Federal Court  Cour fédérale

Date: 20210430

Docket: T-1184-17

Citation: 2021 FC 317

Ottawa, Ontario, April 30, 2021

PRESENT: The Associate Chief Justice Gagné

BETWEEN:

MERCK SHARP & DOHME CORP. and MERCK CANADA INC.

Plaintiffs

And

WYETH LLC

Defendant

PUBLIC JUDGMENT AND REASONS

(Confidential Judgment and Reasons issued April 14, 2021)

TABLE OF CONTENTS

I. Overview

[1] Merck Canada Inc. and Merck Sharp & Dohme Corp. [together Merck], seek to impeach three Canadian patents, one composition patent and two formulation patents, property of Wyeth LLC [Wyeth], pertaining to a 13-valent pneumococcal polysaccharide protein conjugate vaccine commercialized under the name Prevnar® 13.

[2] Merck states that Prevnar® 13 lacks inventiveness and that it was not worthy of patent protection. Merck takes its position despite the fact that it took years of research and clinical testing to develop Prevnar® 13; that Wyeth succeeded where several competitors had failed; and, that Wyeth has immunized over 1.5 billion people around the world during the decade when Prevnar® 13 benefited from a monopoly.

[3] If Wyeth invented anything – and Merck submits that Wyeth did not, owing to anticipation and obviousness – the invention is at most a 13-serotype vaccine. To the extent that any of the claims are not limited to those 13 serotypes, Merck contends they are overbroad and one could not soundly predict them.

[4] Wyeth, on the other hand, states that its patents disclosed to the world a platform to make polysaccharide conjugate vaccines comprising 13 or more serotypes of pneumococcus. According to Wyeth, Prevnar® 13 is the result of years of experimental work by teams of scientists, and it is the gold standard of the industry to this day. It argues that its monopoly is not limited to 13 serotypes, and that it would cover any pneumococcal polysaccharide conjugate

vaccines that contain the 13 serotypes recited in the claims of its patents, plus any other known serotypes or clinically relevant serotypes.

[5] At the onset of the trial, Merck's standing to take action was a live issue. Wyeth now concedes it is no longer an issue since during the trial Merck Canada Inc. filed a New Drug Submission for approval to sell a 15-valent pneumococcal polysaccharide protein conjugate vaccine [V114] in Canada. Since the parties are both innovative pharmaceutical companies that have been competing to make newer and better pneumococcal vaccines since the early 1980s, Merck believes that Wyeth will try to use its patents to block V114 from entering the Canadian market.

[6] That said, Wyeth's patents are deemed valid. Merck bears the burden to proof otherwise.

II. The Composition Patent

A. *The Story of the Composition Patent*

[7] Dr. Peter R. Paradiso, formerly responsible for research and development at Wyeth, is one of the named inventors of Canadian Patent No. 2,604,363 [the 363 Patent or Composition Patent]. He testified to Wyeth's history of conjugate vaccine development and the story behind the invention of the 363 Patent.

[8] During his professional career with Wyeth, he engaged in the discovery, development and clinical research that led to the licensure of various conjugate vaccine products, including:

> HibTITER® (*Haemophilus influenzae* serotype b (Hib) conjugate vaccine);
>
> Tetramune® (combined diphtheria, tetanus, and pertussis and HibTITER);
>
> Meningitec® (*Neisseria meningitidis* group C conjugate vaccine);
>
> Prevnar® (7-valent *Streptococcus pneumoniae* conjugate vaccine); and,
>
> Prevnar® 13 (13-valent *Streptococcus pneumoniae* conjugate vaccine).

[9] All of these vaccines are either monovalent (comprising a single serotype) or multivalent (comprising multiple serotypes) and conjugated with Wyeth's preferred protein carrier, CRM_{197}, a cross-reactive derivative of the diphtheria toxoid.

[10] Beginning in the 1980s and throughout the 1990s, at the same time that Wyeth was developing HibTITER®, Tetramune® and Meningitec®, it was also working on developing its first pneumococcal polysaccharide protein conjugate vaccine [PCV].

[11] *Streptococcus pneumoniae* (also referred to as *S. pneumoniae*) is a bacteria that causes many pneumococcal infections including serious diseases such as meningitis, pneumonia, and bacteraemia, as well as milder infections such as sinusitis and otitis media. Infants and young children are especially susceptible to *S. pneumoniae* and are at serious risk for pneumococcal infections. *S. pneumoniae* is classified into different serotypes (*i.e.* strains) depending on the polysaccharide that encapsulates the bacteria.

[12] When Wyeth was developing its first PCV, some 90 serotypes were known, and some were part of a same serogroup. Each serotype is identified by a number, and where more than one is known in the same serogroup, they are also given a letter.

[13] Despite the successful use of bacterial polysaccharides to immunize adults and older children, polysaccharides were not very immunogenic in children under the age of two. Previously, immunization of that age group took place with bacterial proteins, also with moderate success.

[14] However, it had been shown that, by conjugating polysaccharides to carrier proteins, the immune response to the polysaccharide could be enhanced. Studies performed in the 1980s and 1990s showed that such conjugation resulted in vaccines that had a better immune response (than polysaccharides alone) in children under two years of age.

[15] Wyeth was thus working to create a multivalent conjugate formulation to protect against multiple serotypes of the *S. pneumoniae* bacteria in a single vaccine.

[16] [redacted]

[17] In 2000, Prevnar® [Prevnar 7] became the first licensed PCV in the world. It contained coverage for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

[18] Wyeth never sought a patent for its invention and never disclosed the serotype-specific methodology used to make the conjugates found in Prevnar 7.

[19] Although Prevnar 7 was a successful vaccine, there remained a global need for increased serotype coverage, particularly in the developing world. Wyeth thus developed a 9-valent vaccine for sub-Saharan Africa, which included serotypes 1 and 5 (PCV-9).

[20] However, by year 2000, GSK and Aventis Pasteur were developing 11-valent PCVs covering additional serotypes 3 and 7F (PCV-11). PCV-11 was expected to protect against 90% of invasive pneumococcal disease worldwide.

[21] As a result, Wyeth determined that it had to develop a new product to expand protection and remain competitive. It decided to pursue PCV-13, adding serotypes 6A and 19A to the PCV-11, all conjugated to CRM_{197}. While CRM_{197} was Wyeth's carrier protein of choice, Wyeth had concerns about immune interference. [redacted] but chose to use CRM_{197} after the data described in the 363 Patent became available.

[22] The immunogenicity data obtained showed that Wyeth's PCV-13 was dozens to hundreds of times more immunogenic than the corresponding free polysaccharides. The data made Dr. Paradiso confident that Wyeth could develop even higher-valency PCVs using CRM_{197} as the sole carrier protein, and the data made Wyeth affirm that it invented a 13-valent "platform".

B. *The Issues for the 363 Patent*

[23] Merck argues that each of claims 1 to 6, 13, 14, 17 to 19, 22 to 30 and 36 to 38 of the 363 Patent [the Impugned Claims] are invalid.

[24] The 363 Patent was filed on March 31, 2006 and claims priority to US 60/669,605 dated April 8, 2005. The 363 Patent was issued on June 16, 2015 and has not expired.

[25] Merck raises three main issues regarding the 363 Patent:

(1) Are the Impugned Claims limited to compositions made from 13 serotypes?

(2) In any event, are the Impugned Claims invalid because:

(a) *They are anticipated by Peña (Claim 1 only)?*

(b) *They are obvious (all Impugned Claims)?*

(3) To the extent that the Claims cover compositions made from more than 13 serotypes, are they invalid for overbreadth and/or lack of utility?

C. *The 363 Patent Experts*

[26] Both parties tendered evidence from two experts on the 363 Patent.

Dr. James Cleland Paton and Dr. Dennis Kasper testified on behalf of Merck.

Dr. Neil Ravenscroft and Dr. Ron Dagan testified on behalf of Wyeth.

[27] All experts heard at trial are well-respected scientists that have extensive knowledge and experience with encapsulated bacteria and, to varying degrees, with conjugation methods. They all are prolific authors of numerous articles and papers published in the most prestigious scientific publications around the world. Unfortunately, perhaps with the exception of Dr. Kasper, the experts all lost some of their objectivity during cross-examination and, at times, became argumentative and non-responsive.

(1) Merck's Experts

[28] **Dr. Paton** is Merck's pneumococcal expert. He is a professor of Microbiology and Director of the Research Center for Infectious Disease at the University of Adelaide in Australia.

[29] Merck presents him as having had benchtop experience making a polysaccharide-protein conjugate before 2005. On the other hand, in addition to listing several omissions, admissions and inconsistencies in his testimony, Wyeth submits that Dr. Paton has never worked on a multivalent conjugate vaccine and has mainly focused his work on protein alone vaccines. Indeed, Dr. Paton admitted he never worked on the development of a multivalent conjugate vaccine, but stated that he had made a polysaccharide-protein conjugate in the 1990s.

[30] **Dr. Kasper** is Merck's polysaccharide-protein conjugate expert and immune interference expert. He is a physician-scientist and currently holds the positions of William Ellery Channing Professor of Medicine and Professor of Immunology at Harvard Medical School.

[31] His testimony focussed on the Method/Process claims of the 363 Patent. Merck rightly notes that Dr. Kasper made concessions where fair, and digressed less in cross-examination than others did.

[32] Without attacking Dr. Kasper's credibility, Wyeth states that all but four pages of his report are irrelevant to this case. Dr. Kasper opines that general steps set out in the Method/Process claims were known at the relevant time, without considering whether these claims were inventive because of the new 13-valent immunogenic composition.

[33] In addition, Wyeth notes that Dr. Kasper is not an expert in pneumococcus and that no more than 10 of the 400 papers he has authored deal with pneumococcus.

(2) Wyeth's Experts

[34] **Dr. Ravenscroft** is Wyeth's expert in multivalent pneumococcal conjugate vaccines. He currently is Associate Professor and Deputy Head of the Department of Chemistry at the University of Cape Town in South Africa.

[35] Wyeth points to the fact that he is the only expert who has actually worked to develop a licensed pneumococcal conjugate vaccine.

[36] Wyeth concedes that while Dr. Ravenscroft's testimony was difficult to reconcile at times, his testimony was forthright and it was not argumentative, despite having been unnerved during cross-examination and asked to adopt assumptions that were opposite to his actual views.

[37] On the other hand, Merck argues that Dr. Ravenscroft made fatal concessions in cross-examination and that he was unable to defend his initial tortured construction of the claims of the 363 Patent, just as he was unable to support his initial position on anticipation and obviousness.

[38] **Dr. Dagan** is Wyeth's expert on the development of pneumococcal vaccines, including serotype selection and immune interference. He is currently a Distinguished Professor of Pediatrics and Infectious Diseases of the Ben-Gurion University of the Negev, and Emeritus Director of the Pediatric Infectious Disease Unit at the Soroka University Medical Center, both in Israel.

[39] Wyeth suggests that his expertise is unparalleled in the scientific community, and that the Court should entirely accept his evidence. Wyeth acknowledges that his cross-examination became heated on occasion but Wyeth blames Merck's counsel for putting propositions to Dr. Dagan that rephrased his prior statements.

[40] Merck notes that Dr. Dagan is a clinician with no experience making conjugate vaccines himself. As the father of the doctrine of immune interference, Merck warns the Court that Dr. Dagan's knowledge on the subject well-exceeds that of the skilled person at the relevant time. Merck also points to the fact that Dr. Dagan openly disagreed with Dr. Ravenscroft, Wyeth's other expert, on an important issue. Finally, Merck says that Dr. Dagan's testimony was generally evasive and that he was unwilling to concede even basic points where fair.

D. *The Person of Skill in the Art [PSA]*

[41] The parties' experts generally agree that the 363 Patent is directed to the following person or team of persons possessing the ordinary skill and knowledge of the particular art to which the 363 patent relates (*Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44 [*Free World*]):

> One or more vaccinologists with an interest in the development of pneumococcal conjugate vaccines, having relevant experience in chemistry, microbiology, immunology, epidemiology, and clinical infectious disease. The intended audience would have had an M.D., M.Sc., and/or Ph.D., as well as applied expertise in the context of pneumococcal conjugate vaccine development. In particular, the PSA would have had actual experience in carbohydrate chemistry and the preparation of polysaccharide-protein conjugates and conjugate vaccines.

E. *Claims Construction – Legal Principles*

[42] Subsection 27(4) of the *Patent Act*, RSC 1985, c P-4 [*Patent Act*] requires that claims define "distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed."

[43] As stated in *Free World* at paragraph 14, citing from *Minerals Separation North American Corp v Moranda Mines, Ltd*, [1947] Ex CR 306 at 352, the claims must not be flexible, but rather must provide a "bright line demarcation" of the monopoly claimed:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

[44] The words of the claims must be read through the eyes of the PSA, in light of that person's common general knowledge, in an informed and purposive way, and with a mind willing to understand (*Free World* at paras 31(c) and 44; *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 49 [*Whirlpool*]).

