Molecular Evaluation of Fluoroquinolone Resistance in *Pseudomonas aeruginosa*.”

9. At the University of Manitoba, I teach medical students, internal medicine residents, medical microbiology and infectious diseases postdoctoral

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 5 of 77

fellows, and Masters and Doctoral students (as well as M.D./Ph.D. trainees) in both Medical Microbiology and Infectious Diseases and Clinical Pharmacology, as well as nurse practitioners, physician assistants, and undergraduate students in Science, Pharmacy, and Medical Technology.

10. The focus of my teaching since 1987 has been microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases including treatment and prevention of pneumococcal infections. My teaching focuses on antimicrobials and agents with antimicrobial activity (which include substances also referred to as antimicrobials/antibacterials/anti-infectives, antiseptics, sterilizers, preservatives, disinfectants, antituberculars, antifungals, antivirals, and antiparasitics). My teaching covers topics such as physicochemical properties; medicinal chemistry; mechanisms of action and resistance; microbiological activity; pharmacokinetics; pharmacodynamics; animal studies (including efficacy and toxicity studies); clinical uses including indications and adverse effects in humans, including effects on the human microbiome (i.e., "normal microbiota"); drug interactions; and the risks versus benefits of treatment. I also teach extensively about the usage of vaccination to prevent infectious diseases including pneumococcal polysaccharide and pneumococcal conjugated vaccines for prevention of invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) and associated cardiovascular morbidity and mortality.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 6 of 77

11. Over the last 35 plus years, my work has focused on microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases including treatment and prevention of pneumococcal infections. I gave my first presentation on the clinical usage of antimicrobials to treat infectious diseases in 1985 while working towards my Doctorate in Clinical Pharmacy. In addition, as early as 1985, I began advising clinicians regarding the optimal use of drugs for the treatment of infectious diseases as well as how best to prevent infectious diseases using vaccination.

12. A focus of my research is the study of microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases. My research group, CARA, does research in the areas of microbiology, treatment of infectious diseases and prevention of infectious diseases. We study epidemiology, which deals with the prevalence and incidence of infections throughout the United States and Canada. We also study clinical epidemiology, trying to understand the patient risk factors that are associated with being infected with pathogens including resistant strains; as well as molecular epidemiology, trying to understand what genetic types of pathogens cause infections. We also study rapid diagnostics, which aims to design and test methods to rapidly, sensitively, and specifically identify pathogens. Finally, we study the mechanistic ways that organisms and pathogens use to become resistant to drugs.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 7 of 77

13. A major focus of CARA is treatment and prevention of infectious diseases including treatment and prevention of pneumococcal infections. Our group is actively trying to identify the cellular and molecular mechanisms of resistance that organisms and pathogens use to avoid being killed by drugs. We study both existing (already marketed) and investigational antimicrobials as well as agents with antimicrobial activity to understand their microbiological activity, molecular mechanisms of action and resistance, pharmacokinetic and pharmacodynamic properties, and influence on patient outcome from both clinical (safety and efficacy) and economic perspectives.

14. I have extensive experience researching, writing, presenting, and teaching about pharmacokinetics, pharmacodynamics, microbiology, treatment of disease, and prevention of disease and disease progression including treatment and prevention of pneumococcal infections. I have published approximately 500 articles, approximately 750 abstracts and 13 book chapters in the fields of pharmacokinetics, pharmacodynamics, microbiology, and treatment of disease and prevention of disease and disease progression. I have presented our research findings (more than 1,300 invited presentations) in the fields of pharmacokinetics, pharmacodynamics, microbiology, and treatment of disease and prevention of disease and disease progression in North and South America, Western and Eastern

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 8 of 77

Europe (including Iceland and Russia), the Middle East, Northern and Southern Africa, Asia and Southeast Asia, and Australia.

15. Regarding my work with *Streptococcus pneumoniae*, I have 30 years of experience researching, writing, presenting, and teaching *S. pneumoniae* pathogenesis, infectious causes (including invasive pneumococcal disease-IPD, community acquired pneumonia-CAP and other respiratory tract infections, acute otitis media and sinusitis), associated morbidity and mortality, antimicrobial resistance, serotype epidemiology, serotype evolution, genotype evolution, antimicrobial treatment and usage of polysaccharide and conjugate pneumococcal vaccines for prevention. I have presented some > 300 presentations, published approximately 100 articles, approximately 250 abstracts/posters and several book chapters discussing *S. pneumoniae* pathogenesis, infectious causes, associated morbidity and mortality, antimicrobial resistance, serotype epidemiology, serotype evolution, genotype evolution, antimicrobial treatment and usage of polysaccharide and conjugate pneumococcal vaccines for prevention.

16. In terms of awards and accomplishments in teaching and research, I have received or been nominated for more than 118 teaching awards, including the Canadian Association for Medical Education (CAME) merit teaching award in 2020. I am a member of the Who's Who in Medical Sciences Education (WWMSE). In 2022, I was elected as a fellow of the Canadian Academy of Health

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 9 of 77

Sciences (CAHS) in recognition of sustained excellence in research and teaching within the health sciences. Fellowship in the Academy is considered one of the highest honors for individuals in the Canadian health sciences community. Since 2022 and each year thereafter, Web of Science, an online platform offering access to academic databases, identified me as one of the world's most influential researchers, selecting me from among an elite group recognized for exceptional research influence, demonstrated by the production of multiple highly-cited papers that rank in the top 1% by citations for field and year.

17. My work on microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases has led me to serve as a consultant (through advisory boards or otherwise) to several major pharmaceutical and other manufacturers. As part of my research and consultancy role for these companies, I am routinely called on to provide advice concerning my expertise in microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases. I am called on to make comparative evaluations among drugs, antimicrobials as well as vaccines. Topics on which I am asked to advise include comparative mechanism of action, microbiological activity and factors that influence antimicrobial activity, pharmacokinetic and pharmacodynamic properties, animal studies (including efficacy and toxicity studies), and clinical uses including indications, adverse effects in humans, drug interactions, and the

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 10 of 77

risks versus benefits of therapy. The guidance I provide to companies on scientific matters generally pertains to particular situations and indications and uses for drugs, antimicrobial compounds and vaccines.

18. I am frequently consulted by adult and pediatric clinical specialists and generalists on matters pertaining to microbiology, pharmacology, treatment of infectious diseases and prevention of infectious diseases. These consultations include the selection of specific therapy (or vaccine), dosage, dosage regimen including duration of treatment, prophylaxis, suppression or eradication, assessment of potential drug interactions and the risks versus benefits of treatment, and monitoring for efficacy and toxicity, and range from accompanying physicians to bedside visits to phone calls (local or from all over North America), electronic consultations, and hallway discussions and discussions at medical/scientific meetings.

19. From 1990 to 2005, I was a consultant and senior consultant to the Manitoba Drug Standards and Therapeutics Committee ("MDSTC"), a Manitoba Government committee. I was the antimicrobial, pharmacokinetic and pharmacodynamic expert on this committee. The MDSTC assessed generic drug applications and new drug applications from all drug and therapeutic categories including antimicrobials and vaccines and made recommendations to the Provincial government (Manitoba Health) regarding the indications for which the

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 11 of 77

government should provide insurance benefits to the citizens of the Province. Over the 15 years on the committee, I was responsible for reviewing hundreds of generic drug applications, including applications for antimicrobials as well as vaccines, and assessing pharmacokinetic, bioequivalence, interchangeability, and at times pharmacodynamic data from a variety of dosage formulations. I have also been consulted on similar matters to those at MDSTC since my departure from the committee in 2005, by other provinces and jurisdictions in Canada and across North America.

20. In view of my education, experience, and qualifications, I consider myself an expert in the areas of microbiology and pharmacology, treatment of infectious diseases and prevention of infectious diseases. I am also an expert in preventing and treating pneumococcal infections including *S. pneumoniae* pathogenesis, infectious causes (including invasive pneumococcal disease-IPD, community acquired pneumonia-CAP and other respiratory tract infections, acute otitis media and sinusitis), associated morbidity and mortality, antimicrobial resistance, serotype epidemiology, serotype evolution, genotype evolution, antimicrobial treatment and usage of polysaccharide and conjugate pneumococcal vaccines for prevention.

21. My work on pharmacokinetics, pharmacodynamics, microbiology, and treatment of disease and prevention of disease and disease progression has led

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 12 of 77

me to serve as a consultant (through advisory boards or otherwise) to many pharmaceutical and biotech companies. These companies include the following companies, their affiliates, or both: Abbott, Achaogen, Affinium, Allergan, Astellas, AstraZeneca, Avir, Bayer, Cangene, Cerexa/Forest Labs, Cipher, Cubist, Galderma, GlaxoSmithKline, Iterum, Janssen Ortho/Ortho McNeil, Kane BioTech, Meitheal, Merck, Novexel, Optimer, Paladin Labs, Paratek, Pfizer, Procter & Gamble, Red Leaf Medical, Sandoz, Sanofi-Aventis, Sepracor, Shionogi, Sterimax, Sunovion, The Medicines Co., Tetraphase, Theravance, Triton, Trius, Venatorx, Verity, Xediton, Zambon, and Zoetis.

III. LEGAL PRINCIPLES

Ordinary Skill in the Art

22. My opinions in this declaration are based on the understandings of a person of ordinary skill in the art—sometimes referred to as an "ordinary artisan" or by the acronym "POSA"—as of the time of the invention, which I understand to be the March 31, 2016 filing date of the earliest application leading to the '757 patent. I understand that the person of ordinary skill in the art is a hypothetical person who is presumed to have known the art relevant to the Challenged Claims of the '757 patent at the time of the invention.

23. I understand that, in assessing the level of skill of a person of ordinary skill in the art, one should consider the type of problems encountered in the art, the

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 13 of 77

prior solutions to those problems found in the prior art references, the rapidity with which innovations are made, the sophistication of the technology, the level of education of active workers in the field, and one's own experience working with those of skill in the art at the time of the invention.

24. I understand that Petitioner submits that a POSA at the time of the '757 patent 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 at 12–13 (emphasis added)). I further understand that in a separate IPR Petition challenging the '757 patent, a different petitioner—Merck—submitted that a POSA at the time of the '757 patent 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).

25. I note that Merck's definition does not require the underlined portion of Petitioner's definition. In my opinion, a POSA would not need experience in

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 14 of 77

drug delivery of vaccines as Petitioner's POSA definition articulates, as an individual "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" would have sufficient knowledge of drug delivery for the field of the '757 patent. Thus, in my opinion, a POSA would include "a research team with one or more researchers with an M.D. or Ph.D. in immunology, virology, microbiology, biochemistry, chemistry, or a related discipline, and several years of work experience in vaccinology or related fields" (Petition at 12-13).