[45] Construction of a patent is a question of law left to the Court to decide (*Whirlpool* at para 61). However, expert evidence provides the technical knowledge that enables the Court to step into the shoes of the PSA faced with the claims as of the publication date (October 19, 2006 for the 363 Patent).

[46] The PSA will appreciate the nature and description of the invention on a technical level, making sense of the words used in the claims in light of the common general knowledge (*Whirlpool* at para 53).

F. *Claims Construction – Are The Impugned Claims Limited to 13 serotypes*

[47] Five of the Impugned Claims are independent claims: Claims 1, 13, 17, 36 and 38.

[48] The 363 Patent includes three groups of claims: (i) Composition Claims; (ii) Use Claims; and (iii) Method/Process Claims:

> **The Composition Claims**: The 363 Patent has claims to compositions with 13 or more serotypes (according to Wyeth), or it has claims to compositions with exactly 13 serotypes (according to Merck).
>
> Claim 1 claims a multivalent immunogenic composition comprising 13 distinct polysaccharide serotypes conjugated to CRM_{197}.

> Claims 2-5 add adjuvants.
>
> Claim 17 claims a 13-valent immunogenic composition conjugated to CRM_{197} using reductive amination.
>
> Claims 18 and 19 add adjuvants.
>
> **The Use Claims**: The 363 Patent has claims for the use of the composition as a medicament and as a vaccine.
>
> Claim 6 is a medicament claim relating to a conjugate composition of 13 (Merck) or more serotypes (Wyeth).
>
> Claims 22-30 claim the use of a conjugate composition of 13 serotypes for vaccination.
>
> **The Method/Process Claims**: Claims 13-14 and 36-38 claim the general methods and processes to arrive at compositions containing conjugates of the 13 serotypes.

[49] Claim 1 is the only claim for which Wyeth contends that its scope exceeds the 13 specific serotypes listed in the 363 Patent. Claim 1 describes a multivalent immunogenic composition comprising 13 distinct conjugates prepared from 13 serotypes each individually conjugated to CRM_{197}:

> A multivalent immunogenic composition, comprising 13 distinct polysaccharide-protein conjugates, together with a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumonia* conjugated to a carrier protein, and the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, wherein the carrier protein is CRM_{197}.

[50] Merck asserts that all experts agreed that Claim 1 is limited to 13 serotypes.

[51] Wyeth responds that the Court should be very prudent in relying on the admissions obtained by Merck's counsel in cross-examination of its experts, as counsel used an approach

that should be rejected: an approach that focused on “excessive literalism”. Wyeth reminds the Court that patent specifications are not to be read using a “dictionary approach” nor are they addressed to grammarians, etymologists or laypeople (*Whirlpool* at paras 52-53).

[52] Based on their general knowledge at the time, Wyeth argues that the PSA would have appreciated that the 363 Patent was about expanding coverage while retaining the key benefits of conjugation: increasing immunogenicity. The PSA would have understood that the 363 Patent describes the “next generation” of Wyeth’s conjugate development program and that Wyeth had managed to exceed the known limits of serotype coverage with its PCV-13. Finally, the PSA would have understood that the 363 Patent describes a “platform” technology; it discloses the details of Wyeth’s conjugation technology that were needed in order to replicate its success. The PSA would have used the platform to add other serotypes in a future vaccine, just as Merck did with its V114.

[53] As to the number of additional serotypes that this “platform” covers, Wyeth’s position is somewhat elastic. Dr. Ravenscroft first stated in his report that it should include all 50 serotypes of known structure; he later suggested that it be limited to clinically relevant serotype. Finally, he landed on the 23 serotypes contained in Pneumovax® 23 (a polysaccharide only pneumococcal vaccine).

[54] Wyeth’s notion of a “platform” basically comes from the use of the word “comprising” in Claim 1, which Wyeth asks the court to replace with “including but not limited to”. Claim 1 would then read as follows:

> A multivalent immunogenic composition, [**including but not limited to**] 13 distinct polysaccharide-protein conjugates, together with a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of Streptococcus pneumonia conjugated to a carrier protein, and the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, wherein the carrier protein is CRM_{197}.

[55] On the other hand, Merck asserts that the word "comprising" allows for more elements in the composition, such as acceptable physiological vehicles and/or adjuvants, and that the two "wherein" clauses limit both the serotypes and carrier protein that can be used:

> A multivalent immunogenic composition, **comprising** 13 distinct polysaccharide-protein conjugates, together with a physiologically acceptable vehicle, **wherein** each of the conjugates comprises a capsular polysaccharide from a *different* serotype of Streptococcus pneumonia conjugated to a carrier protein, and the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, **wherein** the carrier protein is CRM_{197}.
>
> [Emphasis added by Merck.]

[56] For several reasons, I prefer Merck's proposed construction. I find that a purposive interpretation of both Claim 1 and the 363 Patent in its entirety supports the view that Claim 1 is limited to 13 serotypes.

[57] In *Purdue Pharma v Canada (Attorney General)*, 2011 FCA 132 at para 22 [*Purdue Pharma*], the Federal Court of Appeal held that even if the word "comprising" used in claim language could be regarded as open-ended, the inclusion of other elements requires some justification. The basis for such an inclusion must be found within the confines of the patent. No such basis existed in *Purdue Pharma*, and none can be found in the 363 Patent.

[58] When one reads the patent as a whole, one finds sufficient bases for adding adjuvants, buffers and other excipients. However, there is no basis to go beyond 13 serotypes.

[59] First, the Summary of the Invention describes the invention as providing a 13-valent pneumococcal conjugate composition comprising the seven serotypes contained in Prevnar 7 (4, 6B, 9V, 14, 18C, 19F and 23F), plus six additional serotypes (1, 3, 5, 6A, 7F and 19A). This is very specific and limited.

[60] Second, in the Detailed Description of the Invention, a rationale is provided for the inclusion of the original seven serotypes: they were responsible for 82% of the invasive pneumococcal diseases in children under the age of two. A very detailed rationale is also provided for the inclusion of each of the additional six serotypes. For example, serotypes 6A and 19A account for more invasive pneumococcal disease in US children under two than serotypes 1, 3, 5 and 7F combined, in addition to being commonly associated with antibiotic resistance. There is no mention in the 363 Patent of a need, a desire, or a basis for adding any other serotype. Again, some 90 serotypes were known at the time.

[61] Third, all of the 16 examples provided in the 363 Patent, which contain instructions needed by the PSA, refer only to the specific 13 serotypes recited in the claims, no others.

[62] Fourth, I find that Dr. Ravenscroft's reference to Figure 1 of the 363 Patent to support his view that the inventors also contemplated serotype 12F and others is misplaced. Figure 1 conveys information that was publically available in April 2005; it shows the increase of

invasive pneumococcal disease rates in US children under the age of two, from baseline (1998/99) to 2001. As admitted by Dr. Ravenscroft on cross-examination, this figure was added for the sole purpose of making a point: to address prevalence/antibiotic resistance and justify the addition of serotypes 6A and 19A. Serotype 12F being entirely penicillin sensitive, Dr. Ravenscroft admitted that Figure 1 cannot be used as a rationale to add it to the invention disclosed in the 363 Patent.

[63] Fifth, Wyeth's argument that the wording of Claim 17 supports its construction of Claim 1 should also fail. Claim 17 reads as follows:

> A multivalent immunogenic composition, comprising polysaccharide-protein conjugates together with a physiologically acceptable vehicle, wherein said polysaccharide-protein conjugates consist of 13 distinct polysaccharide-protein conjugates, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein, and the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, wherein the carrier protein is CRM_{197} and wherein conjugation is effected by reductive amination.

[64] Wyeth admits that Claim 17 is limited to 13 serotypes but argues that in order to differentiate it from Claim 1, Claim 1 must not be limited to 13 serotypes. Dr. Ravenscroft's interpretation of Claim 1 is grounded in the fact that "in claims drafting, when different terms are used, they are presumed to have different meanings. Consequently, the use of '*consist of*' in claim 17 would have indicated to the PSA that '*comprising*' must have a different—and broader—meaning" (Ravenscroft Report at para 246).

[65] I disagree. The word “comprising” along with a few “wherein” clauses (that have the same limiting effect as for Claim 1) are also used in Claim 17. Moreover, Claim 17 is not without purpose if both claims are limited to 13 serotypes. Dr. Ravenscroft acknowledges that unlike Claim 1, which allows for the use of any conjugation technology, Claim 17 excludes conjugates made using any approach other than reductive amination. Thus, Claim 17 is different from Claim 1. They each have a different scope, and they are not redundant (*MIPS AB v Bauer Hockey Ltd*, 2018 FC 485 at para 134).

[66] Finally, if the Court were to side with Wyeth on the construction of Claim 1, the Court would have to choose a cap on the number of serotypes covered by the invention or that could be added using Wyeth’s so-called “platform”. It would also mean that the ambit of Wyeth’s monopoly could grow over the life of the 363 Patent as new serotypes – or their structure – are discovered. This would be contrary to the fundamental principles of claims construction (*Free World* at para 57).

[67] For these reasons, I find that Claim 1 of the 363 Patent is limited to 13 serotypes and does not disclose any “platform” for making a vaccine with greater coverage.

G. *Claims Construction – meaning of “Immunogenic”*

[68] Antibodies may be measured in an enzyme-linked immunosorbent [ELISA] assay, which is a common assay technique designed for detecting and quantifying antibodies to an antigen. On the other hand, an opsonophagocytic activity [OPA] assay measures whether the antibodies elicited by a vaccine are functional; that is, that they are shown to efficiently kill the bacteria.

[69] According to Merck, the PSA would read "immunogenic" in the claims of the 363 Patent to mean that the composition generates "an immune response" or that it elicits antibodies for each of the serotypes, without any particular level of antibody response. Merck emphasizes the fact that Dr. Ravenscroft conceded on cross-examination that the ordinary meaning of "immunogenic" in the art is that the composition elicits an immune response, and most studies at the time demonstrated immunogenicity based on IgG responses in ELISA assays alone.

[70] Wyeth responds that this definition is nonsensical. As stated by Dr. Dagan, the body produces an immune response to almost all stimuli: "If I drink milk, I get antibodies to milk… eating elicits antibodies. Living, breathing, everything else, it is antibodies" (Trial Transcript Vol 9, page 1229, lines 23-27).

[71] Wyeth contends that the PSA would understand the term "immunogenic" to mean that each conjugate elicits an immune response greater than the polysaccharide alone. That is the whole purpose of conjugating. That is what the data tables in the 363 Patent demonstrate: the 13-valent conjugate composition is more immunogenic than the polysaccharide alone, and the antibodies elicited are functional.

[72] At paragraph 249 of his report, Dr. Ravenscroft, Wyeth's expert in multivalent pneumococcal conjugate vaccines, states the following:

> The [PSA] would have also understood that the compositions were "***immunogenic***". At the most basic level, the [PSA] would have understood that the term "*immunogenic*" referred to the fact that the compositions generate an immune response when administered. The [PSA] would have recognised that the polysaccharides themselves are classified as antigens (*i.e.*, antibody generators).

> Further, such polysaccharides can be conjugated to a carrier protein to achieve a greater immune response. In other words, for a composition of "*polysaccharide-protein conjugates*", the [PSA] would have understood "*immunogenic*" to mean that each conjugate would have been expected to elicit an immune response that was greater than the polysaccharide alone. The 363 Patent itself recognises that the conjugates of the composition produce "*higher serum IgG titers and overall greater functional antibody activity than seen with the free polysaccharide alone or mixed with unconjugated* CRM_{197}." As of the relevant date, the accepted means of measuring the immunogenicity of pneumococcal conjugates were (1) serotype-specific ELISA to detect serum IgG titers and (2) OPA to detect functional (*i.e.*, opsonophagocytic) antibodies.
>
> [Footnotes Omitted.]

[73] I must first say that Dr. Dagan's analogy with milk (which Wyeth took up in its closing argument) does not convince me. Drinking milk, eating, living, and breathing will not elicit antibodies to the pathogens a vaccine aims at protecting against, hence the research for a vaccine. This argument says nothing about the quantity (ELISA assay) or quality (OPA assay) of the immune reaction the 363 Patent is referring to, and in that sense, it does not advance the debate on the issue.

[74] I also have to consider the fact that the Impugned Claims themselves do not state any particular level of immunogenicity or any particular assays for measuring immunogenicity.

[75] I therefore have to turn to other information convened by the 363 Patent and to the common general knowledge of the PSA to determine whether the term "immunogenic" means that the invention claims an immune response for each of the 13 serotypes that is greater than the polysaccharide alone (ELISA), and that the antibodies elicited are functional (OPA).

[76] I am willing to accept that, at the time, the PSA would have known that the purpose of conjugating was to elicit an improved immune response, especially in children under the age of two. Additionally, the PSA would have known that since 2003, the World Health Organization required functional antibodies in immunogenic compositions.