Claim Construction

26. I understand that the Challenged Claims of the '757 patent in this IPR are generally interpreted according to their ordinary and customary meaning taking into consideration the so-called "intrinsic evidence" of the patent consisting of (1) the claim language; (2) the specification; and (3) the prosecution history.

27. I understand that claim terms may be explicitly defined in the patent specification or they may be implicitly defined through consistent usage in the specification. I also understand that the scope of claim terms may be limited by statements in the specification or prosecution history where the applicant clearly disavows or disclaims subject matter.

28. I understand that claim construction is a matter of law.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 15 of 77

Anticipation

29. I have been informed that a claim is invalid as anticipated under 35 U.S.C. § 102 if a prior art reference discloses, either expressly or inherently, all limitations of a claim as those limitations are arranged in the claim.

30. I have been further informed that 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.

31. I have also been informed that an anticipating prior art reference must disclose all elements of the claim arranged or combined in the same way as in the claim, without any need for picking, choosing, and combining various disclosures.

32. I have been informed that that where a reference contains a list of items that may be combined to form a claimed combination, the reference can only be anticipatory if the number of categories and components disclosed in the prior art reference is small enough that the claimed combination would be immediately apparent to one of ordinary skill in the art.

33. I have been informed that a limitation is disclosed inherently in a reference if it is necessarily present in the process or product described in the prior art reference. I understand that probabilities or possibilities are insufficient to show that a prior art reference inherently discloses something beyond what it discloses explicitly.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 16 of 77

Obviousness

34. I have been instructed by counsel and understand that a combination of prior-art references may render a claim obvious if, at the time of the invention, a person of ordinary skill in the art would have selected and combined those prior-art elements in the normal course of research and development to yield the claimed invention.

35. I understand that for a reference to be considered in an obviousness analysis, it needs to be analogous to the claimed invention. I further understand that a reference is considered analogous prior art if the reference is from the same field of endeavor as the claimed invention, or if the reference is reasonably pertinent to the problem the claimed invention attempts to solve.

36. Counsel has informed me, and I understand, that an issued patent claim is invalid as obvious if it can be shown that the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art.

37. I understand that in making the obviousness inquiry, one should consider the *Graham* factors: the scope and content of the prior art; the differences between the claimed inventions and the prior art; the level of ordinary skill in the art; and certain secondary considerations, identified below. I further understand the

obviousness analysis is to be performed on a claim-by-claim basis. I understand that a person of ordinary skill in the art is a person of ordinary creativity, not an automaton.

38. I have been instructed by counsel and understand that obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. I understand obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have been motivated to combine those references, and, in making that combination, a person of ordinary skill in the art would have had a reasonable expectation of success.

39. I also understand that an obviousness analysis must be conducted with awareness of the distortion caused by hindsight bias and with caution of arguments reliant upon *ex post* reasoning. Counsel has instructed me that when considering obviousness, I should not consider what is known today or what was learned from the asserted patents. Instead, I should put myself in the position of a person of ordinary skill in the field at the time of the invention.

40. In particular, I understand that it is improper to use the invention as a roadmap to find its prior-art components because such an approach discounts the value of combining various existing features or principles in a new way to achieve a new result.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 18 of 77

41. I understand that an invention would not have been obvious to try when one would have had to try all possibilities in a field that is not small and easily traversed, and that is unreduced by direction of the prior art. Stated another way, when what would have been "obvious to try" would have entailed varying all parameters or trying 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 would have been likely to be successful, an invention would not have been obvious. Further, an invention is not obvious to try where prior art does not guide one toward a particular solution.

42. I am informed by counsel and I understand that the secondary considerations of nonobviousness could include factors such as commercial success, long felt but unresolved needs, the failure of others, skepticism by experts, praise by others, award and accolades, and copying.

43. Counsel has informed me, and I understand, that a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant of the '757 patent.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 19 of 77

IV. OVERVIEW OF THE '757 PATENT AND TECHNOLOGY BACKGROUND

44. The '757 patent, entitled "Saccharide-Polypeptide Conjugate Compositions and Methods of Use Thereof," issued on July 13, 2021, claims priority to U.S. Provisional Application Nos. 62/373,807 (filed one August 11, 2016), 62/372,263 (filed on August 8, 2016), 62/330,245 (filed on May 2, 2026), and 62/316,555 (filed on March 31, 2016).

45. 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 and Jack D. Love.

46. "*Streptococcus pneumoniae* (pneumococcus) can cause serious illness, including sepsis, meningitis, and pneumonia with bacteremia (invasive) or pneumonia without bacteremia (noninvasive)." (Ex. 2007 at 1.) As of the priority date of the '757 patent, there were two pneumococcal vaccines licensed for use in the United States. (*Id.*)

47. 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

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 20 of 77

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 pneumococcal conjugate vaccines (PCVs)—are not immunogenic in children under the age of two.

48. 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 (a nontoxic mutant of diphtheria toxin) to a polysaccharide containing the seven most important serotypes from PPSV23. Prevnar is directed to serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F—all of which are a subset of the serotypes in PPSV23. When Prevnar was launched, pneumococcus remained the most common cause of severe pneumonia and bacterial meningitis, leading to a global estimate at that time of 735,000 deaths per year among children under 5 years old.

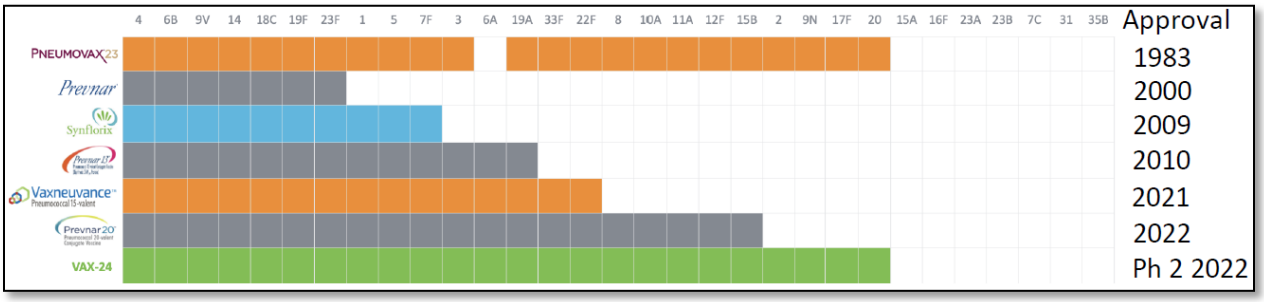
49. PCVs overcame the challenge of poor immunogenicity in infants and young children by using conjugation technology. In PCVs, polysaccharides (or their derivatives) are covalently linked to carrier proteins. However, due to the complexity of the conjugation process, PCVs have contained fewer serotypes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

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 21 of 77

50. Prevnar 13 ("PCV13"), which was approved in 2010, was developed by conjugating CRM197 to polysaccharides 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 of which are a subset of the serotypes in PPSV23, minus serotype 6A.

51. 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 (until well after the priority date) and since 2014 (until well after the priority date) has been recommended for all adults aged 65 and over in combination with PPSV23.

52. 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, as shown in the graphic below:



53. The ’757 patent took a different approach, focusing not on the PPSV23 composition serotypes, but on aligning vaccine coverage with emerging invasive disease serotypes.

54. Through this approach, Pogona developed the novel composition of serotypes described and claimed in the ’757 patent, including, for example:

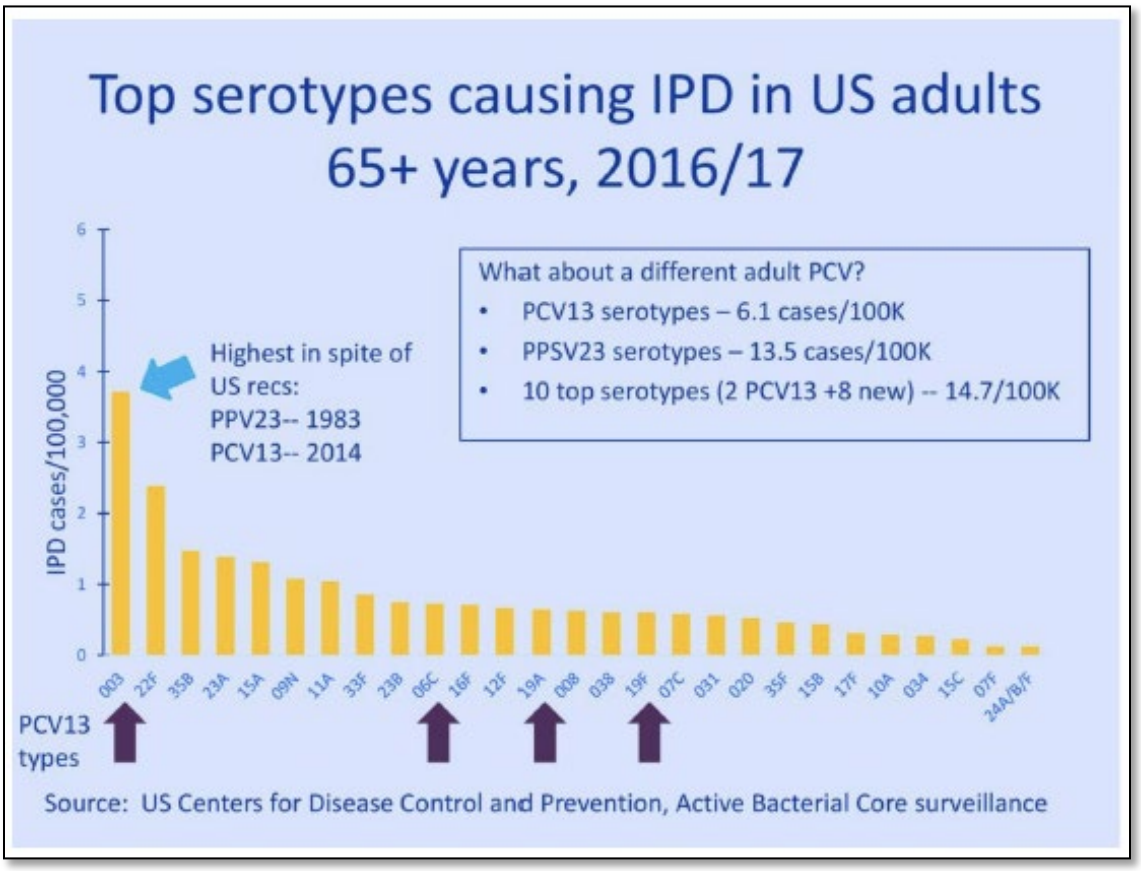
> Claim 1: reciting selecting at least two unique serotypes from the group of serotypes 23A, 23B, and 35B—none of which are serotypes included in PPSV23.
>
> Claim 12: depending from claim 1 and reciting further selecting at least one additional serotype from the group of serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34—of which 6C, 15A, 15C, 16F, 20A, 20B[1], and 34 are serotypes not included in PPSV23.
>
> Claims 13/14: depending from claim 1, wherein the selected serotypes comprise/consist of 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

55. The ’757 patent’s approach proved to be correct. Initially, the serotypes included in PCV13 accounted for approximately 85% of the PPSV23 serotypes that cause disease. However, 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

[1] PPSV includes serogroup 20, but does not specify serotypes 20A and 20B.