[77] The PSA would have understood that the data illustrated in Tables 5 and 6 of the 363 Patent was consistent with the inventors' conclusion "that conjugation of the 13-valent pneumococcal vaccine polysaccharides produces higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}" (363 Patent, Trial Exhibit [TX] 3 at 47, lines 6-9). The inventors say "overall" because the serotype 14 admittedly fell short of demonstrating that it generated functional antibodies in pre-clinical immunogenicity studies.

[78] Having considered all of the evidence, I am of the view that Wyeth confuses what the inventors sought with what the 363 Patent claims. The 363 Patent claims a "multivalent immunogenic composition" without further qualification. Although the PSA would have known that the whole purpose of conjugating is to improve immunogenicity, particularly in young children, Dr. Ravenscroft also admitted that the PSA would understand the word "immunogenic" to mean "elicits an immune response" and that a common way of measuring immunogenicity is with ELISA assays.

[79] In my view, if Wyeth wanted to claim a specific level of immunogenicity, or define immunogenicity otherwise than to illicit an immune response, it could have done so in so many

words. It could have used language similar to that used by GSK in its patent WO 00/56358 where it claimed:

> 1. An antigenic composition comprising one or more *Streptococcus pneumoniae* capsular polysaccharide conjugates adjuvanted with 3D-MPL and substantially devoid of aluminium-based adjuvants, wherein at least one of the *Streptococcus pneumoniae* polysaccharide conjugates **is significantly more immunogenic** in compositions comprising 3D-MPL in comparison with compositions comprising 3D-MPL in conjunction with an aluminium-based adjuvant.
>
> [Emphasis added.]

[80] In my view, those words should not be read in Claim 1 of the 363 Patent.

H. *Validity of the 363 Patent*

(1) Novelty/Anticipation

[81] Subsection 28.2(1) of the *Patent Act* requires that, for a patent to be valid, its subject matter cannot have been previously disclosed. If the subject of the Patent's claims was made available to the public in a single enabling disclosure prior to the claim date, it was anticipated. The two-part test for anticipation is set out in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*]:

> 1. The prior art reference must disclose the claimed invention such that, if performed, it would necessarily result in infringement of the patent; and,
>
> 2. The prior art reference must be sufficiently detailed to enable a PSA to perform the claimed invention without the exercise of inventive ingenuity or undue experimentation.

[82] Anticipation requires the prior publication to contain clear and unmistakable directions to do what the patentee claims to have invented (*Sanofi* at para 21 and *Free World* at para 26). The enablement element is satisfied where there is enough information to allow the subsequently claimed invention to be performed without undue burden (*Sanofi* at para 37).

[83] Disclosure and enablement are two distinct requirements; if disclosure is not proven, enablement does not need to be considered (*Sanofi* at para 42).

(2) Claim 1 of the 363 Patent vs Peña 2004

(a) *Disclosure*

[84] Merck contends that all essential elements of Claim 1 of the 363 Patent were publically disclosed in a 2004 publication by C. de la Peña entitled "Present and future of the vaccination against pneumonia" [Peña 2004], published in Pediátrika, a Spanish journal. It is uncontested that Peña 2004 is a Wyeth publication, written by Wyeth's employees. It discusses the incidence of *S. pneumoniae* related diseases in various groups of young Spanish children. For example, it discusses:

- Pneumococcal disease as a significant cause of morbidity, hospitalization and mortality, where 40% of all deaths due to pneumonia are children under five years of age;
- The impact of antibiotic resistance when prevention of the infection is not possible, and the known relationship between serotypes and resistance;
- The fact that the 23-valent polysaccharide only vaccine is not immunogenic in children under two;

- The fact that conjugation with "an appropriate protein" improves immunogenicity, as demonstrated with the vaccine *Haemophilus influenza* type b.

- Several statistics comparing the incidence of *S. pneumoniae* related diseases among regions in Spain and between Spain and other European countries and the United States;

- The fact that in February 2000, the United States authorized the use of a pneumococcal conjugate vaccine against seven serotypes of *S. pneumoniae* (Prevnar 7), and its observed efficacy;

- The introduction of Prevnar 7 in the Spanish market in June 2001, and its observed efficacy;

[85] What Merck views as disclosure of the elements of Claim 1 are the following excerpts of Peña 2004 at 52-53:

> **Other pneumococcal vaccines**
>
> As we know, there are currently two vaccines available for the prevention of invasive pneumococcal disease: the 23-valent polysaccharide (VNP-23V) and the 7-valent conjugate vaccine (VNC-7V).
>
> There are other pneumococcal conjugates that have not yet been marketed and that are in advanced phases of study:
>
> - The 9-serotype vaccine (adds 1 and 5), which increases the coverage up to 87% in children less than two years of age and in children between two and five years of age.
>
> - The 11-serotype vaccine (adds 3 and 7F). Serotype 3 is the most likely to cause invasive disease in adults in Spain; therefore, the use of these vaccines could have a favourable impact on the incidence of the infection by this serotype.
>
> - The 13-serotype vaccine (adds 6A and 19A)"
>
> …

The future of pneumococcal vaccination

> The 23-valent polysaccharide vaccine was the first step in the fight against pneumococcal disease, and the heptavalent conjugate vaccine has drastically reduced the disease in the youngest of children. Thus, in terms of future pneumococcal vaccinations, we should keep in mind several issues: serotypes and age and geographic distribution, combination with other vaccines, new routes of administration and other strategies.
>
> The geographic variability of pneumococcal serotypes represents a problem when developing a vaccine with worldwide coverage. We would almost have to design a specific vaccine for each geographic area, conducting a prior epidemiological study of the most common serotypes, which would only be possible in developed countries.
>
> Furthermore, we know that the spectrum of serotypes widens with advancing age, which complicates the acquisition of vaccines for age groups other than children, although children are the group at greatest risk and for whom the current vaccine is most effective. In this respect, work is being conducted to incorporate new serotypes to the 7-valent conjugate vaccine, with the 9-valent (which incorporates the serotypes 1 and 5), 11-valent (adding 3 and 7F) and 13-valent (6A and 19a) vaccines in various stages of research. This could broaden the spectrum of ages and countries, although we will continue to have much diversity in coverage. In addition, attempts are being made to incorporate the pneumococci that show the greatest resistance to antibiotics.
>
> [Emphasis added.]

[86] It is uncontested that Peña 2004 is silent on the carrier protein used to conjugate the different serotypes that are listed and that are said to compose the 9-valent, 11-valent and 13-valent vaccines, although there is a citation pointing to a prior publication which disclosed a 9-valent conjugated to CRM_{197} (Obaro 2002).

[87] Peña 2004 is also silent on the immunogenicity of the upcoming 13-valent vaccine. Peña 2004 uses two different ways to describe the ongoing studies performed on the 7, 9, 11 and 13-

valents: they are currently either in “advanced phases of study” or in “various stages of research”.

[88] Merck contends that the PSA would have inferred that all 13 serotypes would have to be individually conjugated with a single carrier protein: CRM_{197}. The PSA would have inferred that much because it was known at the time that Wyeth’s Prevnar 7 contained seven serotypes all individually conjugated with CRM_{197}. Merck argues that that was the opinion of Dr. Paton, with which Dr. Ravenscroft finally agreed in the following excerpt of his cross-examination:

> Q. And so the skilled person reading this would understand that what Wyeth was doing was, starting with Prevnar, conjugating individually to CRM, then going to a nine, 11, and now a 13, in various stages of research. Right?
>
> A. I don’t think you can assume that.
>
> Q. I am not asking you to assume. I am saying that the skilled person who is a conjugate maker, who has all the credentials you talked about and has access to the knowledge that you have talked about in your report, when they read that, that is what it means to them. Fair?
>
> A. It could mean that.
>
> (Trial Transcript Vol 7, page 989, line 21 to page 990, line 4.)

[89] Merck asserts that if the PSA is given the serotypes to include and the carrier protein to use, they can come up with a conjugate vaccine that elicits an immune response. The 363 Patent is disclosed by Peña 2004, in that way.

[90] Wyeth, on the other hand, relies on the result of its counsel's long cross-examination of Dr. Paton, where Dr. Paton finally admits that the PSA might not infer that much by reading Peña 2004:

> Q. Okay. My question was does it tell you what is in the 13-valent vaccine explicitly? And the answer is no. Correct?
>
> A. It doesn't tell you explicitly; you would have to infer that from the language.
>
> Q. Well, you don't have to infer it. You might not infer it; you might just say I don't know.
>
> A. I think in terms of --
>
> Q. Is that a fair way of doing it?
>
> A. Well, that is one way you could do it.
>
> (Trial Transcript Vol 3, page 467, lines 3-12.)

[91] Considering that neither expert was capable of convincing me that his opinion must prevail, I am forced to find that Merck has not met its burden to prove that the PSA would have inferred from Peña 2004 that all 13 serotypes of the 13-valents vaccine had to be individually conjugated with a single carrier protein: CRM_{197}.

[92] In addition, the inventors of the 363 Patent were concerned about immune interference, and that by adding new serotypes, they would reduce the immune response to the serotypes contained in Prevnar 7. They were also concerned with immune interference with other vaccines when co-administered with their 13-valent vaccine. Dr. Paradiso testified to the fact that concerns regarding immune interference caused by large amounts of a single carrier protein were not unique to Wyeth and that, in the field at that time, considerable effort was expended to

explore alternate carrier proteins. [redacted] Dr. Paradiso recalled that Sanofi chose to stay with the traditional toxoid carriers (diphtheria toxoid and tetanus toxoid), but attempted to limit immune interference by using a combination of those two carriers. The PSA must have known and shared those concerns when reading Peña 2004.

[93] I am also not convinced that the PSA would have inferred that the 13 serotypes all conjugated with CRM_{197} would be immunogenic. The PSA knew at that time that the 7-valent was certainly at an advanced stage of study (or rather at post-licensure monitoring) and therefore immunogenic. The PSA would not have known whether the 13-valent was in an advanced stage of study or barely in pre-clinical study (*i.e* its immunogenicity was not proven yet).

[94] As a result, I am of the view that the PSA would not have assumed that the carrier protein of the 13-valent vaccine referred to by Peña 2004 was CRM_{197}, or that the 13-valent had so far been proven immunogenic. Peña 2004 does not clearly and unmistakably disclose those two essential elements from Claim 1 of the 363 Patent.

(b) *Enablement*

[95] Merck argues that if Peña 2004 discloses the essential elements of Claim 1 of the 363 Patent, the PSA would have been able to make the disclosed 13-valent PCV with CRM_{197}, using routine skill and knowledge that is part of their skillset. Considering the PSA of the 363 Patent

includes a conjugate maker with actual experience in the preparation of the polysaccharide-protein conjugate, the PSA knew how to make polysaccharide conjugate vaccines. In fact, the World Health Organization's guideline provided a checklist for how to make such conjugates and control for their quality.

[96] Wyeth responds that Peña 2004 does not enable the PSA to perform the invention without undue burden.

[97] As stated by the Supreme Court in *Sanofi* at para 37, there is no enablement if prolonged or arduous trial and error is required to achieve the invention:

> … experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be laid down; however, prolonged or arduous trial and error would not be considered routine.

[98] Again Dr. Paton and Dr. Ravenscroft took diametrically opposed positions on this issue.

[99] For several reasons, I prefer Dr. Ravenscroft's views.

[100] As stated above, he is the only expert who has actually worked in the development of a licensed pneumococcal conjugate vaccine.

[101] As he explained in his report:

> 300. … Without guidance, the [PSA] would have had to conduct extensive experiments in order to develop an appropriately tailored approach to each serotype. This work would have included

> theoretical analysis based on information regarding the known structure of the capsular polysaccharide, trial-and-error experimentation, and analysis of the resulting conjugates to determine their activity. Each of these steps could be repeated many times for each serotype. Work of this kind would have taken at least several months to complete for each serotype and cumulatively, it could have taken years.

[102] His position remained unchanged during cross-examination.

[103] In fact, all of the experts to the 363 Patent agreed that the conjugation process is a very complex one. Dr. Paton said it was a time consuming, costly and complex endeavour with hundreds of quality assurance steps. In an article that he co-authored in 2008, he wrote:

> The PCVs are complex vaccines from a development and manufacturing perspective, given that each capsular PS serotype is chemically distinct and has to be individually optimized with respect to protein/polysaccharide ratios, conjugation technology, and other characteristics.
>
> (TX 20 at 421.)

[104] Dr. Kasper similarly said that the conjugation process is highly empirical and it involves a process of trial and error. He also co-authored a publication where he acknowledges that:

> The focus of achieving a chemical link between [polysaccharide] and protein by trial and error has necessitated long, complex development efforts.
>
> (TX 29 at 8.)

[105] In my view, the evidence adduced at trial confirms these opinions.

[106] It took Wyeth years of research and clinical testing to develop Prevnar® 13. Dr. Paradiso testified to the fact that the conjugate development process is complex. Many variables affect the process, including: the structure of the polysaccharide, the length of the polysaccharide chain, use of linker, the carrier protein, the ratio of polysaccharide to protein, how the polysaccharide is activated and conjugated to the carrier protein, and the conditions of conjugation (pH, temperature, time, reactants, etc.). [redacted] The project was the culmination of [redacted] work on PCVs and was only possible because of the extensive expertise that Wyeth had developed over this time.

[107] In addition, Wyeth succeeded where competitors failed. Dr. Paradiso testified to the fact that by 2003, he became aware that GSK's PCV-11 was facing immunogenicity issues. Sanofi was also working on a PCV-11 that was never licensed.

[108] In my view, even if Peña 2004 disclosed the 13 serotypes, the unique protein carrier being CRM_{197}, and the immunogenicity of the conjugates – which I do not accept that it did – it would not have enabled the PSA to make the invention claimed in the 363 Patent without undue burden. In that sense, Peña 2004 did not anticipate the 363 Patent.

(3) Obviousness of the 363 Patent

[109] According to section 28.3 of the *Patent Act*, an invention worthy of patent must be non-obvious. As stated by the Federal Court of Appeal in *Beloit Canada Ltd v Valmet OY* (1986), 8 CPR (3d) 289 at 294, and affirmed regularly since:

> The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.

[110] The four part test for obviousness is also set out in *Sanofi* at para 67:

> i. Identify the notional PSA and the relevant common general knowledge of that person;
>
> ii. Identify the inventive concept of the claim in question, or if that cannot readily be done, construe it;
>
> iii. Identify what, if any differences, exist between the inventive concept and the common general knowledge and state of the art; and
>
> iv. Viewed without any knowledge of the patent do these differences constitute steps which would have been obvious to the PSA or do they require a degree of inventiveness?

[111] The PSA is not risk adverse. The PSA is assumed to be a person who is going to try to achieve success, not one seeking failure (*Free World* at para 44). Patent protection is afforded to

"creative work" not "skilled work" (*Amgen Canada Inc v Apotex Inc*, 2015 FC 1261 at para 101).

[112] All prior art is citable for obviousness, whether or not it would be located in a reasonable diligent search (*Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 at para 86 [*Hospira*]).

[113] The obviousness test requires the Court to undertake a claim-by-claim analysis at the priority date – April 8, 2005. My analysis will focus on the two sets of claims challenged by Merck: i) the Composition Claims (Merck includes the Use Claims under that heading); and ii) the Method/Process Claims.

(4) Obviousness of the Composition Claims

(a) *Inventive Concept of the Composition Claims (Claims 1 to 6, 17 to 19, and 22 to 30)*

[114] The parties agree that the inventive concept of the Composition Claims is a multivalent immunogenic conjugate composition containing polysaccharides with 13 specified pneumococcal serotypes each individually conjugated with CRM_{197}, and potentially containing adjuvants.

[115] Merck argues again, at the obviousness front, that every essential element of the claims were in the public domain, having been disclosed by Peña 2004. To the extent any differences existed, Merck states that they could have been bridged using the PSA's common general

knowledge and routine skillset. Since I have found that the essential elements of Claim 1 of the 363 Patent were not disclosed by Peña 2004, I will concentrate my analysis on other prior art.

(b) *The Common General Knowledge*

[116] Wyeth's expert first opined that a PSA attempting to develop an improved vaccine to Prevnar 7 would have started with a pneumococcal protein-only vaccine, not a conjugate. However, at trial, Dr. Ravenscroft conceded that in light of the fact that the PSA is, amongst other things, a vaccinologist already involved with conjugate technology, the PSA would not have started with a protein-only vaccine. [redacted]

[117] All experts agreed: Prevnar 7 was a game changer in the industry and any subsequent pneumococcal vaccines had to be at least as efficacious. The PSA knew that Prevnar 7 contained pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated individually to CRM_{197} by reductive amination. The PSA would have known that as of April 2005, despite the success of Prevnar 7, there remained significant global pneumococcal disease burden due to the prevalence of serotypes not included in Prevnar 7. Prevnar 7 was the starting point and any higher valency vaccine would have to include those same seven serotypes.

[118] The PSA would also have known that in the early 2000s, four major pharmaceutical developers were working on PCVs:

i. Merck had attempted to develop a 7-valent vaccine conjugated to OMPC. While the vaccine was immunogenic for the 7 serotypes, clinical data showed that it afforded no cross-protection. Merck's PCV development program was abandoned in the early 2000s;

ii. Aventis Pasteur had attempted to develop an 11-valent vaccine that used two carrier proteins (diphtheria toxoid (DT) and tetanus toxoid (TT)) in an attempt to minimize immune interference. Aventis Pasteur ultimately abandoned its PCV development program;

iii. GSK was working on an 11-valent vaccine with a new carrier protein (Protein D), which was chosen to minimize immune interference. In addition, it did not confer protective immunity against serotype 3; and

iv. Wyeth had successfully licensed Prevnar 7 and conducted clinical trials in Africa on its PCV-9. Wyeth had been working on an 11-valent vaccine that had been stuck at the preclinical stage for at least 4 years.

[119] The literature observed that common protein carriers (*i.e.* TT, DT and CRM_{197}) were less favoured because of concerns of immune interference with other childhood vaccines. Dr. Paton admitted to having been one of the strongest advocates for the use of pneumolysin and other proteins, as pneumolysin has shown to be a very effective carrier protein in a tetravalent conjugate vaccine. At the time, he wrote that, unlike CRM_{197}, pneumolysin had the capacity to target and elicit an immune response against pneumococcal serotypes. It also had the capacity to minimise any problem associated with the overuse of existing carrier protein, a form of immune interference.

[120] Dr. Dagan, known as the father of the doctrine of immune interference, testified that as of April 2005, the PSA would have paid attention to the fact the GSK and Sanofi were both developing an 11-valent conjugate vaccine (using the same 11 serotypes). Further, that GSK and

Sanofi were the only two large companies to have tested a greater-than 9-valent vaccine in humans. The PSA would also have known that some prior art (*e.g.* Klein, Overturf, O'Brien) disclosed that Wyeth was working on an 11-valent, all serotypes individually conjugated to CRM_{197}.

[121] The PSA would have read that, "[a]lthough it would be preferable to include a larger number of different polysaccharides in a conjugate vaccine, technically this becomes challenging. In addition, incremental benefits in coverage from increasing the number of serotypes remain low after the standard 11 serotypes have been included" (Plotkin 2004 at 596).

[122] Further, the PSA would have read a few opinions on which serotypes could be advantageously added after the 11-valent conjugate vaccine. For instance, GSK's patent WO 00/56358 identifies serotypes 8, 12F, 15 and 22 for elderly vaccines, and serotypes 6A and 19A for infants and toddlers. The authors of Hausdorff 2000 also identify serotypes 6A and 19A to maximize coverage in younger children. At page 117, the authors state that:

> These analyses offer some implications for the future development of pneumococcal conjugate vaccines for young children. To maximize coverage of IPD in younger children, for example, future vaccines may need to include serotypes 6A and 19A, depending on the degree of cross-protection seen in ongoing efficacy trials with the current vaccine formulations (containing 6B and 19F). To optimize global coverage, future vaccines should also include representatives of serogroups 12 and 15.

[123] Dr. Dagan deposed that as of April 2005, immune interference and carrier-induced epitopic suppression [CIES] were a known concern:

> 106. By April 2005 there were a number of published studies that demonstrated that the simultaneous administration of vaccines

> impacted immunogenicity. While interference between vaccines was observed, the exact mechanism of action was unknown. The data suggested that increasing the amount of a carrier protein could "overload" the immune system and suppress the immune response. The extent of the immune suppression was unpredictable.
>
> 107. Based on these studies, vaccine developers recognized that as PCVs with higher valences were developed, more carrier protein would have to be used, which would increase the risk of immune interference. To address this risk, vaccine developers proposed potential solutions.

[124] He then goes on to cite his own 1998 publication showing the results of a study where participants were administered PCV-4 using TT as a carrier protein with Hib also conjugated with TT. The study demonstrated that as the TT load administered increased, antibodies for Hib decreased. Antibodies did not decrease when participants were administered the PCV-4 conjugated with DT.

[125] In light of these results, Sanofi developed a bi-carrier (TT and DT) multivalent PCV.

[126] The year after, Shinefield *et al.* published the result of their study on Prevnar 7, when administered with DTP (diphtheria, tetanus and pertussis) and Hib-CRM_{197}. The authors of Shinefield 1999 found that it reduced the immune response to the Hib, diphtheria, tetanus toxoid and pertussis antigens.

[127] The impact of increasing the CRM_{197} content in PCVs was also examined by Choo *et al.* in 2000. Their study was also designed to assess the immunogenicity of Prevnar 7 when administered with Hib-CRM_{197}. Again, this showed that the antibody response was five times higher after five months when administered alone than when combined with Hib-CRM_{197}. It is

true that the booster dose was able to address the observed immune suppression after fourteen months, but a World Health Organization working group had identified that i) infants were at higher risk of disease in the period following the initial dose regime of Prevnar 7, and ii) many countries did not administer booster shots.

[128] Additional studies were published in 2000 and 2002 by Obaro *et al.* The goal was to assess the effect of the PCV-9 on the immunogenicity of the diphtheria, tetanus and pertussis antigens. The authors noted a reduced tetanus toxoid antibody concentration, although it exceeded the concentration expected to confer protection against tetanus.

[129] In 2003, Anderson *et al.* published the results of their studies on the use of a multi-carrier approach to reduce the risk of CIES. They found that conjugating a PCV-4 with a mixture of TT and CRM_{197} elicited better immune response than by using a single carrier protein.

[130] In 2004, Dr. Dagan co-authored a publication on the results of studies performed on Sanofi's PCV-11 using two carriers, TT and DT. According to Dr. Dagan, they observed interference with the TT conjugated vaccine when the PCV-11 was co-administered with other infant vaccines. The concern that this would also occur if all eleven serotypes were conjugated to DT only led Sanofi to stop developing its PCV-11. Dr. Dagan and his co-authors (employees of Sanofi) concluded as follows:

> This study illustrates the importance of evaluating new vaccines together with concomitantly administered vaccines that are likely to be administered together when licensed. With the increasing use of aP in developed countries and the need to deliver more and more vaccines in the first year of life, new and novel approaches to adjuvants and carrier protein technology are likely to be required.

(Dagan 2004 at 5391.)

[131] All these studies led Dr. Dagan to testify that a body of scientific evidence emerged at the time; immune interference was occurring. Although not yet fully understood, it was known that as the amount of carrier protein administered in a vaccine increased, there were detrimental effects on antigen immunogenicity. There was uncertainty in the field as to how immune interference would affect the immunogenicity of vaccines when PCVs were co-administered, particularly when increasing the number of serotypes in a PCV beyond seven to nine or more, all conjugated to a single carrier protein.

[132] Although Merck asserts that immune interference would have been irrelevant to the PSA, Merck's position is not supported by Dr. Paton's cross-examination. Dr. Paton admitted on cross-examination that Plotkin 2004 directly raised immune interference as a concern and that, further, Plotkin's views on the subject were representative of the state of the art.

[133] Merck argues that no clinically relevant immune interference issues were reported for CRM_{197} and that this Court should not consider Dr. Dagan's interpretation of Obaro 2002 because he has above average knowledge as the "father of the immune interference". I do not agree. Dr. Dagan repeated several times during his cross-examination that he had understood his duty to step into the PSA's shoes and testify as to what the PSA would have known and been interested in at the time.

(c) *Bridging the Gap*

[134] Merck puts significant emphasis on the fact that Dr. Ravenscroft conceded the following during cross-examination, when matters are broken down and isolated:

> - The thirteen serotypes at issue were all part of the Pneumovax 23;
> - They were all of known structure;
> - They were all known to elicit immunogenic response before conjugation;
> - It would be expected that, if the PSA would conjugate those thirteen into a 13-valent with CRM, they would elicit an immune response;
> - Whatever the extent of cross-protection was, penicillin-resistant disease was left on the table by the 19F serotype contained in Prevnar 7;
>
> (Trial Transcript Vol 8, pages 1051-1060.)

[135] Merck also states that, "while you cannot directly compare studies with 5 to 7 to 9 valent PCVs to conclude that there is no loss of immunogenicity, scientists accept there was no negative impact on immunogenicity since it is not disproven." It may be true that "scientists do a funny thing … They assume something is true until it is disproven … That is how the hypothesis theory works in [their] field" (Trial Transcript Vol 8, page 1023, lines 10-15). However, it does not work the same way in the field of law. The party who bears the burden to prove a fact has to adduce positive evidence capable of convincing the Court that, on a balance of probabilities, the fact is accurate.

[136] The burden was on Merck to adduce evidence that the difference between the inventive concept of the Composition Claims and the state of the art was obvious to the PSA.