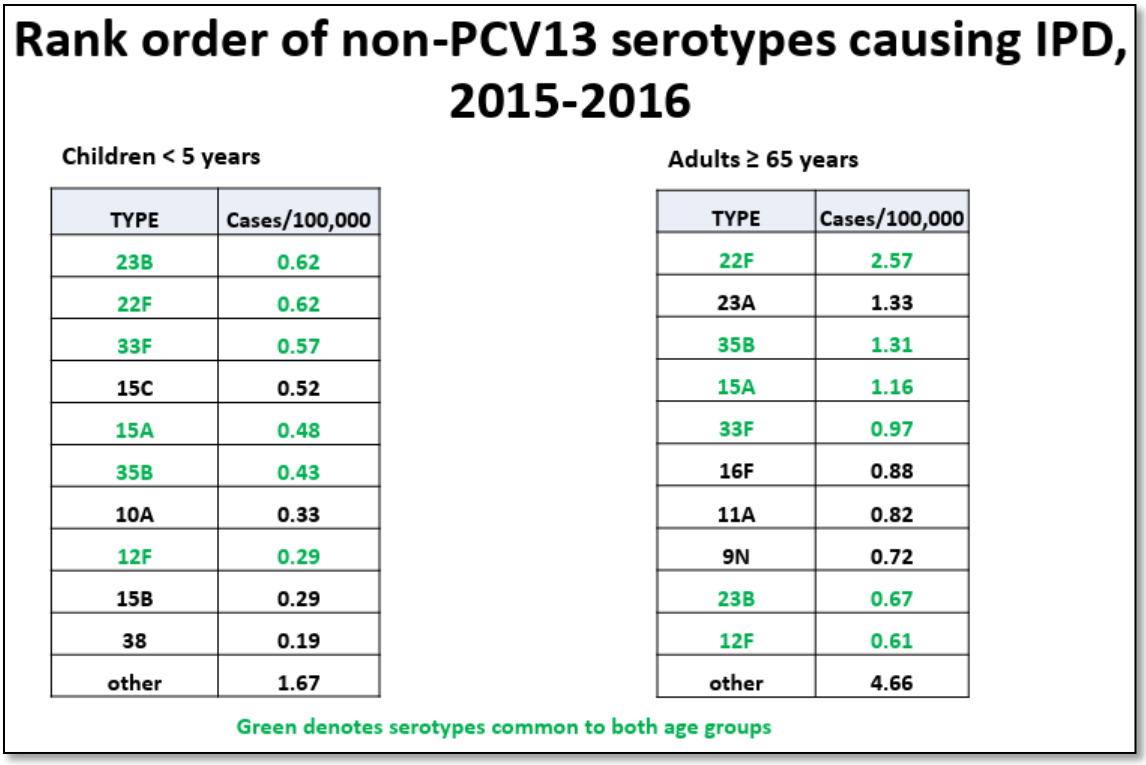
Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 23 of 77

by PCV13 serotypes resulted in an increased rate of disease being caused by non-PCV13 and non-PPSV23 serotypes, as shown in the graphic below, reproduced from a 2018 presentation by Dr. Cynthia Whitney for the Advanced Course of Vaccinology:



(Ex. 2008 at 28.)

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



Rank order of non-PCV13 serotypes causing IPD, 2015-2016

Children < 5 years

TYPE	Cases/100,000
23B	0.62
22F	0.62
33F	0.57
15C	0.52
15A	0.48
35B	0.43
10A	0.33
12F	0.29
15B	0.29
38	0.19
other	1.67

Adults ≥ 65 years

TYPE	Cases/100,000
22F	2.57
23A	1.33
35B	1.31
15A	1.16
33F	0.97
16F	0.88
11A	0.82
9N	0.72
23B	0.67
12F	0.61
other	4.66

Green denotes serotypes common to both age groups

(Ex. 2009 at 9.)

V. CLAIM CONSTRUCTION

57. I have been informed by counsel that the Challenged Claims of the '757 patent are to be 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. In forming my opinions set forth below, I have therefore applied the ordinary and customary meaning of all claim terms.

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

58. Each of the Challenged Claims recites "at least two unique immunogenic saccharide-polypeptide conjugates, … wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B."

59. Alexander discloses 53 serotypes, where from 1 to "30 or more" of the serotypes can be selected for a vaccine, resulting in **over 9 quadrillion** possible combinations from Alexander's list ($2^{53} - 1 = 9{,}007{,}199{,}254{,}740{,}991$).

60. I understand that Petitioner argues that Alexander discloses 55 serotypes, because it discloses serotype 35, which Petitioner argues encompasses 35B (Petition at 25, n.2). I disagree. A POSA would understand that a conjugate comprising "individually a capsular polysaccharide[s] conjugated to a polypeptide" as claim 1 of the '757 recites, where the conjugated serotype is 35, does not include serotype **35B** individually conjugated to a polypeptide because the polypeptide would be conjugated individually to each of 35F, 35A, and 35B.

61. Alexander's quadrillions of possible combinations are so large that the claimed combination of serotypes would not be immediately apparent to a POSA. This is true of the serotypes recited in claim 1: at least 2 of 23A, 23B, and 35B, as well as those recited in claim 12: the claim 1 serotypes with an additional serotype

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 26 of 77

selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. This is also true of the serotypes recited in claims 13 and 14: 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. It is noteworthy that Alexander's lists 53 serotypes yet does not mention serotype 6C, thus, despite listing well more than 50% of all of the known serotypes of *Streptococcus pneumoniae* Alexander does not discuss 6C at all in the specification or in the claims.

62. 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. A POSA could select from 255 distinct possible combinations from Gu's list ($2^8 – 1 = 255$).

63. A POSA reviewing the Alexander and Gu references would find bare lists of serotypes without any teaching about which serotypes to select, how many to select, or which combination patterns correspond to the claimed invention.

64. In the absence of these teachings, Gu's 255 possible combinations are so large that the claimed combination of serotypes would not be immediately apparent to a POSA. This is true of the serotypes recited in claim 1: at least 2 of 23A, 23B, and 35B, as well as those recited in claim 12: the claim 1 serotypes with an additional serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. This is also true of the serotypes

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 27 of 77

recited in claims 13 and 14: 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. It is also noteworthy that Gu makes no mention of key serotypes that appear in the '757 patent (i.e. 6C, 15C, 16F or 34) either the specification or in the claims.

65. It is therefore my opinion that the '757 patent claims therefore cannot be anticipated by Alexander or Gu.

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

66. 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.

67. It is my understanding that without such narrowing, the number of possible combinations for both Alexander and Gu falls beyond the limit that the Federal Circuit has set for obviousness to try.

68. For a POSA to achieve the claimed serotypes based on either Alexander or Gu, a POSA making its way through each combination would not be able to stop when it found a combination of serotypes from Alexander or Gu that was "successful," because there could be "successful" combinations that are different than the claimed serotypes. For this reason, 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.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 28 of 77

69. This is true of the serotypes recited in claim 1: at least 2 of 23A, 23B, and 35B, as well as those recited in claim 12: the claim 1 serotypes with an additional serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. This is also true of the serotypes recited in claims 13 and 14: 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

70. It is therefore my opinion that the '757 patent claims therefore cannot be obvious in light of Alexander or Gu.

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

71. The serotype-selection question was answered by numerous different serotypes in addition to those the Challenged Claims recite.

72. The prior art available to a POSA, even if 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.

73. The prior art available to a POSA makes the serotype-selection question worse than it would be with Alexander or Gu standing alone, as the prior art either suggests potential inclusion in a vaccine or notes the prevalence of even more serotypes listed in each of Alexander and Gu.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 29 of 77

74. 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.

75. A POSA seeking to expand vaccine coverage beyond PCV13 faced a sprawling and constantly shifting field of emerging non-PCV13 serotypes, and nothing in the art singled out the claimed serotypes for selection. This is true of the serotypes recited in claim 1: at least 2 of 23A, 23B, and 35B, as well as those recited in claim 12: the claim 1 serotypes with an additional serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. This is also true of the serotypes recited in claims 13 and 14: 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

76. Claim 1 of the ’757 patent refers to a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide, wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B.

77. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 30 of 77

78. Claim 12 of the ’757 patent depends from claim 1 stating that “The pharmaceutical composition of claim 1, further comprising at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from a unique *Streptococcus pneumoniae* serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34.”

79. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B and a further conjugate comprising a *Streptococcus pneumoniae* serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34.

80. Claims 13 and 14 of the ’757 patent depend from claim 1 stating that “The pharmaceutical composition of claim 1, wherein the plurality of unique immunogenic saccharide-polypeptide conjugate comprising [consisting of] individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.”

81. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising or consisting of all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 31 of 77

82. As of March 31, 2016, the POSA was aware that non-PCV13 emerging serotypes were very numerous, geographically specific, age dependent and even specimen dependent.

83. Based on these data the POSA would not have selected at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B.

84. Based on these data the POSA would not have selected at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B and a further *Streptococcus pneumoniae* serotype from the group consisting of *Streptococcus pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. 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.