[137] In light of the common general knowledge, I do not believe that Merck has met its burden to prove that the PSA would have expected that if you made the 13-valent PCV conjugated with CRM_{197}, it would be immunogenic. The fact that the six serotypes not found in Prevnar 7 were known to be immunogenic because each was included, in unconjugated form, in one or both of Pneumovax® 14 and Pneumovax® 23, does not help Merck either. The evidence shows that conjugating is a complex endeavour; it also shows that the increasing reports on immune interference could have deterred the skilled person to pursue a 13-valent PCV all conjugated with CRM_{197}.

[138] I therefore agree with Wyeth that the composition of independent Claims 1 and 17 were not found in the prior art. The state of the art did not include an immunogenic composition comprising 13 individual pneumococcal conjugates (including 6A and 19A) using CRM_{197} as a single carrier protein. It follows that the composition Claims 2-5, 18 and 19, which depend directly or indirectly on Claims 1 and/or 17, by adding an adjuvant (or specific adjuvant(s)), were also not obvious at the priority date. The same can be said for the Use Claims 6 and 22 to 30.

(d) *Obvious to Try to Make a 13 Serotype Conjugate to CRM_{197}*

[139] In fields where advances are often won by experimentation – like the pharmaceutical industry – the test for obviousness also considers whether it would have been obvious to the

skilled person to try to obtain the invention (*Sanofi* at para 68). To conclude that an invention was "obvious to try" is to conclude that it was more or less self-evident to try to obtain the invention. One factor in the analysis is whether there is an expectation that what is being tried ought to work; however, it is not a formal requirement (*Hospira* at para 90). Yet, the mere possibility that something might turn up is not sufficient (*Sanofi* at para 66).

[140] In that vein, in *Sanofi*, the Supreme Court gave the following guidance regarding the fourth branch of the obviousness test:

> [69] If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> > 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
> >
> > 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
> >
> > 3. Is there a motive provided in the prior art to find the solution the patent addresses?
>
> [70] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.

[141] During a long and quite arduous cross-examination, Dr. Ravenscroft made a few crucial admissions:

- The PSA would have known that Wyeth had been testing an 11-valent (9-valent plus two more) all conjugated to CRM_{197}, in preclinical trials, for over two years;
- Nurkka 2004, a study on the immunogenicity of GSK's 11-valent conjugated with a single carrier protein D, demonstrated that the 11-valent was immunogenic (except for serotype 3) and safe in infants;
- At the time, Wyeth, Merck and GSK were using a single carrier protein, although GSK went to a multi-carrier protein later on. Only Aventis/Sanofi was using a multi-carrier protein – an approach that they later abandoned in favour of a protein only approach, which they also abandoned;
- An 11-valent had been achieved with protein D, but CRM_{197} is present in other childhood vaccines, making it hard to assume that a 13-valent with CRM_{197} would work without immune interference;
- However, the PSA would have tried to obtain a higher valency, with both caution but robust optimism; and,
- There was an apparent lack of cross-protection between serotypes 19F and 19A, as previously observed in polysaccharide alone vaccines.

[142] Wyeth tries to mitigate Dr. Ravenscroft's concessions and adds that in any event, no such concessions were made with respect to the Use Claims.

[143] In my view, it can be argued that Dr. Ravenscroft's concessions allow Merck to satisfy the first and third branches of the "obvious to try" test. It was more or less self-evident that what would be tried ought to work and there was a motive provided in the prior art to find the solution the patent addresses. The evidence shows that all those who were working on multi-valent

pneumococcal vaccines were working with basically the same serotypes, conjugated to a finite number of identified carrier proteins known to the PSA.

[144] However, and again considering the entirety of the evidence in light of who bears the burden, including Wyeth's course of conduct, I am not persuaded that the PSA would have achieved the invention without prolonged and arduous experimentation.

[145] Merck argues that the PSA of the 363 Patent has experience making conjugates and conjugate vaccines. Therefore, the PSA would not have experienced technical difficulties. I do not agree.

[146] First, the same observations as those previously made regarding enablement can be made here. It took Wyeth years of research and clinical testing to develop Prevnar® 13. The conjugate development process is complex and affected by many variables such as: the structure of the polysaccharide, the length of the polysaccharide chain, use of linker, the carrier protein, the ratio of polysaccharide to protein, how the polysaccharide is activated and conjugated to the carrier protein, and the conditions of conjugation (pH, temperature, time, reactants, etc.). [redacted]

The project was the culmination of [redacted] work on PCVs and was only possible because of the extensive expertise that Wyeth had developed over time.

[147] Second, the PSA did not have the extensive experience Wyeth had with CRM_{197}, and the PSA might not have gone to a single carrier solution as fast as Wyeth did. Further still, the PSA may have faced more difficulties than Wyeth did. [redacted] The art discloses that six main carriers were under consideration. The PSA could have selected any one of these or a combination of them. For example, Aventis Pasteur had used two carrier proteins. GSK was using three carrier proteins. There were five possible conjugation chemistries, and neither Aventis Pasteur nor Merck used reductive amination. This means there was extensive experimentation and optimization for each serotype required to produce a composition that resulted in an immunogenic 13-valent conjugate vaccine. In my view, it is unlikely that the PSA would have achieved the invention faster than Wyeth did, without the benefit of insight, and without prolonged and arduous experimentation.

[148] Third, Wyeth rightly points to the fact that, while major competitors were working on an 11-valent PCV, Wyeth leap-frogged its competitors and disclosed that it made a 13-valent immunogenic composition with a single carrier protein. Most experts admitted on cross-examination that it is possible that the competitors abandoned their 11-valent project for commercial reasons. Obviously when one ignores what motivated their decision, it is an easy, and quite trivial admission to make. The fact is that none of these products reached the market. I would add that it took Merck a little over a decade to come up with its 15-valent PCV, increasing the serotype coverage provided by Prevnar® 13 for the first time. Merck proudly argues that after years of clinical development, it has a newer and better vaccine: V114.

[149] In spite of Merck's able attempt to break down and simplify the invention disclosed by the Composition Patent, it did not convince the Court that, on a balance of probabilities, the development of a multivalent immunogenic conjugate composition containing polysaccharides with 13 specified pneumococcal serotypes, each individually conjugated to CRM_{197}, would have been routine work for the PSA. Therefore, Merck's attack on the Composition Claims must fail.

(5) Obviousness of the Method/Process Claims

[150] The inventive concept of the Method/Process Claims (Claims 13-14 and 36-38) is the elements of the claims themselves. Independent Claims 13, 36 and 38 incorporate the inventive concept of Claims 1 and 17; they generally pertain to the compositions of Claims 1 or 17 with the additional features and limitations provided by each claim. The inventive concepts of Claims 13-14 and 36-38 relate to methods or processes for making the compositions by following the particular steps set out in the claims.

[151] Claims 13-14 concern general methods for making the multivalent immunogenic composition of Claim 1. Claim 14 additionally specifies that conjugation is effected by reductive amination.

[152] Claims 36-38 disclose general processes for preparing the multivalent immunogenic composition of Claim 1. Claim 37 additionally specifies that conjugation is effected by reductive amination. Claim 38 specifies that after the conjugates are purified they are compounded to formulate the immunogenic composition.

[153] Since I found that Claims 1 and 17 were neither “obvious” nor “obvious to try”, I am also of the view that the invention disclosed in the Method/Process Claims would not have been achieved by the PSA without prolonged and arduous experimentation. Therefore, it was not “obvious to try”.

I. *Overbreadth/Inutility*

[154] Merck asserts that to the extent the Court finds that the Impugned Claims (other than Claim 17 and its dependents) cover compositions with more than 13 serotypes, those claims are invalid because they are overbroad and they lack utility.

[155] Since I found, in section II F) of these reasons, that Claim 1 of the 363 Patent is limited to 13 serotypes and does not disclose any “platform” for making a vaccine with greater coverage, there is no need for me to consider these additional limitations on the extent of the monopoly claimed by Wyeth.

III. <u>The Formulation Patents</u>

[156] Canadian Patent No. 2,650,056 [056 Patent] is titled “Novel Formulations which Stabilize and Inhibit Precipitation on Immunogenic Compositions”. It was filed on April 19, 2007, claiming priority to US 60/795,261 dated April 26, 2006. The 056 Patent was issued on July 16, 2013 and has not expired.

[157] Canadian Patent No. 2,803,111 [111 Patent] is also titled "Novel Formulations which Stabilize and Inhibit Precipitation of Immunogenic Compositions". It is a divisional application of the 056 Patent. It was filed on April 19, 2007, also claiming priority to US 60/795,261 dated April 26, 2006. The 111 Patent issued on June 16, 2015 and has not expired.

[158] The 056 Patent and 111 Patent together are referred to as the Formulation Patents.

A. *The Issues for the Formulation Patents*

[159] Merck asserts that Claims 1-3, 6-15, 17-24 and 29-38 of the 056 Patent, as well as Claims 1-12 and 16-28 of the 111 Patent [the Impugned Claims] are invalid for anticipation, obviousness and double patenting.

[160] Merck thus raises four main issues with respect to the Formulation Patents:

(1) What is the proper construction of the Impugned Claims?

(2) Are the Impugned Claims anticipated by Chiron?

(3) Are the Impugned Claims obvious?

(4) Are the Impugned Claims invalid for double patenting?

B. *The Formulation Patents' Witnesses*

(1) The Story of the Formulation Patents

[161] Dr. Lakshmi Khandke is Wyeth's fact witness and one of the inventors of the Formulation Patents. She worked on the formulation of vaccines at Wyeth for over 20 years and has relevant first-hand knowledge of the invention story for the Formulation Patents.

[162] Dr. Khandke explained the history of Wyeth's work with different vaccine formulations, the stability testing that Wyeth undertook, and its experience with pre-filled syringes. She provided detailed evidence of how the 13-valent vaccine formulations were developed, the aggregation problems that were encountered, and the solutions that were investigated and ultimately deployed.

[163] [redacted]

[164] [redacted]

[165] [redacted] Wyeth discovered that the precipitation was related to an excess of silicone oil.

[redacted] Tests [redacted] clearly identified silicone oil as the cause and adding a surfactant as the potential solution.

(2) Merck's Expert

[166] Dr. Nikolai Petrovsky is an expert formulator and a medical doctor. He holds a Ph.D. in immunology and vaccinology from The Walter and Eliza Hall Institute of Medical Research at the University of Melbourne. He is an expert in vaccine excipients and works to develop novel adjuvants that require reformulating vaccines. In that capacity, he has worked on formulating several vaccines, including polysaccharide-protein conjugate vaccines as well as vaccines for conditions from Swine Flu to cancer and Herpes to SARS, and most recently, COVID-19.

[167] Wyeth asserts that Dr. Petrovsky has an "unorthodox pedigree", and that he misled the Court when stating that "[s]urfactants were used in many protein and polysaccharide protein conjugate commercial vaccine formulations", but only one of the 16 products contained in a list he produced for the Court was a conjugate vaccine with a surfactant. However, aside from few inconsistencies, he was able to support his opinions during cross-examination. In fact, Wyeth's main attack on Dr. Petrovsky's credibility focused on his views regarding the origins of COVID-19 and his political views regarding the Chinese Communist Party, as well as the specific wording of his report.

(3) Wyeth's Expert

[168] Dr. Mark C. Manning is a pharmaceutical formulator who holds a Ph.D. in chemistry from Northwestern University. He has published papers on surfactants, protein stability and pharmaceutical formulations and he teaches other scientists how to formulate compositions. Manufacturers regularly hire him to solve formulation issues.

[169] Merck points to the facts that he has not published a single paper on polysaccharide-protein conjugate vaccines, nor on vaccines in general. Merck also points to inconsistencies revealed during his cross-examination and states that Dr. Manning "was thinking more about the impact his answers would have on the litigation than about his role as an independent expert." He did make some concessions in cross-examination.

C. *The Skilled Person of the Formulation Patents*

[170] There is no dispute that the PSA to whom the Formulation Patents are directed is a skilled formulator with protein expertise. However, Dr. Manning believes that the PSA would have more specific experience with vaccine formulations.

[171] Wyeth states that Dr. Petrovsky's suggestion that the PSA only needs experience with protein formulation makes little sense in the context of his report. After all, his common general knowledge is focused entirely on vaccines and his mandates are focused on vaccines.

[172] However, Wyeth ignores part of Dr. Petrovsky testimony at trial when he explained his position:

> And so this person would have had experience with protein-based formulations, and typically would have a PhD or a Master's degree, although not essentially, and they would have relevant work experience, generally in formulating protein-based compositions, both therapeutic proteins but also vaccine proteins.
>
> (Trial Transcript Vol 4, page 648, lines 1-6.)

[173] In other words, Dr. Petrovsky's PSA has broader expertise that subsumes the specific field of expertise recommended by Dr. Manning. Dr. Petrovsky explained why he prefers a broader approach:

> Because I think that the problems that we encounter in formulation very much revolve around the core molecules which, in this case, are the proteins. And therefore, it would be too restrictive to say it is someone who is working with just vaccines. And, in my experience, a lot of the people I employ to formulate and to be technicians working with me often have come from a background where their past experience has been in protein therapeutics. And therefore, you know, these people move back and forward.
>
> It is not that there is a profession of vaccine formulators and a different profession of protein formulators. I think, as we have heard from various experts in their reports, a lot of the people who work in this field, 90 per cent or more of their work is done in proteins, and in therapeutic proteins even, not as much in vaccines.
>
> So it is just the bulk of the work is in the field of protein formulation, and so the people who have this knowledge are generally protein formulators.
>
> (Trial Transcript Vol 5 Confidential, page 84, line 23 to page 85, line 14.)

[174] In my view, Dr. Petrovsky's approach makes sense both intrinsically and in the context of his entire testimony. The PSA of the Formulation Patents has experience generally in formulating protein-based compositions, both therapeutic proteins and vaccine proteins.

D. *The Formulation Patents – Claims Construction*

[175] Merck's position on claims construction is that the 056 Patent claims a stable formulation (including physical and chemical stability), and nothing else. In his report, Dr. Petrovsky states the following at paragraph 151:

> The term "stabilize" is not specifically defined in the 056 Patent but it does refer to both chemical stability (e.g. hydrolysis of saccharides, de-polymerization of polysaccharides proteolysis or fragmentation of proteins) as well as physical/thermal stability of the immunogenic composition (e.g. aggregation, precipitation, adsorption). No particular degree of stability is required by this claim and the Skilled Person would understand that reduction, or inhibition of aggregation would fall under the definition of a formulation which stabilizes a polysaccharide protein conjugate.
>
> [Footnote omitted.]

[176] In addition to arguing against reading in the limitation of "physical stability only", Merck points to the one occurrence where the Formulation Patents (under Background of the Invention) refers to chemical stability:

> Thus, when developing a formulation for an immunogenic composition, many factors must be considered to ensure a safe, stable, robust and cost effective product. Such considerations include, but are not limited to, chemical stability of the immunogenic composition (*e.g.*, hydrolysis of saccharides, de-polymerisation of polysaccharides, proteolysis of fragmentation of proteins), physical/thermal stability of the immunogenic composition (*e.g.* aggregation, precipitation, adsorption)
>
> (TX 1 at 2, lines 12-17.)

[Emphasis added.]

[177] As for the 111 Patent, Merck asserts that it claims a siliconized container means comprising certain specified ingredients, and nothing else.

[178] Wyeth, on the other hand, does not distinguish between the Formulation Patents, and instead argues the PSA would understand that the Formulation Patents speak specifically to physical stability, which refers to the inhibition of aggregation/precipitation, including precipitation caused by silicone oil. Dr. Manning opines that a fair reading of the Formulation Patents makes clear that the inventions are directed to the inhibition of precipitation and not stability more broadly. He refers to the plain words used to describe the Field of the invention and that are repeated throughout the Formulation Patents:

> The present invention generally relates to the fields of immunology, bacteriology, vaccine formulation, protein stability and process development. More particularly, the invention relates to novel formulations which inhibit precipitation of immunogenic compositions.
>
> (see TX 1 at 1, lines 12-15.)

[179] In construing the claims of a patent, recourse to the disclosure portion of the specification is permissible only to assist with understanding the terms used in the claims. It is precluded where the words are plain and unambiguous, and it is improper to vary the scope or ambit of the claims (*Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at para 39 [*Mylan*]).

[180] The disclosure portion of the 056 Patent and 111 Patent are identical. Both patents are entitled "Novel Formulations which Stabilize and Inhibit Precipitation of Immunogenic Compositions".

[181] Under the "Background of the Invention" section, the inventors state that "improving the stability of an immunogenic composition (e.g., a protein immunogen, a polysaccharide-protein conjugate) is a necessary and highly desirable goal" and that literature has suggested that silicone oil, "a necessary component of plastic syringes", might be responsible for the aggregation/precipitation seen in various protein based pharmaceutical preparations. Under this same section, the inventors go on to state that silicone oil, in addition to being a "necessary component of plastic syringes", is used for the following purposes: i) as a coating for glass vials to minimize protein adsorption, ii) as a lubricant to prevent conglomeration of rubber stoppers during filing procedures, iii) as a lubricant crucial to the processability/machinability of glass and elastomeric closures, and iv) as a lubricant to ease needle penetration of vial rubber stoppers.

(1) The 056 Patent

[182] Claim 1 is the only independent claim for the 056 Patent. It claims:

> A formulation which stabilizes a polysaccharide-protein conjugate, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) a surfactant and (iii) one or more polysaccharide-protein conjugates.

[183] I agree with Merck that the term "stabilizes" is not limited in the claims. The inventors could have limited the claims to physical stability but they chose otherwise. I believe, however, that this is a case where recourse to the disclosure portion of the specification does assist in

understanding the term “stabilizes” as used in the claims. The Field of the Invention states: “the invention relates to novel formulations which inhibit precipitation of immunogenic compositions.” That statement is repeated in the title, the Background, the Summary of the Invention, the Detailed Description of the Invention, and the Examples. In my view, the PSA would clearly have understood that, read as a whole, the claims of the 056 Patent were directed at a formulation that physically stabilizes and inhibits precipitation of immunogenic compositions.

[184] I also agree with Wyeth that the claims are limited to mean “stability against aggregation/precipitation”. I side with Wyeth on this for the same reason as before: the inventors make it clear throughout the patent that the invention relates to “novel formulations which stabilize and inhibit precipitation of immunogenic compositions”. In my view, that is equivalent to saying that the invention claims formulations that stabilize by way of inhibiting precipitation.

[185] However, I agree with Merck that the claims include precipitation caused by any factor.

[186] The Formulation Patents state that the terms “aggregation” and “precipitation” may be used interchangeably and are meant to refer to “any physical interaction or chemical reaction which results in the ‘aggregation’ of a polysaccharide-protein conjugate”. The patent provides a non-exhaustive list of factors that can cause precipitation/aggregation, including shear forces, shipping agitation, silicone oil interactions, adsorption, temperature, and humidity. In fact, Dr. Manning easily conceded that much in cross-examination:

Q. And if you go over to page 15 we see that the inventors specify what the invention is directed to. And on page 15 where it says "thus." …

"Thus the invention is as set forth herein as directed to novel formulations which stabilize and inhibit aggregation or precipitation of immunogenic compositions such as polysaccharide protein conjugates or protein immunogens against the various factors which influence the stability of immunogenic compositions."

Do you see that?

A. I do.

Q. So it's stabilizing and inhibiting aggregation or precipitation against various factors which influence the stability of immunogenic compositions, and they specify, or give examples at least, about what some of those factors are which can influence the stability of immunogenic compositions, and that includes sheer forces, shipping agitation, silicone oil interactions, absorption (sic), manufacturing processes, temperature, humidity, length of time between manufacture and usage, et cetera.

So this is a non-exhaustive list of factors which influence the stability of immunogenic compositions, correct?

A. It's a list of a variety of stresses that could cause problems, correct.

Q. And the inventors are telling us that the invention is directed to novel formulations which stabilize and inhibit aggregation or precipitation against those various factors, correct?

A. Yes. Against -- yes, against aggregation or precipitation that could be caused by one of these stresses.

Q. And silicone oil is one of those factors but not the only one, fair?

A. In this list it's among others, that's correct.

(Trial Transcript Vol 11, page 1475, line 23 to page 1477, line 2)

[187] I therefore find that the 056 Patent claims novel formulations that stabilize and inhibit aggregation/precipitation of immunogenic compositions, caused by any factor.

(2) The 111 Patent

[188] Claim 1 is also the only independent claim of the 111 Patent. It claims:

> A siliconized container means filled with a formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminum salt and (iii) one or more polysaccharide-protein conjugates comprising one or more pneumococcal polysaccharides.

[189] The 111 Patent contains claims to a siliconized container means filled with a formulation comprising a buffer, an aluminum salt and one or more polysaccharide-protein conjugates comprising one or more pneumococcal polysaccharides.

[190] Wyeth is asking the Court to construe the 111 Patent to claim a stable formulation that prevents precipitation, just as it did for the 056 Patent. Despite the fact that the claim makes no mention of stability or preventing aggregation, Dr. Manning reads that into the claim through the words “aluminum salt”. In Dr. Manning’s view, “the [PSA] would have understood, based on the description provided, that the aluminum salt functions to stabilize the polysaccharide-protein conjugate(s) against silicone oil induced aggregation” (Manning Report at para 243(b)).

[191] I agree with Merck that the 111 Patent claims a formulation in a siliconized container with specific excipients. It does not reference stability or stabilizing a formulation by preventing precipitation.

[192] In any event, I also agree with Merck that, to the extent the 111 Patent claims a formulation that stabilizes against precipitation, the PSA would understand that it protects against precipitation caused by any physical interaction. Although Dr. Manning expressed a contrary view in his report, he revised his position at trial:

> Q. I would suggest to you based on what we've just read in the patent and the definition of aggregation we've seen, that if the skilled person is going to read the inventive concept of the claim to include an aluminum salt that stabilizes the conjugates against aggregation, it's not going to be limited to silicone oil-induced aggregation but rather to stabilize the conjugates against any type of aggregation, or any cause of aggregation. Agreed?
>
> A. Yeah. I stated, like you said, and other places and I probably should have been more careful to do so.
>
> Q. What this should read like the '056 patent is that the aluminum salt stabilizes the conjugates against aggregation?
>
> A. And in particular, silicone oil-induced aggregation. I think that's how I phrased it earlier, yes.
>
> Q. But it is not limited to stabilizing the conjugates against silicone oil-induced aggregation. That's just one example. Fair?
>
> A. That is one example.
>
> Q. It would also include aggregation caused by other factors that are set out in the patent, for example. Yes?
>
> A. Yes. As we talked about before, the person of skill would understand there is other stresses that could lead to the aggregation process.
>
> Q. And one of those stresses that the aggregation -- that the inventive concept of claim is '111 would include would be aggregation that is caused by , for example?
>
> A. That's what the inventors list, yeah.
>
> (Trial Transcript Vol 11, page 1492, line 13 to page 1493, line 16.)

E. *Anticipation: The Formulation Patents v Chiron*

[193] As discussed above, a patent is anticipated if the subject matter of its claims was disclosed and enabled before the claim date, in a single piece of prior art.

(1) The Chiron Patent

[194] Merck asserts that as of April 26, 2006, the Chiron patent number WO 03/009869, filed on July 22, 2002 and published in English on February 6, 2003 [Chiron Patent], anticipated the subject-matter of certain claims found in the Formulation Patents – specifically, Claims 1 to 3, 6 to 12, 15, 17, 21 to 24 and 29 to 38 of the 056 Patent as well as Claims 1 to 7, 9 to 12, 16 to 17 and 22 to 28 of the 111 Patent.

[195] The title of the Chiron Patent is "Vaccines Comprising Aluminium Adjuvants and Histidine". Its abstract states that, "[t]o improve the stability of vaccines comprising aluminium salt(s), the invention uses the amino acid histidine. This can improve pH stability and adjuvant adsorption and can be [sic] reduce antigen hydrolysis. Histidine is preferably presen [sic] during adsorption to the aluminium salt(s). The antigen in the vaccine may be a protein or a saccharide and is preferably from N. meningitidis."

[196] The inventors disclose that they were able to achieve a stable formulation by discovering that "the amino acid histidine enhances the stability of vaccines which include aluminium salt adjuvants" (Chiron Patent at 1, lines 31-32). The inventors state that, "[t]he invention thus

provides a composition comprising an antigen, an aluminium salt and histidine" (Chiron Patent at 2, line 1).

(2) Disclosure

[197] Merck argues that all essential elements of the Formulation Patents are disclosed by the Chiron Patent because it discloses a formulation comprising:

> (a) a polysaccharide-protein conjugate, wherein the carrier protein is CRM_{197} and the antigen is a saccharide from *Streptococcus pneumoniae*;
>
> (b) a saline solution;
>
> (c) a buffer with a pKa of about 3.5 to about 7.5;
>
> (d) an aluminum salt adjuvant; and,
>
> (e) possibly a surfactant.

[198] Wyeth denies any disclosure for the following reasons:

> (a) Chiron focuses on chemical stability; it does not disclose a formulation containing a surfactant that stabilizes against aggregation, as the Formulation Patents do;
>
> (b) The optional surfactant included in Chiron focuses on adsorption, not aggregation;
>
> (c) Chiron does not disclose siliconized container means.