85. Based on these data the POSA would not have selected all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

86. The POSA was aware that many non-PCV13 serotypes (non 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) were emerging and demanded attention regarding possibly adding them to a new pneumococcal conjugate vaccine.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 32 of 77

87. Data from 32 IPD surveillance datasets including from the United States (5 different US based surveillance systems), Canada, Australia, and throughout Europe reported that non-PCV13 serotypes 2, 8, 9A, 12A, 12F, 15B, 45 and 46 were amongst the most commonly reported serotypes causing IPD in the world (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2024 Feikin 2013 Supplementary Table). Researchers in England and Wales analysed the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease as well as serotype evolution 4 years after PCV13 introduction. IPD cases in children < 5 years of age caused by non-PCV13 serotypes 24F, 15B/C, 22F, 8, 38, 11A and 21 increased during PCV13 exposure (Ex. 1017 Waight 2015 page 540 Figure 3). Researchers in Germany investigated serotype changes in adult and pediatric IPD and meningitis cases after implementation of national conjugate pneumococcal vaccine recommendations. Meningitis cases caused by non-PCV13 serotypes 10A, 11A, 12F and 33F in children <16 years of age increased post PCV13 exposure (Ex. 2025 Imohl page 9 Table 4). A slightly contrasting picture was reported in adults ≥ 16 years of age where meningitis cases caused by non-PCV13 serotypes 10A, 22F and 6C decreased while 11A, 12F and 20 increased post PCV13 exposure (Ex. 2025 Imohl page 10 Table 5). A POSA would note from these data that vaccinating children

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 33 of 77

with PCV13 may affect the prevalence of emerging serotypes quite differently in children versus adults (age dependent).

88. Investigators from Taiwan assessed pneumococcal serotype evolution from 2008-2012 after the introduction of PCV7. After analysis of 3, 659 IPD isolates from 160 hospitals distributed across Taiwan, they identified 53 serotypes with the most prevalent non-PCV13 serotypes being 23A, 15B and 10A (Ex. 2026 Chiang 2014 pages 3346 and 3347 and Figure 1). Researchers in Saudi Arabia analyzed all cases of IPD (including meningitis and pneumonia) in children aged less than 15 years recorded at King Khalid University Hospital, King Saud University, between 2009 and 2012. Non-PCV13 serotypes reported included 15, 23A, 24, 12F, 11, 23B, 22 and 8 (Ex. 1011 Al-Sherikh 2014 Figure 1 page 213). In the US, researchers reported increases in non-PCV13 serotypes 7C, 10, 11, 15A, 15C, 17, 21, 23A, 23B, 33F, 35B and 37 causing meningitis post PCV13 implementation into the routine pediatric immunization schedule (Ex. 2027 Olarte page 770 Table 2). Researchers in China, assessed the serotype prevalence in hospitalized children. Of the 193 *S. pneumoniae* isolates, non-PCV13 serotypes reported to be associated with infection in children were 6C, 15B/C, 15F/15A, 23A, 20, 10B, 28F/28A and 34 (Ex. 2028 Jin 2016 pages 1 and 6). Researchers in the US described pneumococcal serotypes recovered from middle ear and mastoid cultures in 8 children's hospitals. Emerging non-PCV13 serotypes included: 15F,

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 34 of 77

16, 20, 23B, 33F, 34 and 35F (Ex. 1015 Kaplan page 1341 Table 2 and page 1342 Table 3).

89. The available prior art data suggested to the POSA that many non-PCV13 serotypes were emerging especially post PCV13 implementation including: 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. Emerging serotypes were dependent on geographic location, age and even type of clinical specimen.

90. There was no motivation to specifically select at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B, to the exclusion of other emerging serotypes to design a new conjugate pneumococcal vaccine and thus a POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B.

91. There was no motivation to specifically select at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B, and a further *Streptococcus pneumoniae* serotype from the group consisting of *Streptococcus pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34, to the exclusion of other emerging serotypes to design a new conjugate pneumococcal vaccine. Thus, a POSA would not have been motivated to

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 35 of 77

make a new conjugate pneumococcal vaccine comprising at least two of *Streptococcus pneumoniae* serotypes 23A, 23B, and 35B and a further *Streptococcus pneumoniae* serotype from the group consisting of *Streptococcus pneumoniae* serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34.

92. There was no motivation to specifically select all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B, to the exclusion of other emerging serotypes to design a new conjugate pneumococcal vaccine and thus a POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

2. A POSA Seeking to Expand Pneumococcal Conjugate Vaccine Coverage Would Have Been Motivated to Conjugate the Remaining PPSV23 Serotypes—Not Select Unrelated Serotypes Outside PPSV23

93. As of the priority date, the POSA was motivated to make a new conjugated version of PPSV23 containing the same serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) as the current polysaccharide based PPSV23.

94. The POSA knew that although the current polysaccharide vaccine PPSV23 was broad spectrum it suffered from various disadvantages compared to conjugated pneumococcal vaccines such as PCV13. Unlike conjugated vaccines

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 36 of 77

which stimulate the immune system in a T-cell dependent fashion, PPSV23 stimulated the immune system in a T-cell independent fashion meaning it only stimulated B cells to produce antibodies. This T-cell independent immune response resulted in PPSV23 not being immunogenic in children aged <2 years, immunological memory being absent, and lack of induction of mucosal immunity thus not affecting nasopharyngeal colonization (Ex. 2029 Steens 2014 page 2472). Developing a conjugated version of PPSV23 would create a broad-spectrum pneumococcal vaccine that would have a T-cell dependent immune response like PCV13.

95. As of the priority date the POSA knew that PPSV23 provided the broadest vaccine coverage, in all age groups, of any pneumococcal vaccine. The ECDC (European Centre for Disease Prevention and Control) in their 2012 report entitled "Surveillance of invasive bacterial diseases in Europe 2012" described that PPSV23 covered the 8 most common serotypes across Europe causing IPD (Ex. 1018 ECDC pate 24). PPSV23 covered the 8 most common serotypes causing bacteremia, meningitis and bacteremia with pneumonia in all of Europe (Ex. 1018 ECDC page 26). PPSV23 vaccine coverage was 79% (all age groups) (Ex. 1018 ECDC page 24). In the 2013 PHAC (Public Health Agency of Canada) annual summary of invasive Streptococcal disease in Canada, researchers reported PPSV23 vaccine coverage of 70.6% (all age groups) compared to only 35.4% with

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 37 of 77

PCV13 (Ex. 1019 PHAC page 34) and more importantly that PPSV23 unique serotypes (not in PCV13) [2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F] increased in all age groups, with an overall increase from 24.7% to 37.6% between 2010 and 2013 (Ex. 1019 PHAC page 36) informing the POSA that PPSV23 unique serotypes were emerging and needed to be covered.

96. The efficacy of PPSV23 has been recognized and endorsed by national vaccine advisory bodies including ACIP (American Committee on Immunization Practices) and NACI (National Advisory Committee for Immunization) (Ex. 2030 Nuorti MMWR 2010 pages 1103, 1104, and 1105). Randomized controlled trials have demonstrated that PPSV23's efficacy is 74% against IPD (Ex. 2030 Nuorti MMWR 2010 page 1103). Based on its well-established efficacy and safety, ACIP recommended that PPSV23 be administered to all adults ≥ 65 years of age (Ex. 2030 Nuorti MMWR 2010 pages 1103 and 1105). In addition, ACIP also recommended that PPSV23 be administered to adults aged 19-64 with underlying medical conditions such as chronic heart, lung, liver and kidney diseases as well as individuals immunocompromised by disease or therapy (Ex. 2030 Nuorti MMWR 2010 pages 1104 and 1105). After the introduction of PCV13 in 2014, ACIP recommended that both PCV13 and PPSV23 be routinely administered in series to all adults aged ≥ 65 years of age (Ex. 2031 Tomczyk MMWR 2014 page 823). ACIP stated that "PPSV23 contains

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 38 of 77

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" (Ex. 2031 Tomczyk MMWR 2014 page 823).

97. PPSV23 was well known to be effective at reducing IPD due to the 23 pneumococcal serotypes in the vaccine, however, some data also suggested that PPSV23 may reduce the likelihood of community-acquired pneumonia caused by the serotypes in the vaccine. A review and meta-analysis demonstrated that PPSV23 administration was weakly associated with prevention of all cause pneumonia especially among target adults (those aged ≥ 65 years of age and those aged 19 to 64 years at high risk for pneumonia) (Ex. 2039 Diao Vaccine 2016, pages 1496 and 1502). The researchers reported that PPSV23 provided weak protection against all-cause pneumonia in an immunocompetent population, especially among the target population. In addition, PPSV23 exhibited protective trends in preventing pneumococcal pneumonia and mortality due to pneumococcal pneumonia which led to their conclusion that the additional benefit of PPSV23 in preventing CAP further supports its administration to adults aged ≥ 65 years of age and those aged 19 to 64 at high risk for pneumonia (Ex. 2039 Diao Vaccine 2016, pages 1496 and 1502).

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 39 of 77

98. In addition to PPSV23's efficacy and effectiveness in preventing IPD and pneumococcal CAP, data demonstrated that administration of PPSV23 may be associated with reduced risk of myocardial infarction and stroke. Researchers used health databases to obtain hospital diagnoses and vaccination status and compared patients who had been admitted for treatment of myocardial infarction with patients admitted to a surgical department in the same hospital for a reason other than myocardial infarction. They reported that pneumococcal vaccination was associated with a decrease of more than 50% in the rate myocardial infarction 2 years after PPSV23 exposure, concluding that this study of patients at risk for vascular disease suggests an effect of pneumococcal vaccination in reducing episodes of new myocardial infarction (Ex. 2040 Lamontagne CMAJ 2008, pages 773 and 776). Researchers in Spain performed a prospective cohort study conducted in primary care centers assessing whether there was an association between pneumococcal vaccination and the risk of myocardial infarction or stroke and reported that their study supports a benefit of PPSV23 against ischaemic stroke (35% reduction) and myocardial infarction (17% reduction) among the general population over 60 years of age, concluding that PPSV23 may have a protective role against some acute thrombotic events (Ex. 2041 Vila-Corcoles 2012; pages 1 and 6).

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 40 of 77

99. A POSA would view this data that there was both an established and emerging medical need to develop a new conjugated version of PPSV23 using the identical serotypes in the polysaccharide based PPSV23 (i.e. 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F).

100. Thus, a POSA would not design a new conjugated pneumococcal vaccine with serotypes 6C, 15A, 16F, 23A, 23B, 34, or 35B as these serotypes were not included in PPSV23. This new conjugated version of PPSV23 would provide by far the broadest pneumococcal vaccine coverage, expected protection for both IPD and CAP, be expected to reduce thrombotic events and be rapidly adopted and recommended by immunization bodies such as ACIP and NACI for extensive usage in adults at risk of pneumococcal infection.

101. The teachings of Alexander and Gu reinforce my 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. 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. Gu specifically identifies serotypes 2, 9N, 17F, and 20, each of which is included in PPSV23 but absent from PCV13,

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 41 of 77

confirming that the art continued to focus on conjugating the remaining PPSV23 serotypes rather than selecting unrelated serotypes outside the PPSV23 framework.