(a) *Use of Surfactants/Aluminum Salt in the Chiron Patent*

[199] According to Dr. Manning in his Report, a PSA reviewing the Chiron Patent would have learned about the use of histidine in a vaccine formulation with an aluminum adjuvant and an antigen:

> 252. …
>
> (a) Histidine can be used to keep the pH of the vaccine formulation stable (i.e., minimize shifts in the pH value). A [PSA] would have understood that this is one function of a buffer.
>
> (b) Moreover, the Chiron Application teaches that the modulation of pH can reduce the hydrolysis of saccharide antigens. In other words, the control of pH appears to prevent polysaccharide antigens from breaking down into smaller fragments. The [PSA] would have understood that maintaining the chemical stability of the polysaccharide antigen would be important to maintaining the immunogenicity of the vaccine.
>
> (c) The Chiron Application also notes that control of pH can help prevent desorption of the antigens from the adjuvant. As I have described above, antigens bound to an adjuvant are understood to be more immunogenic. Thus, it is suggested in the Chiron Application that, by controlling the pH, histidine can prevent the desorption of the antigen from the surface of the adjuvant, which could result in the loss of immunogenicity.
>
> (d) It is also suggested that histidine, which can exist as a positively charged molecule (in its conjugate acid form), could improve the binding of negatively charged antigens to negatively charged aluminum salt adjuvants, like aluminum hydroxyphosphate, by masking their negative charges.
>
> [Footnotes omitted.]

[200] In simpler words, Dr. Manning is of the view that the Chiron Patent focuses on chemical stability. As he rightfully pointed out, there is not a single mention of aggregation or precipitation in the Chiron Patent, which addresses a different formulation issue: the use of histidine to stabilize pH, which, in turn, prevents the degradation of antigens.

[201] While each of the claims of the 056 Patent call for a surfactant to be used, in combination with a buffered saline solution, to stabilize conjugate vaccine formulations against aggregation, the Chiron Patent teaches that a surfactant “may” be added to the formulations disclosed in order

to “minimize adsorption of antigens to containers.” Dr. Manning notes that the Chiron Patent refers to a surfactant, polysorbate 80 (also known as Tween 80), in three places:

> 1. On page six, under the heading “Further Characteristics of the Invention”, the inventors discuss various formulation permutations. Between the observation that the composition will “generally be sterile” and the observation that the composition “preferably does not contain a preservative”, there is the following sentence:
>
> > The composition may comprise a detergent (*e.g.* a Tween, such as Tween 80) in order to minimize adsorption of antigens to containers.
>
> 2. On page seven, under the heading “Further Components of the Invention”, the inventors describe additional components that may be added to the composition of the invention like certain “pharmaceutically acceptable carriers”. In this section, the inventors also suggest that the composition could include a second adjuvant in addition to the aluminum adjuvant contemplated in the invention. In three cases, that second adjuvant includes a surfactant in its composition.
>
> 3. In three interconnected examples provided in the Chiron Patent (examples 7, 8 and 9), there is mention of a surfactant. According to Dr. Manning, a PSA would have understood that Tween 80 was added to these formulations to minimize adsorption of the antigen to the container.

[202] Although Dr. Manning agrees that, in certain circumstances, adsorption could potentially lead to denaturation, which can possibly lead to aggregation, there is no direct link between these concepts. In his view, the PSA would have known that adsorption (or “sticking”) of the antigen to the container could affect immunogenicity by reducing the amount of antigen available in the formulation. The PSA would have understood that adsorption to container walls would be of a particular concern when antigen concentrations are low (<1 mg/mL). The PSA would not have understood that a surfactant should be added to eliminate aggregation/precipitation.

[203] In addition, the Chiron Patent only refers to aluminum salts as adjuvants (generally used to boost the immunogenicity of a vaccine), but not for use to prevent aggregation/precipitation.

[204] Again, citing the Supreme Court in *Sanofi* at para 21 (which cited *General Tire & Rubber Co v Firestone Tyre & Rubber Co*, [1972] RPC 457 (Eng CA) at 486), "[a] signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee." In my view, the Chiron Patent is just that: a signpost upon the road to Wyeth's claimed invention.

(b) *Siliconized Container Means*

[205] The only direct reference to a container in the Chiron Patent is to vials, which are not systematically siliconized. On the other hand, there is no doubt that the Chiron Patent refers to vaccines being "injected" or being prepared as an "injectable" and therefore implicitly discloses the use of syringes. [redacted]

However, Dr. Manning points to the fact that the formulations in the Chiron Patent are meant to be held in vials until injection. As a result, the formulation only comes into contact with the syringe at the moment of administration. He provides a simple and logical explanation for why silicone container means are not essential to the Chiron Patent:

> A. … Keep in mind that this is being done after -- one stores it in the vial, they are withdrawing it into the syringe. The syringe would be siliconized in order to allow the plunger to move up and down easily. But the length of time it would be exposed to any silicone oil there, and presumably over that period of time virtually all the silicone oil would hopefully stay in place on the surface.

> And so as a result, the amount of exposure is unknown, but probably extremely small.
>
> (Trial Transcript Vol 10, page 1326, lines 5-13)

[206] Dr. Manning also pointed out that the Chiron Patent does not include any discussion of silicone oil aggregation. Since silicone oil is used to prevent adsorption, the use of Tween 80 in the Chiron Patent for that same purpose rather suggests that the vials are not siliconized.

[207] For these reasons, I agree with Wyeth that the Chiron Patent does not disclose "siliconized container means".

(3) Enablement

[208] Given that I find the Chiron Patent did not disclose the subject matter of the invention, I need not consider enablement. In any event, there is, in my view, no evidence of enablement.

[209] As indicated above, the test for enablement is that the prior patent must provide enough information to allow the performance of the subsequently claimed invention without undue burden (*Sanofi* at para 37).

[210] The only evidence adduced by Merck on enablement is a single sentence found in Dr. Petrovsky's report:

> 229. … The Skilled Person could have readily made the formulations described in the Chiron Patent using reasonable skill and knowledge.

[211] The Court, not being a PSA of the Formulation Patents, cannot fill in the blanks in Merck's evidence.

[212] Moreover, I agree with Wyeth that Dr. Petrovsky's evidence misses the target. The question is whether using the disclosures in the Chiron Patent, the PSA could have made the claims in the Formulation Patents. Dr. Petrovsky does not address this question, and in the absence of this evidence, Merck cannot meet its burden.

F. *Obviousness*

[213] The legal principles concerning the obviousness analysis are set out above. As Merck rightfully notes, in the context of vaccine formulation, the often time-consuming and expensive work of optimizing a vaccine, conducting clinical trials and obtaining regulatory approvals for a safe and immunogenic composition, while important, is not inventive (see *Amgen Inc v Pfizer Canada ULC*, 2020 FC 522 at para 425, aff'd 2020 FCA 188). In considering the question of obviousness, the Court will consider whether the invention as claimed would have been obvious to the PSA.

[214] In my view, Merck has met its burden to prove that the Formulation Patents are invalid for obviousness, with the exception of the serotype selection claims that are, in my view, invalid for double patenting and which I will discuss in the next section. Merck met its burden mainly by way of its cross-examination of Dr. Manning.

(1) The Common General Knowledge and State of the Art

[215] The experts' respective descriptions of the PSA drive their positions on obviousness, and they are diametrically opposed. Dr. Manning's focus is on multivalent polysaccharide conjugate vaccines; as there were only two at the relevant time – Prevnar 7 and Menactra® – he views the common general knowledge of the PSA as rather limited. In the absence of information directly on point, Dr. Manning concedes that the PSA would have looked to information on monovalent conjugate vaccines. Again, there was little information on formulating conjugate vaccines. Dr. Manning recognizes that the PSA would eventually consider vaccine art in general, although not readily transferable to conjugate antigens. At the outer ring of relevance, Dr. Manning identified information related to therapeutic protein formulations, with several layers of caveats. For him, silicone oil induced aggregation was an unknown problem with an unknown solution at the time.

[216] However, Dr. Manning considerably departed from his initial position during cross-examination.

[217] Dr. Petrovsky, on the other hand, views the common general knowledge of the PSA as including prior art on all protein formulations; after all, aggregation/precipitation is a problem caused by the protein antigens, not by the polysaccharide component of the vaccine.

[218] As I already found that the PSA of the Formulation Patents has experience generally in the formulation of protein-based compositions, both therapeutic proteins and vaccine proteins, I

prefer Dr. Petrovsky's approach to common general knowledge and his consideration of the relevant prior art.

[219] That said, the experts agree that as of April 2006, there were a limited number of common vaccine excipients, such as buffers, adjuvants, surfactants, stabilizers and preservatives, which were routinely considered and tested when formulating vaccines.

(a) *Buffers*

[220] As of April 26, 2006, buffers were commonly used vaccine excipients that were known to improve vaccine stability. There were a limited number of buffers that were used in vaccine formulations. Phosphate buffers were, and remain, the most commonly used. While Dr. Manning downplayed the prevalence of buffers in his report, he ultimately acknowledged that buffers were present in 42% of licensed vaccines available at the time.

[221] Dr. Manning conceded in his report that it was common general knowledge that buffers could be used to maintain the pH of a formulation at a level that optimally maintained vaccine stability. He also agreed on cross-examination that a leading textbook, Akers 2002 at 52 (TX 82), disclosed buffers as a solution to aggregation and precipitation problems and that the solutions presented in Akers 2002 were common general knowledge (Trial Transcript Vol 10, page 1405, lines 1-26). Therefore, a PSA would have added a buffer if required to control the pH of a 13-valent polysaccharide-protein conjugate vaccine (Trial Transcript Vol 11 page 1451, line 4 to page 1452, line 6).

(b) *Aluminum Salts*

[222] Before April 26, 2006, aluminum salts were widely used and were known stabilizers. A PSA would have used an aluminum salt if a formulation had an aggregation or precipitation issue. Aluminum salt adjuvants were known and used in vaccines including the Vaxem HIB, PedvaxHIB, Meningitec, Mejugate and JEV vaccines, as well as Prevnar 7. There is no dispute that aluminum was the most commonly used adjuvant.

[223] In his report, and in his testimony in chief, Dr. Manning testified that aluminum salts were not known to have a stabilizing effect or to prevent aggregation; rather, they were mainly known to act as boosters. However, on cross-examination, he revised his position. Powell & Newman 1995, the leading vaccine formulation textbook , expressly teaches that an aluminum adjuvant can be used to prevent adsorption and stabilize a formulation:

> Protein adsorption can be prevented by increasing the protein concentration in the formulations or by the addition of appropriate carrier molecules, such as particulate alum[inum] or surfactants.
>
> (TX 79 at 25.)

[224] In any event, since Dr. Manning's focus is on multivalent polysaccharide protein conjugate vaccines, he had to agree that if a PSA were asked to formulate a 13-valent polysaccharide-protein conjugate vaccine, they would have included an aluminum salt because one was present in Prevnar 7 (Trial Transcript Vol 10 at page 1433, line 22 to page 1434, line 14). Dr. Manning also conceded that if the PSA was trying to match the composition of Prevnar 7, which is stable, then perhaps the ratio of aluminum salt is important to consider. If a PSA is in fact trying to make minimal changes to the formulation, as formulators normally do,

then the ratio of aluminum salt is one of the first things to consider. A PSA would have known how to perform experiments to adjust the ratio of aluminum salt and determine whether it prevented aggregation (Trial Transcript Vol 10, page 1434, line 25 to page 1436, line 26).

(c) *Siliconized Containers*

[225] Through dependent Claim 36 of the 056 Patent and dependant Claims 25 and 28 of the 111 Patent, the inventors include a stable formulation in a siliconized pre-filled glass syringe. As indicated above, it was well known in April 2006 that syringes were siliconized to facilitate sliding the plunger into the syringe. The Formulation Patents clearly states:

> Paradoxically, silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (*i.e.*, silicone oil improves the syringeability of the formulation)
>
> (TXs 1 and 2 at 2, lines 34-37.)

[226] In any event, if the Court were to follow Dr. Manning's views on common general knowledge (*i.e.* somewhat restricted to the two previous multivalent polysaccharide conjugate vaccines), the PSA formulating a 13-valent polysaccharide protein conjugate vaccine would have followed the teaching of Prevnar 7 and used pre-filled siliconized syringes.

(d) *Surfactants*

[227] In his report, Dr. Manning provides some useful background information on aggregation/precipitation:

> 114. **Aggregation** occurs when molecules clump together, usually irreversibly, through strong, non-specific and non-covalent

> interactions. The resulting groups of molecules, known as **aggregates**, may be soluble or insoluble. Aggregates that are insoluble may or may not be large enough to be visible to the naked eye. Proteins, for example, could be induced to aggregate by various mechanisms in response to exposure to different types of stress (*e.g.*, elevated temperature, changes in pH, freezing). By April 2006, it was known that aggregation could occur in vaccine formulations containing aluminum salt particles upon exposure to freezing temperatures.
>
> 115. **Precipitation** can occur when aggregates become too large to remain in solution and form insoluble particles that are visible and can sediment to the bottom of the container. This solid is known as a **precipitate**. Thus, some, but not all, aggregation may result in precipitation. By April 2006, it was known that precipitation in a pharmaceutical formulation could be the consequence of poor solubility of formulation components or the formation of insoluble aggregates due to various environmental factors. Precipitates could cause a loss of a vaccine's potency because they could reduce the amount of antigen that is effectively administered. Furthermore, precipitation may raise concerns among medical personnel and patients that the formulation is not safe or effective.
>
> [Emphasis in original; Footnotes omitted.]