3. A POSA Would Have Been Motivated to Make a Non-Serotype Based PCV (i.e. a conserved SPN antigen associated with the cell membrane)

102. A POSA was aware that serotype-specific pneumococcal conjugate vaccines such as PCV7 and PCV13 suffered from many limitations. Pneumococcal conjugate vaccines are serotype-specific or serotype-based vaccines and therefore elicit only serotype-specific immunity. Thus, PCV13 would be expected to confer limited immune protection (or coverage) covering only 13 of the > 90 pneumococcal serotypes meaning that it was a narrow-spectrum vaccine (Ex. 2043 Pichichero 2016 page 194). The POSA was also aware that the distribution of serotypes causing pneumococcal disease varies geographically, hence effective vaccine coverage varies by region, and includes many more serotypes than are currently covered by a single narrow-spectrum PCV vaccine.

103. A major limitation of serotype-based vaccines is the ongoing development of serotype replacement disease resulting in an increase in invasive infection by non-vaccine pneumococcal serotypes (Ex. 2043 Pichichero 2016 page 194 and 195). This vaccine-induced serotype "Whac-A-Mole" following the introduction of PCV7, then PCV10 then PCV13 continued with the introduction of new non-vaccine serotype disease shortly after introduction of these serotype-

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 42 of 77

specific pneumococcal conjugate vaccines (Ex. 2043 Pichichero 2016 page 195 and Ex. 2044 Feldman 2014 page 313). The POSA believed that the proliferation of recently generated NVT (non-vaccine type) capsular switch variants would continue to be favoured by PCV13 vaccination programs just like after PCV7 implementation. In addition, a worry was that serotype-based vaccine-induced selective pressure may favour nasopharyngeal colonisation by non-vaccine type, penicillin-non-susceptible transformants which have undergone capsular switching together with simultaneous transfer of closely associated penicillin-binding protein genes (pbp2x and pbp1a) (Ex. 2044 Feldman 2014 page 313).

104. Serotype-specific pneumococcal conjugate vaccines such as PCV13 were known to be less effective in protecting against non-invasive disease such as non-bacteremic pneumonia and acute otitis media compared to invasive pneumococcal disease (Ex. 2043 Pichichero 2016 page 194). Another limitation of serotype-based vaccines is the need for boosting the immune system with several doses of PCV13 being required in young children to optimally prime the immune system and adults at high risk for invasive pneumococcal requiring ongoing boosting to maintain immune protection. In addition, the complicated manufacturing process (e.g. PCV13 requires the manufacture of 13 different and separate antigens) resulted in high cost, thus limiting the effective usage in many countries (Ex. 2043 Pichichero 2016 page 195).

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 43 of 77

105. Discussing the development of PCV13, researchers stated, "Higher 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" (Ex. 1040 Jefferies 2011 page 1015). These same researchers discussing the potential of increasing the valency of existing serotype-specific pneumococcal conjugate vaccines such as PCV13 stated that "data suggests 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" (Ex. 1040 Jefferies 2011 page 1015).

106. Thus, it was clear to the POSA that serotype-specific pneumococcal conjugate vaccines suffered from many limitations resulting in "tremendous interest in developing serotype-independent pneumococcal vaccines that would confer protection against both mucosal and invasive disease across age groups" (Ex. 2045 Rosch 2014 page 3000). The limitations of existing serotype-specific pneumococcal conjugate vaccines both real and perceived provided the impetus for development of novel vaccines based on broadly representative, serotype-independent (i.e. non-serotype), highly-conserved pneumococcal protein antigens. Several such vaccine development strategies had reached varying stages of advancement, including vaccines based on: i) recombinant protein antigens individually or in combination; ii) recombinant protein antigens individually or in

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 44 of 77

combination as carriers of pneumococcal capsular polysaccharides; iii) recombinant pneumococcal protein carriers combined with traditional carriers; iv) traditional conjugate vaccines with added pneumococcal proteins; v) recombinant pneumococcal fusion proteins; vi) DNA vaccines; and vii) attenuated whole cell vaccines with low level expression of capsular polysaccharides (Ex. 2044 Feldman 2014 page 314).

107. Researchers were studying serotype-independent (i.e. non-serotype), pneumococcal vaccines identifying major pneumococcal protein virulence factors all of which are immunogenic such as surface adhesins and enzymes which promote attachment to, and invasion of respiratory epithelial cells and other types of host cells as well as virulence factors that suppress host defenses (Ex. 2044 Feldman 2014 page 314). Some 20 different serotype-independent pneumococcal protein adhesins and invasins as well as some 8 different pneumococcal protein virulence factors which subvert host defenses, all with vaccine potential, had been identified (Ex. 2044 Feldman 2014 page 316 Table 1, page 317 Table 2). A major area of development was serotype-independent "conserved" pneumococcal protein vaccines (CPPV) that would not target the polysaccharide capsule and therefore would prevent pneumococcal disease and carriage without resulting in the selective pressure that is thought to drive serotype replacement (non-vaccine type) disease as

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 45 of 77

well as negating the need for costly conjugation processes (Ex. 1040 Jeffries 2011 pages 1015 and 1016).

108. The POSA believed that serotype-independent protein-based pneumococcal vaccines candidates would ideally satisfy criteria including: i) they must be highly conserved and "universally" representative of all clinical pneumococcal isolates; ii) there must be compelling evidence of immunogenicity and protective efficacy in animal models of experimental infection; iii) immunogenicity should encompass both antibody (IgG) and cell-mediated (T-cell) immune responses; and iv) immunity should be of long duration (Ex. 2044 Feldman 2014 page 317). Based upon these criteria, 5 pneumococcal virulence factors, PspA (Pneumococcal surface adhesin A), PspC (Pneumococcal surface protein C, PcpA (Pneumococcal choline-binding protein A), Ply (pneumolysin), and PhtD (Polyhistidine triad protein D) individually and in combination or as fusion proteins were being actively investigated (Feldman 2014 pages 316 and 317). All of these activate potentially protective antibody- and cell-mediated immune responses and would be anticipated to provide protection from pneumococcal infections. A potential significant advantage that serotype-independent pneumococcal protein vaccine formulations could offer over serotype-specific vaccines is their potential for natural priming and boosting to all strains of *Streptococcus pneumoniae* (Ex. 2043 Pichichero 2016 page 194). A protein based

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 46 of 77

vaccination strategy would likely require less or no boosting because natural boosting should continue to occur since *S. pneumoniae* would not be eliminated as a colonizing bacteria (Ex. 2043 Pichichero 2016 page 202).

109. Another area of focus regarding developing serotype-independent pneumococcal vaccines was the development of whole cell pneumococcal vaccines. These vaccines would be expected to present many cellular surface proteins in native configuration unoccluded by capsule and would elicit immune responses to pneumococci of varying capsular type, isolation site, and genetic background (Ex. 2044 Feldman 2014 page 319). Researchers were also investigating a serotype-independent pneumococcal vaccines that could engender mucosal and systemic protection. One potential means by which this could be accomplished is via the development of a live attenuated vaccine administered to the nasal passages. Live vaccines provide the advantage of a level of antigen exposure higher than that of traditional vaccines (Ex. 2045 Rosch 2014 page 3001). After generating positive animal safety and immunogenicity data, several of these serotype-independent pneumococcal protein based and whole cell vaccines were in clinical development in Phase I or Phase II (Ex. 2044 Feldman 2014 page 319 Table 3; Ex. 2046 Leroux-Roels 2014 page 6845).

110. A POSA would take away from these data that the development of serotype-independent (i.e. non-serotype), pneumococcal vaccines could offer many

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 47 of 77

advantages compared to serotype-specific pneumococcal vaccines including: a) providing the broadest spectrum (100%) vaccine with coverage versus all *S. pneumoniae* regardless of serotype which would be expected to result in much greater efficacy versus invasive pneumococcal disease; b) providing the broadest spectrum (100%) vaccine with coverage versus all *S. pneumoniae* regardless of serotype which would be expected to result in much greater efficacy versus non-invasive pneumococcal disease such as community-acquired pneumonia; c) lack of selection of serotype-replacement disease (including penicillin-resistant strains) including through capsular switching; d) potential for natural priming and boosting to all strains of *Streptococcus pneumoniae* thus not requiring vaccine booster administration. These serotype-independent vaccines would thus not include any specific one of, or all of, serotypes 6C, 15A, 16F, 23A, 23B, 34, or 35B. These serotype-independent vaccines would be expected to replace PCV13 and PPSV23 and be recommended by ACIP for protecting children and adults from both invasive and non-invasive pneumococcal disease. Lastly, these serotype-independent or non-serotype based pneumococcal vaccines would be expected to protect individuals from poor cardiovascular outcomes (e.g. decreasing acute myocardial infarctions, decreasing stroke) to a greater extent than serotype-dependent pneumococcal vaccines.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 48 of 77

4. A POSA Would Have Been Motivated to Improve Existing PCVs

111. A POSA was aware that serotype-specific pneumococcal conjugate vaccines such as PCV13 suffered from many limitations. Pneumococcal conjugate vaccines are serotype-specific or serotype-based vaccines and therefore elicit only serotype-specific immunity. For PCV13, a major limitation was the poor immunological response to serotype 3 which is contained in PCV13. The POSA was aware that serotype 3 continued to be a common serotype associated with serious disease and serious outcomes despite the usage of PCV13 and thus a medical need existed to not simply expand the valency of existing PCVs, rather to improve existing PCVs (such as PCV13) by improving the immunological response and clinical protection to serotypes such as serotype 3.

112. It was well known that serotype 3 isolates "are an important cause of invasive pneumococcal disease, particularly pneumonia in both children and adults" (Ex. 2042 Choi 2016 page 162). The POSA was aware that serotype 3 (contained in PCV13) was one of the most common serotypes associated with IPD in children across the globe (United States, Canada, Australia, and throughout Europe) despite the availability of PCV13 (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2024 Feikin 2013 Supplementary Table). It was known that pneumococcal capsular polysaccharide-CPS synthesis of the serotype 3 capsule was unlike most other serotypes (Ex. 2042 Choi 2016 page 162). The serotype 3 capsular

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 49 of 77

polysaccharide unlike other pneumococcal capsules was not covalently attached to the peptidoglycan, allowing abundant release of free capsular polysaccharide during growth which was available for non-functional antibody binding.

113. Researchers studying why PCV13 was poorly clinically effective versus serotype 3 noted that for serotype 3, the calculated anti-capsular antibody correlate of protection was 2.83ug/ml (unlike the ~0.35ug/ml serum threshold of anti-capsular antibody for aggregated serotypes that was used as a correlate of protection for the licensure of pneumococcal conjugate vaccines), the highest of all the serotypes in PCV13 (Ex. 2042 Choi 2016 page 165). After performing a variety of in vitro and in vivo testing the researchers stated, "In summary, our results suggest that the failure of the serotype 3 conjugate in PCV13 may be a direct consequence of the CPS release by the organism, a process that differentiates type 3 from other serotypes included in current conjugate vaccines. While our study points to a possible mechanistic explanation for the finding that higher anti-capsular antibody concentrations may be required for protection against type 3. Indeed, our results demonstrated that compared to other serotypes included in PCV13, the ST3 strain releases the most CPS during in vitro growth and infection in mice, which then interferes with antibody-mediated killing in an opsonophagocytic assay and reduces the protective efficacy of preexisting anti-CPS antibody (Ab) in a murine model of sepsis". (Ex. 2042 Choi 2016 pages 166

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 50 of 77

and 167). These researchers then discussed that alternative strategies, such as protein-based or whole-cell vaccines may be required for optimal protection against serotype 3 (Ex. 2042 Choi 2016 pages 166 and 167).

114. Researchers performed a double-blind, randomized non-inferiority trial comparing infant immune responses to PCV7 and PCV13 after 3 (primary series) and 3 (primary infant vaccination series) + 1 (toddler booster) doses, respectively, in healthy US infants. PCV13 demonstrated a much lower pneumococcal anti-polysaccharide IgG GMC versus serotype 3 compared to the other 5 unique serotypes 1, 5, 6A, 7F and 19A (Ex. 1024 Yeh Table 4 page 500) both before, and after the toddler dose of PCV13.

115. Researchers assessing serotype-specific vaccine effectiveness and correlates of protection of PCV13 reported that vaccine effectiveness was only 26% for serotype 3 and this was commensurate with the very high calculated serum concentration of anti-capsular antibody needed to provide PCV13 vaccine effectiveness of 2.83ug/ml for serotype 3 (Ex. 2033 Andrews 2014 page 843 Table 3). These data were interpreted as suggesting that a serum concentration of anti-capsular antibody of 0.35ug/ml is a significant underestimate for serotype 3 in terms of predicting vaccine effectiveness (Ex. 2033 Andrews 2014 page 842 and Table 3 page 843).

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 51 of 77

116. A POSA would take away from these data that it was well known that serotype 3 was recognized as a globally common and important pneumococcal serotype, associated with serious disease and outcomes in both children and adults and that PCV13 vaccination was associated with a poor immunological response and more importantly, poor vaccine effectiveness versus serotype 3. The POSA would view that an important medical need with PCVs was to increase the immunological response versus serotype 3 and increase vaccine effectiveness against this serotype. The POSA would view that potential alternative strategies such as protein-based or whole-cell vaccines existing may be required to improve vaccine immunogenicity and effectiveness against this serotype.

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

117. Claims 13 and 14 of the '757 patent depend from claim 1 stating that "The pharmaceutical composition of claim 1, wherein the plurality of unique immunogenic saccharide-polypeptide conjugate comprising [consisting of] individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B."

118. Three of the eight serotypes in claims 13 and 14 recite—16F, 6C, and 15C—were each, independently, serotypes a POSA had affirmative reasons *not* to select. The prior art not only failed to direct a POSA to these serotypes, it also affirmatively counseled against their inclusion, whether because the serotype was

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 52 of 77

clinically insignificant, because cross-protection from an already-marketed vaccine component was expected to address it, or both.

a. **Serotype 16F**

119. Claim 1 of the ’757 patent refers to a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide, wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B. Claims 13 and 14 of the ’757 patent depend from claim 1 stating that “The pharmaceutical composition of claim 1, wherein the plurality of unique immunogenic saccharide-polypeptide conjugate comprises individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.”

120. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

121. Researchers using a standardized approach described serotype-specific IPD changes among multiple sites after PCV7 introduction. Data from 32 IPD surveillance datasets including from the United States (5 different US based surveillance systems), Canada, Australia, and throughout Europe reported that the

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 53 of 77

21 most common serotypes causing IPD in the world were 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 2, 3, 5, 6A (true), 7F, 8, 9A, 12A, 12F, 15B, 19A, 45 and 46 (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2024 Feikin 2013 Supplementary Table). Serotype 16F was not reported as a common nor emerging serotype. A POSA would note that this global study reported that non-PCV13 serotypes 2, 8, 9A, 12A, 12F, 15B, 45 and 46 were amongst the most commonly reported serotypes causing IPD in the world.

122. Researchers in England and Wales analysed the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease as well as serotype evolution 4 years after PCV13 introduction. IPD caused by serotype 16F was uncommon and did not significantly increase over time (Ex. 1017 Waight 2015 page 540 Table 2). Importantly IPD cases due to serotype 16F in children < 5 years of age decreased over time while non-PCV13 serotypes 24F, 15B/C, 22F, 8, 38, 11A and 21 increased during PCV13 exposure (Ex. 1017 Waight 2015 page 540 Figure 3). Researchers in Germany investigated serotype changes in adult and pediatric IPD and meningitis cases after implementation of national conjugate pneumococcal vaccine recommendations. After analysing data from 1,766 adult isolates and 1,320 pediatric isolates, no cases of serotype 16F meningitis were reported in children or adults (Ex. 2025 Imohl 2015, Tables 1-5 pages 7-10). Importantly, meningitis cases caused by non-PCV13 serotypes 10A,

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 54 of 77

11A, 12F and 33F in children <16 years of age increased post PCV13 exposure (Ex. 2025 Imohl page 9 Table 4). A slightly contrasting picture was reported in adults ≥ 16 years of age where meningitis cases caused by non-PCV13 serotypes 10A, 22F and 6C decreased while 11A, 12F and 20 increased post PCV13 exposure (Ex. 2025 Imohl page 10 Table 5). A POSA would note from these data that vaccinating children with PCV13 may affect the prevalence of emerging serotypes quite differently in children versus adults.

123. Investigators from Taiwan assessed pneumococcal serotype evolution from 2008-2012 after the introduction of PCV7. After analysis of 3, 659 IPD isolates from 160 hospitals distributed across Taiwan, they reported that 53 serotypes were identified with the most prevalent 12 serotypes 14, 19A, 3, 23F, 19F, 6B, 23A, 6A, 15B, 9V, 4, 10A accounting for 87.0% of all isolates (Ex. 2026 Chiang 2014 pages 3346 and 3347). No cases of IPD were reported with serotype 16F. Notably non-PCV13 serotypes 23A and 15B remained unchanged post vaccine exposure while serotype 10A decreased over time (Ex. 2026 Chiang 2014 page 3347 Figure 1). Researchers in Saudi Arabia analyzed all cases of IPD (including meningitis and pneumonia) in children aged less than 15 years recorded at King Khalid University Hospital, King Saud University, between 2009 and 2012. Of all the pneumococcal serotypes, 23F, 6B, 19F, 18C, 4, 14, and 19A represented 77% of all serotypes (Ex. 1011 Al-Sherikh 2014 page 212). Although

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 55 of 77

IPD caused by 20 different serotypes was observed, no cases of serotype 16F disease were reported (Ex. 1011 Al-Sherikh 2014 Figure 1 page 213). Notably IPD caused by non-PCV 13 serotypes included 24, 12F, 11, 22 and 8 (Ex. 1011 Al-Sherikh 2014 Figure 1 page 213). In the US, researchers reported increases in non-PCV13 serotypes 33F, 21, 11, 37 and 17 causing meningitis post PCV13 implementation into the routine pediatric immunization schedule (Ex. 2027 Olarte page 770 Table 2). Meningitis caused by serotype 16 (not identified as 16F) was reported in only 1 case post PCV13 vaccine implementation (Ex. 2027 Olarte page 770 Table 2). Researchers in China, a country with high prevalence of pneumococcal infections, assessed the serotype prevalence in hospitalized children. Of the 193 *S. pneumoniae* isolates, serotypes reported to be associated with infection in children were PCV13: 19F, 23F, 19A, 14, 6B, 6A, 9V/9A and non-PCV13: 6C, 15B/C, 15F/15A, 23A, 20, 10B, 28F/28A and 34 (Jin 2016 pages 1 and 6). In this study, no cases of infection were reported with serotype 16F.

124. The available prior art data suggested to the POSA that serotype 16F was neither a common nor an emerging serotype and thus there was no motivation to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. In contrast, a variety of non-PCV13 serotypes were emerging including 2, 8, 10A, 11A, 12A, 12F, 15B, 20, 21, 22F, 24F, 38, 45 and 46.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 56 of 77

125. As serotype 16F is not a common or emerging serotype, limited data are available regarding its biological properties. Researchers studying serotype 16F in Australian aboriginal children concluded that this serotype was: associated with nasopharyngeal colonization, had the potential to cause IPD though was not reported to be associated with severe outcomes, was genetical diverse and susceptible to antibiotics (Ex. 2032 Marsh 2007 pages 2434 and 2435). A POSA would take away that serotype 16F is not common, not emerging, not associated with invasive disease resulting in severe clinical outcomes, not a MDR serotype and not associated with clonal spread. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

b. **Serotype 6C**

126. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. The POSA was aware that the existing PCV13 vaccine contained serotypes 6A and 6B and would not have been motivated to make a new conjugate pneumococcal vaccine containing serotype 6C, assuming that PCV13 induced 6A antibodies (and perhaps to some extent also 6B antibodies) would provide immunological cross protection against serotype 6C, resulting in decreased prevalence and importance of serotype 6C over time.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 57 of 77

Researchers had 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 its carbohydrate composition (Ex. 2036 Park 2007 pages 1231-1232). This very small structural difference is the reason why in the past anti-sera typed serotype 6A and serotype 6C both as 6A (Ex. 2036 Park 2007 page 1232).