[228] Merck presented convincing evidence that by April 2006, surfactants were a well-known solution to aggregation in a formulation. Dr. Manning did not deny that surfactants were known to prevent aggregation in therapeutic protein formulations but suggested that it was unknown that a surfactant could be used to prevent aggregation in a vaccine.

[229] Both experts agreed that Powell & Newman 1995, the leading textbook on subunit vaccines (such as polysaccharide-protein conjugate vaccines), is relevant to the Formulation Patent and was familiar to the skilled formulator in April 2006. Chapter 1 is entitled "Immunological and Formulation Design Considerations for Subunit Vaccines", which is the

subject matter of the Formulation Patents, and Chapter 1 teaches that the use of surfactants stabilizes a formulation and prevents adsorption and aggregation:

> Physical instability of proteins that are used as immunogens may compromise vaccine formulation stability. This can occur in several ways such as loss of protein via adsorption of the protein immunogen to the surface of the container or possibly by protein aggregation and subsequent denaturation … A well characterized example is insulin which readily adsorbs to hydrophobic surfaces and subsequently denatures. Denatured insulin molecules then accumulate resulting in the formation of non-functional aggregates…
>
> Protein adsorption can be prevented by increasing the protein concentration in the formulations or by the addition of appropriate carrier molecules, such as particulate alum or surfactants. Surfactants, such as those used in many emulsion-based adjuvant formulations, are useful because they bind to the hydrophobic areas of both the soluble protein and the container surfaces and inhibit protein adsorption.
>
> (TX 79 at 25.)

[230] Dr. Manning's view that protein literature is at the outer ring of relevance for the PSA of the Formulation Patents was compromised by the reference to his article on protein stability made by Powell & Newman 1995 while discussing the stability of vaccines:

> To better understand the factors affecting the stability of subunit vaccines, we recommend several excellent reviews on protein stability in parenteral formulations covering general stability concerns for pharmaceuticals (Mollica *et al*., 1978, Manning *et al*., 1989)
>
> (TX 79 at 24.)

[231] In Dr. Manning's 1989 article, he wrote:

> Detergents [*i.e*. surfactants] have often been employed as additives for the stabilization of proteins … nonionic detergents, such as Tween … have been evaluated for their ability to prevent

> adsorption of proteins to surfaces … [and] to inhibit aggregation and precipitation.
>
> (TX 80 at 911.)

[232] In 2005, Dr. Manning co-authored another article teaching the use of a surfactant to prevent aggregation. The authors wrote:

> There are several known mechanisms for protein stabilization by surfactants. First, non-ionic surfactants can protect proteins against surface-induced damage by competing with proteins for adsorption sites on surfaces. In addition, as has been demonstrated with human growth hormone (hGH), nonionic surfactants can protect protein against surface-induced aggregation by binding to hydrophobic regions of the surface of the protein molecule, and thus decrease intermolecular interactions.
>
> (Chou 2005, TX 81 at 1369.)
>
> [Footnotes omitted.]

[233] Other prior art made it abundantly clear that in April 2006, aggregation was a common stability problem and surfactants were a common solution (see for example, Akers 2002 at 52; Wang 2005, TX 90 at 13).

[234] Confronted with those publications, Dr. Manning had to concede that the stability problems that are listed by the authors, and their possible solutions, were common general knowledge to the PSA: they were "presenting information that was, yes, widely known" (Trial Transcript Vol 10, page 1405, lines 25-26).

[235] Dr. Manning agreed that the skilled person would know how to select a surfactant and determine the appropriate concentration (Trial Transcript Vol 11, page 1481, lines 19-24). He

also agreed that the skilled person could perform experiments in a “fairly short period of time” to confirm a surfactant would prevent aggregation (Trial Transcript Vol 10, page 1420, line 13 to page 1421, line 3).

[236] Dr. Manning’s concessions combined with the literature available in April 2006 support Dr. Petrovsky’s opinion that it would have been obvious to the PSA to try adding a surfactant to a vaccine formulation to solve an aggregation problem.

(e) *Serotype Selection*

[237] The 7-valent claims (Claims 19 of the 056 Patent and Claim 20 of the 111 Patent) were obvious as of April 2006. Prevnar 7 had been on the market for years and was well known.

[238] However, I agree with Wyeth that the 13-valent claims (Claims 18 and 20 of the 056 Patent and Claims 19 and 21 of the 111 Patent) raise unique obviousness issues that must be considered separately. These claims specify stable formulations for a 13-valent composition of pneumococcal polysaccharides each conjugated to CRM_{197}.

[239] As indicated above, while Wyeth had previously disclosed the serotypes in its 13-valent conjugate vaccine, it did not disclose the carrier protein(s) it was using. More importantly, neither Dr. Petrovsky’s nor Dr. Manning’s PSA would have had any experience with conjugation or carrier protein selection. In these circumstances, the selection of CRM_{197} as a single carrier protein would not have been obvious; neither would the serotype selection claims of the

Formulation Patents. However, and as will be discussed below, they would have been obvious in light of the claims of the Composition Patent (obviousness-type double patenting).

(2) State of the Art vs Inventive Concept

[240] For several reasons, I agree with Merck that the formulations disclosed in the Formulation Patents (except for the serotype selection claims) would have been obvious to the PSA in light of the common general knowledge and the state of the art. As of April 26, 2006:

a. The experts agree that siliconization of containers was common and that siliconization of syringes was the norm. The PSA attempting to formulate a 13-valent polysaccharide-protein conjugate vaccine would have used a siliconized syringe.

a. The use of aluminum adjuvants was common. Several vaccine formulations included aluminum adjuvants, and it was known that aluminium adjuvants had a stabilizing function and could prevent aggregation (Powell & Newman 1995 at 25). A PSA attempting to formulate a 13-valent polysaccharide-protein conjugate vaccine would have used an aluminum salt.

b. The use of buffers was also common. Numerous vaccines included buffers, and it was known buffers had a stabilizing effect (Akers 2002 at 52). The PSA formulating a 13-valent polysaccharide-protein conjugate vaccine would have included a pH buffered saline solution, if necessary.

[241] All that was left to decide for the PSA facing an aggregation problem was whether it would have been obvious to use a surfactant to solve it. In my view, the prior art is abundantly clear that it would have been at least obvious to try to obtain stability by adding a surfactant.

[242] By April 26, 2006 surfactants – Polysorbate or Tween 80 in particular – were a commonly used excipient that are described throughout the literature as a "common" and "simple" solution to prevent adsorption and aggregation. The leading textbook on vaccine formulation (Powell & Newman 1995) taught the use of a surfactant to stabilize a formulation and prevent aggregation. In my view, there was nothing inventive about trying a surfactant to see if it would work in a polysaccharide-protein conjugate formulation. It was an obvious solution to a well-known problem. Wyeth's course of conduct, in my view, confirms this finding.

(3) The Inventors' Course of Conduct

[243] The experts' take away on Wyeth's course of conduct is, again, diametrically opposed. Dr. Petrovsky focuses on what Wyeth did when confronted with the problem of aggregation, whereas Dr. Manning extended his review of Wyeth's course of conduct to the work its scientists conducted on [redacted]

[244] Considering that one cannot search for a solution before being faced with a problem, I prefer Dr. Petrovsky's chronology of events.

[245] [redacted]

[246] [redacted] It has nothing to do with obviousness or inventiveness.

[247] While it took some time to optimize the formulation and complete the regulatory process, Wyeth was able to quickly confirm the effectiveness of the formulations disclosed in the Formulation Patents.

[248] [redacted]

[249] In my view, the fact that the formulations disclosed in the Formulation Patents (except for the 13-valent claims) were obvious is demonstrated by the time it took Wyeth to determine the following: [redacted]

[redacted] Wyeth did exactly what the PSA would have done to solve a similar problem.

G. *Double Patenting*

[250] The doctrine of double-patenting prevents a patentee from "evergreening" or from extending the monopoly given by a first patent by filing a new patent that does not disclose a new invention to the public (*Mylan* at para 26).

[251] There are two types of double-patenting. One type occurs when the claims of the second patent are "identical or coterminous" to the first. The other occurs when the second patent, while not identical, is nonetheless not "patently distinct" from the first. In all cases, the focus is on the earlier patent and "any other prior art is only relevant insofar as it contributes to the common general knowledge of the PSA" (*Mylan* at para 29).

[252] Claim 31 of the 363 patent claims:

> A single dose syringe filled with a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F individually conjugated to CRM_{197}, wherein each 0.5 ml dose is formulated to contain 2.2 μg of each saccharide, except for 6B at 4.4 μg; 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant; and sodium chloride and sodium succinate buffer.

[253] I agree with Merck that the 111 Patent claims a formulation comprising the same ingredients. I also agree, as stated above, that as of April 8, 2005 or April 26, 2006, the use of a siliconized container means would have been obvious. Example 15 of the 363 Patent also

provides that the vaccine formulation is filled into “Type 1 borosilicate glass syringes” which were known by the PSA to be siliconized.

[254] As for the 056 Patent, it broadly claims a formulation containing one or more polysaccharide protein conjugates, a pH buffered saline solution with a pKa of about 3.5 to 7.5, and a surfactant. For the reasons described above, adding a surfactant to a polysaccharide protein conjugate vaccine was routine, common, and would have been obvious.

[255] In my view, the claims of the Formulation Patents are all obvious variants of the invention claimed in the 363 Patent that claims a composition of 13 specific pneumococcal polysaccharides conjugated to the carrier protein CRM_{197} in a buffer with aluminum phosphate.

[256] The 13-valent claims (Claims 18 and 20 of the 056 Patent and Claims 19 and 21 of the 111 Patent) of the Formulation Patents are therefore invalid for obviousness-type double patenting.

IV. Conclusion

[257] The parties ably argued their respective positions before this Court. Merck has partly succeeded in meeting its burden.

[258] Merck successfully argued that Claim 1 of the 363 Patent is limited to 13 serotypes and that no particular level of immunogenicity should be read into Claim 1 of the 363 Patent.

However, I find that Claims 1-6, 13-14, 17-19, 22-30, and 36-38 of the 363 Patent are valid, though limited to 13 serotypes.

[259] Merck successfully argued that the Formulation Patents are invalid for obviousness, with the exception of the serotype selection claims that are invalid for double patenting.

[260] As a result, I find that Claims 1-3, 6-15, 17-24, and 29-38 of the 056 Patent as well as Claims 1-12, 17-28 of the 111 Patent are invalid, void, unenforceable and of no effect.

V. Costs

[261] The parties are invited to provide the Court with submissions as to the granting of costs. Submissions may not exceed five pages and must be filed within 30 days of this Judgment and Reasons.

PUBLIC JUDGMENT in T-1184-17

THIS COURT'S PUBLIC JUDGMENT is that:

1. The Plaintiff's action is granted in part;
2. Claims 1-6, 13-14, 17-19, 22-30, and 36-38 of Canadian Patent No. 2,604,363 are valid but limited to 13 serotypes;
3. Claims 1-3, 6-15, 17-24, and 29-38 of Canadian Patent No. 2,650,056 and Claims 1-12, 17-28 of Canadian Patent No. 2,803,111 are invalid, void, unenforceable and of no effect pursuant to subsection 60(1) of the *Patent Act*;
4. The parties shall provide submissions regarding costs, not exceeding five pages, within 30 days of this Judgement and Reasons.

"Jocelyne Gagné"
Associate Chief Justice

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1184-17
STYLE OF CAUSE:	MERCK SHARP & DOHME CORP., and MERCK CANADA INC. v WYETH LLC
PLACE OF HEARING:	HELD BY VIDEOCONFERENCE BETWEEN OTTAWA, ONTARIO (COURT) AND TORONTO, ONTARIO (PARTIES)
DATES OF HEARING:	NOVEMBER 30, 2020 and DECEMBER 1-4, 7-11, 14, 21-22, 2020
JUDGMENT AND REASONS:	GAGNÉ A.C.J.
CONFIDENTIAL JUDGMENT AND REASONS ISSUED:	APRIL 14, 2021
PUBLIC JUDGMENT AND REASONS ISSUED:	APRIL 30, 2021

APPEARANCES:

Steven G. Mason Sarit E. Batner Rebecca Crane Fiona Légère Edwin Mok Richard Lizius Laura E. MacDonald Sharanya Thavakumaran	FOR THE PLAINTIFFS
Orestes Pasparakis Joanne Chriqui Amy Grenon Christopher A. Guerreiro Andrea Campbell Morgan Westgate Jonathan Chong Fortunat Nadima Nadima Shantelle Lafayette	FOR THE DEFENDANT

SOLICITORS OF RECORD:

McCarthy Tétrault LLP Toronto, ON	FOR THE PLAINTIFFS
Norton Rose Fulbright Canada LLP Toronto, ON	FOR THE DEFENDANT