127. The very similar structural features of pneumococcal serotypes 6A and 6C lead to assumptions that antibodies elicited to serotype 6A might recognize and cross protect versus serotype 6C. Researchers at Pfizer, assessed whether the 6A conjugate in PCV13 could potentially induce functional anti-6C antibody responses using opsonophagocytic assay (OPA). Immune sera collected from infants receiving 3 doses of PCV13 (contains both 6B and 6A) were tested in OPA assays for serotype 6A, 6B and 6C. PCV13 immune sera showed strong OPA responses to serotypes 6A (100% responders), 6B (100% responders) and 6C (96% responders) (Ex. 2037 Cooper 2011 page 1). The researchers believed that the results supported the conclusion that the cross-functional antibody responses to serotype 6C in the PCV13 immune sera were primarily elicited by the serotype 6A conjugate and that the serotype 6A (perhaps with some help from 6B) conjugate in PCV13 would routinely elicit functional responses to serotype 6C and that

immunization with PCV13 would protect against serotype 6C disease in a high proportion of humans (Ex. 2037 Cooper 2011 pages 4 and 5).

128. Researchers studying Alaskan children assessed both invasive pneumococcal disease and pneumococcal serotypes 6A and 6C before and after implementation of a PCV7 (which contains 6B) vaccination program. They reported that IPD rates caused by serotype 6A or 6C did not change from the pre- to post-PCV7, however, the proportion of serotype 6A carriage isolates decreased while the proportion of serotype 6C carriage isolates increased over time (Ex. 2047 Rudolph 2013 page 271). These researchers concluded that the usage of PCV13 (which contains both 6A and 6B) in the routine childhood vaccination schedule is expected to cause further declines in serotype 6A IPD and perhaps serotype 6C IPD as a result of cross-protecting antibodies to the 6A antigen (Ex. 2047 Rudolph 2013 page 275). Data from England and Wales analyzing the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease as well as serotype evolution 4 years after PCV13 introduction, demonstrated reductions in serotype 6C disease in all age groups (Ex. 1017 Waight 2015 page 540 Table 2 and Figure 3).

129. Researchers assessing serotype-specific effectiveness of PCV13 described PCV13 vaccine effectiveness versus seven serotype 6A isolates, 3 mixed serotype 6A/6C isolates and seven serotype 6C isolates lumping PCV13

effectiveness together for serotypes 6A and 6C (Ex. 2033 Andrews 2014 pages 842 and 843 Tables 2 and 3). PCV13 vaccine effectiveness was depicted versus extra (non-PCV7) PCV13 serotypes including serotype 6C (with and without excluding serotype 3) as part of assuming cross-protection for serotype 6C from serotype 6A antigen contained in PCV13 (Ex. 2033 Andrews 2014 page 843 Table 3).

130. The POSA's summary of these prior art data was that serotypes 6A and 6C were structurally and antigenically related, PCV13 vaccination due to containing serotype 6A (and perhaps in part also due to 6B) generates functional cross-reactive protective antibodies against both serotypes 6A and 6C, and that preliminary data from PCV13 vaccination programs suggested reductions in serotype 6C carriage and disease. A POSA would thus have expected that PCV13 induced 6A antibodies (and perhaps in part also due to 6B) would provide immunological cross protection against serotype 6C, resulting in decreased prevalence and importance of serotype 6C over time and hence would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

131. The POSA was also aware that studies demonstrated that serotype 6C may not be an important serotype to add to a new conjugate pneumococcal vaccine. Researchers describing serotype-specific IPD changes (after PCV7 introduction) from 32 IPD surveillance datasets including from the United States (5

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 60 of 77

different US based surveillance systems), Canada, Australia, and throughout Europe reported that the 21 most common serotypes causing IPD in the world were 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 2, 3, 5, 6A (true), 7F, 8, 9A, 12A, 12F, 15B, 19A, 45 and 46 (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2024 Feikin 2013 Supplementary Table). Serotype 6C was not reported as a common or emerging serotype globally or regionally (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2024 Feikin 2013 Supplementary Table). Data from England and Wales analyzing the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease as well as serotype evolution 4 years after PCV13 introduction demonstrated reductions in serotype 6C disease in all age groups (Ex. 1017 Waight 2015 page 540 Table 2 and Figure 3).

132. In the US researchers through the Active Bacterial Core surveillance network analysed IPD isolates recovered from children aged <5 years before and after 13-valent pneumococcal conjugate vaccine (PCV13) implementation, reporting no serotype 6C pediatric IPD in 2013 (post PCV-13 implementation) (Ex. 2038 Metcalf 2016 page 11). This did not surprise these researchers stating "the minor paediatric IPD serotype 6C is also predicted to be targeted by PCV13 through cross-protection from the 6A antigen" (Ex. 2038 Metcalf 2016 page 11).

133. Data from the PCV13 era assessing serotype evolution in middle ear isolates and mastoid isolates in US pediatric hospitals demonstrated that the

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 61 of 77

prevalence of serotype 6C was decreasing over the study and no serotype 6C was isolated from mastoid cultures in 2012 and 2013 (Ex. 1015 Kaplan 2015 pages 1341-1341 tables 2 and 3). A US study assessing the impact of PCV13 on invasive and noninvasive pneumococcal disease reported serotype 6C decreased in prevalence post PCV13 implementation (Ex. 1013 Richter 2015 page 6486).

134. The POSA's summary of these prior art data were that serotype 6C: was a distinct pneumococcal serotype but structurally and antigenically related to 6A; many studies showed that this serotype was not common, not emerging, and that usage of PCV13 due to 6A generated cross-reactive protective anti-6C antibodies resulted in serotype 6C decreasing and that this decrease in prevalence would continue to decrease due to PCV13 implementation. Thus, a POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

c. **Serotype 15C**

135. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B. The POSA was aware that the existing PPSV23 vaccine contained serotype 15B and would not have been motivated to make a new conjugate pneumococcal vaccine containing serotype 15C, assuming

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 62 of 77

that induced 15B antibodies may provide at least partial immunological cross protection against serotype 15C. The POSA would instead be focused on making a new conjugated version of PPSV23 with serotype 15B (and not 15C). The POSA was aware that serotypes 15B and 15C were structurally very similar and that serotypes 15B and 15C could undergo phase variation and not be distinguished with serotyping methods. In addition, it was understood that antigenic cross-reactivity between these 2 serotypes would result in at least partial cross-protection (Ex. 2034 Rajam 2007 page 1224 Table 1).

136. In addition, the POSA was aware that serotype 15C was not a common or emerging serotype. Researchers using a standardized approach described serotype-specific IPD changes among multiple sites after PCV7 introduction. Data from 32 IPD surveillance datasets including from the United States (5 different US based surveillance systems), Canada, Australia, and throughout Europe reported that the 21 most common serotypes causing IPD in the world were 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 2, 3, 5, 6A (true), 7F, 8, 9A, 12A, 12F, 15B, 19A, 45 and 46 (Ex. 2023 Feikin 2013 page 5 Table 1 and Ex. 2034 Feikin 2013 Supplementary Table). Serotype 15C was not reported as a common nor emerging serotype. A POSA would note that this global study reported that non-PCV13 serotypes 2, 8, 9A, 12A, 12F, 15B (not 15C), 45 and 46 were amongst the most commonly reported serotypes causing IPD in the world.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 63 of 77

137. Investigators from Taiwan assessed pneumococcal serotype evolution from 2008-2012 after the introduction of PCV7. After analysis of 3,659 IPD isolates from 160 hospitals distributed across Taiwan, they reported that 53 serotypes were identified with the most prevalent 12 serotypes 14, 19A, 3, 23F, 19F, 6B, 23A, 6A, 15B, 9V, 4, 10A accounting for 87.0% of all isolates (Ex. 2026 Chiang 2014 pages 3346 and 3347). No cases of IPD were reported with serotype 15C. Researchers in Saudi Arabia analyzed all cases of IPD (including meningitis and pneumonia) in children aged less than 15 years recorded at King Khalid University Hospital, King Saud University, between 2009 and 2012. Of all the pneumococcal serotypes, 23F, 6B, 19F, 18C, 4, 14, and 19A represented 77% of all serotypes (Ex. 1011 Al-Sherikh 2014 page 212). Although IPD caused by 20 different serotypes was observed, no cases of serotype 15C (only 2 cases of serogroup 15) disease were reported (Ex. 1011 Al-Sherikh 2014 Figure 1 page 213).

138. A POSA would take away that serotype 15C is not a common or emerging serotype. In addition, the structural similarity of serotypes 15B and 15C, and their in vivo phase variation resulting in antigenic cross-reactivity would be expected to provide some cross-protection of 15C after 15B vaccination. A POSA would not have been motivated to make a new conjugate pneumococcal vaccine

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 64 of 77

comprising all of *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.

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

139. I agree that there existed a motivation to include more serotypes in a pneumococcal vaccine, and particularly the remaining non-conjugated PPSV23 serotypes as I describe above. However, the fact that researchers desired to include more serotypes in a pneumococcal vaccine says nothing to a POSA about whether they could successfully select and conjugate the claimed serotypes and achieve immunogenicity.

140. 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.

141. 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 31st of 2016—is the concern over immune interference.

142. A POSA was aware that multivalent serotype-specific pneumococcal conjugate vaccines such as PCV13 suffered from limitations. Pneumococcal conjugate vaccines such as PCV13 are serotype-specific and therefore elicit

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 65 of 77

serotype-specific immunity. A POSA would have known that multivalent pneumococcal conjugate vaccines are subject to potential immune interference (also referred to as antigenic interference) due to exposure of multiple antigens to the immune system. A POSA would have been concerned that adding more and more additional serotype-specific polysaccharide conjugates (antigens) to an existing pneumococcal conjugate vaccine (e.g. PCV13) could reduce the immune response and vaccine efficacy to one or more individual serotypes within the vaccine.

143. Discussing the development of PCV13, researchers stated "Higher 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" (Ex. 1040 Jefferies 2011 page 1015). These same researchers discussing the potential of increasing the valency of existing serotype-specific pneumococcal conjugate vaccines such as PCV13 stated that "data suggests 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" (Ex. 1040 Jefferies 2011 page 1015).

144. The POSA knew that PCV13 contained the same 7 (also referred to as shared) serotypes as PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), as well as 6 new serotypes (1, 3, 5, 6A, 7F and 19A). The POSA was aware that adding 6 new

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 66 of 77

serotypes to create PCV13 could influence the immune response, particularly but not exclusively to the shared 7 serotypes in PCV7, due to the additional exposure of 6 new antigens to the immune system. The POSA was concerned that increasing the valency of a new pneumococcal vaccine could increase the likelihood of immune interference through proposed mechanisms including: carrier-specific T-helper cell interactions, T-cell bystander interferences or carrier induced epitopic suppression (Ex. 2035 Findlow 2016 page 226).

145. Researchers performed a double-blind, randomized non-inferiority trial comparing infant immune responses to PCV7 and PCV13 after 3 (primary series) and 3 (primary infant vaccination series) + 1 (toddler booster) doses in healthy US infants. Serum IgG responses to 2 shared serotypes 6B, 9V and 1 PCV13 unique serotype (serotype 3) after three infant doses (primary series) did not meet the pre-defined non-inferiority criterion (difference in percentage of infants achieving an IgG serum concentration of ≥0.35 μg/ml) one month after the third dose of PCV13 (Ex. 1024 Yeh 2010 page 497 and page 498 Table 2). Even more concerning, were the immune response data of the 7 common serotypes of PCV7 and PCV13 after the infant vaccination series. These data showed that the serotype-specific antipolysaccharide IgG GMC ratios were higher for PCV7 compared to PCV13 for all 7 common serotypes (Ex. 1024 Yeh 2010 page 498 Table 2). With regard to opsonophagocytic activity (OPA) GMT (an assessment of

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 67 of 77

the functional immune response), PCV7 demonstrated higher OPA responses versus 5 shared serotypes 4, 6B, 14, 18C and 23F (Ex. 1024 Yeh 2010 ex page 498 Table 2). In table 4, the results demonstrate that after the toddler booster dose, PCV7 demonstrated superior antipolysaccharide IgG GMC versus all shared serotypes relative to PCV13, except 19F (Ex. 1024 Yeh 2010 page 500 Table 4). With regard to OPA GMT after the toddler booster dose, PCV7 demonstrated higher OPA responses than PCV13 versus 6 shared serotypes 4, 6B, 9V, 14, 18C and 23F (Ex. 1024 Yeh 2010 page 501 Table 5). A POSA would take away from these data that comparing the immune response of PCV13 with PCV7 demonstrated that the immune response in the PCV13 group for all shared serotypes after the primary immunization series was reduced and inferior to PCV7 in terms of IgG concentration and that this pattern continued for all shared serotypes, except 19F after the toddler booster dose. In addition, the functional immune response data also suggested a reduced functional immune response in the PCV13 group for the majority of shared serotypes after both the primary immunization series as well as the toddler booster dose.

146. These data suggested to the POSA that adding 6 additional serotype antigens to PCV7 (i.e. to formulate PCV13) resulted in an inferior immune response to the shared serotypes due to the fact that the immune system has now been exposed to too many antigens (13 vs only 7) and is not able to respond

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 68 of 77

sufficiently to the same extent versus all 13 serotypes. The POSA was concerned because PCV13 was approved only based on immunological testing and thus no data was available that PCV13 demonstrated equal clinical effectiveness compared to PCV7 for the 7 shared serotypes. The POSA was even more concerned that developing a new pneumococcal conjugate vaccine containing even more serotypes (beyond PCV13) would result in even greater immune interference, as immune system exposure to greater and greater number of individual serotype antigens would continue to reduce the serotype-specific immunological response in the host and result in reduced clinical effectiveness due to additional serotypes being added. This expectation of reduced immunological response and reduced clinical effectiveness would likely be magnified in using this new higher valency pneumococcal conjugate vaccine (even greater valency than PCV13) in adults 65 years and older as well as adults at high risk for invasive pneumococcal disease (such as immunocompromised hosts) as these individuals would be expected to mount an inferior immunological response compared to the healthy children studied in the phase III PCV13 program. Thus, a POSA would be concerned that developing a new pneumococcal conjugate vaccine with higher valency than PCV13 would result in a vaccine with an inferior immunological response and reduced clinical effectiveness due to the introduction of too many antigens being exposed to the immune system.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 69 of 77

147. I understand that Pfizer has previously stated to the Board 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, 3 (PTAB Mar. 12, 2018).)

148. Because I understand 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. This concern would only be magnified in adults 65 and older and immunocompromised patients least able to compensate for an already age based and/or disease based reduced immune response.

149. The Petition's Serotype Prevalence References, at best establish that some claimed serotypes were known and prevalent. However, knowledge of a serotype's existence does not provide a POSA with a reasonable expectation that its immunogenic conjugate can be successfully made.

150. Roughly 100 pneumococcal serotypes were known as of March 31, 2016, yet by that date, only 13 had been successfully incorporated into a conjugate vaccine. Had mere knowledge and prevalence of the serotypes sufficed to successfully conjugate a pneumococcal vaccine, all roughly 100 serotypes would

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 70 of 77

have been included in a vaccine by March 31st of 2016. The fact that only 13 serotypes had been incorporated into a conjugate vaccine by March 31st of 2016, despite a known need for greater coverage against known pneumococcal serotypes, decades of research, and commercial incentive, shows that technical feasibility—not knowledge or desire—is the rate-limiting factor, and the reason that a POSA would not have believed there to be a reasonable expectation of success in conjugating the claimed compositions based and Alexander or Gu, even in combination with the Petition's Serotype Prevalence References and so-called Vaccine Recommendation References.

151. The unpredictability of the immune response to conjugated pneumococcal vaccines, in particular, is borne out by the very correlate of protection used to license PCVs.

152. A POSA was aware that for a conjugate pneumococcal vaccine to receive licensure it was required to demonstrate a threshold serum concentration of 0.35ug/ml of anti-capsular antibody aggregated for all serotypes within the vaccine which was used as a correlate of vaccine protection (Ex. 2033 Andrews 2014 page 839). This correlate of protection has been used for the licensure of vaccines containing additional serotypes (e.g. PCV13) without the need for formal efficacy studies prior to regulatory approval (Ex. 2042 Choi 2016 page 165).

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 71 of 77

153. It was however, well known that although the threshold serum concentration of 0.35ug/ml of anti-capsular antibody aggregated for all serotypes within the vaccine was used as a correlate of protection, there was a wide variability between individual serotypes in the calculated serum concentration of anti-capsular antibody needed to provide vaccine effectiveness (Ex. 2033 Andrews 2014 page 843 Table 3). PCV13 vaccine effectiveness was reported to range from 26% for serotype 3 to 98% for serotype 6A (Ex. 2033 Andrews 2014 page 843 Table 3). This was commensurate with the calculated serum concentration of anti-capsular antibody needed to provide PCV13 vaccine effectiveness for serotype 6A which was 0.16ug/ml while it was 2.83ug/ml for serotype 3 (Ex. 2033 Andrews 2014 page 843 Table 3). These data were interpreted as suggesting that a serum concentration of anti-capsular antibody of 0.35ug/ml is an underestimate for some serotypes (e.g. serotype 3) and an overestimation for other serotypes (e.g. serotype 6A) in terms of predicting vaccine effectiveness (Ex. 2033 Andrews 2014 page 842 and Table 3 page 843). Researchers recalculating an aggregate correlate of protection for the PCV7 serotypes (using relevant values for IgG concentration after receipt of PCV13), reported that the correlate of protection was 0.59ug/ml, stating 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" (Ex. 2033 Andrews 2014 page 844) and later stating that "serotype-specific correlates

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 72 of 77

of protection vary widely" (Ex. 2033 Andrews 2014 page 839) and "This finding shows that the notion of a threshold concentration of circulating serotype-specific IgG that is protective is overly simplistic" (Ex. 2033 Andrews 2014 page 845).

154. Even more concerning were functional antibody studies where researchers concluded that opsonophagocytic antibody titres of 1 in 8 or higher did not predict vaccine protection (Ex. 2033 Andrews 2014 page 839) stating "With 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" (Ex. 2033 Andrews 2014 page 843). In addition, they later stated regarding OPA titres that "The 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" (Ex. 2033 Andrews 2014 page 845).

155. The POSA takes away from these studies that the serotype-specific IgG serum concentration associated with vaccine effectiveness is very serotype-specific and cannot be generalized and assumed. In addition, functional antibody studies using OPA titres are also serotype-specific and have not been correlated with protective efficacy. The POSA would know that there were no data regarding the serotype-specific serum IgG antibody concentrations versus serotypes 23A, 23B and 35B needed to provide protection against invasive pneumococcal disease.

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 73 of 77

In addition, the POSA also knew of no data regarding the serotype-specific OPA (opsonophagocytosis assay) titres versus serotypes 23A, 23B and 35B needed to provide protection against invasive pneumococcal disease (IPD).

156. Thus, individual testing with serotypes 23A, 23B and 35B needed to be studied as a POSA could not predict whether the serotype-specific serum IgG antibody concentrations would predict or confer vaccine protection and whether the OPA titres would be sufficient to confer or predict vaccine protection.

157. No such data, for either serum IgG concentration or OPA titer, existed for any of the serotypes recited in the Challenged Claims.

158. 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.

159. For each of these reasons, it is my opinion that a POSA would not have had a reasonable expectation of success in achieving the compositions as claimed in the ’757 patent.

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

160. Claim 1 of the ’757 patent refers to a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide, wherein each of the capsular polysaccharides is from a

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 74 of 77

Streptococcus pneumoniae serotype selected from a group consisting of 23A, 23B, and 35B.

161. I understand that the Petition acknowledges that Gu does not literally disclose the recited "plurality of at least two unique immunogenic saccharide-polypeptide conjugates," and that Petitioner relies on an inherency argument based on Gu's claim reciting "[a]n immunogenic composition comprising *at least one* glycoconjugate" (Petition at 41 (emphasis in Petition)). I further understand that the Petition 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."

162. I disagree. 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.

163. For example, the Santiesteban-Lores study uses multiple glycoconjugates with a single serotype (6B) conjugated to two different carrier proteins, PspA1 and PspA3 (Ex. 2015 pages 1-5).

164. I further understand that the Petition argues that Gu discloses conjugating multiple serotypes based on 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." However, this passage appears in Gu in a paragraph about preservatives, not the selection of multiple serotypes (Ex. 1009 at 57:12–20).

165. I further understand that the Petition argues that Gu discloses conjugating multiple serotypes based on 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." However, a POSA would understand that this passage in Gu addresses the weight of a component, not the number of serotypes selected (Ex. 1009 at 63:6–1.).

166. Because each of the Petition's arguments as to why Gu allegedly discloses conjugating multiple serotypes is based on an incorrect reading of Gu, it is my opinion that Gu does not disclose conjugating multiple serotypes as recited in claim 1 of the '757 patent.

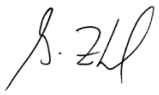
167. I currently hold the opinions expressed in this declaration, but my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

*****

Pogona Ex. 2018
Pfizer v. Pogona, IPR2026-00189
Page 76 of 77

Under penalty of perjury, I declare that all statements made herein of my own knowledge are true and accurate and that all statements made on information and belief are believed to be true and accurate, and that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Executed this _4_ day of August, 2026.



George G. Zhanel, Ph.D.