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Case Number: T 0787/14 - 3.3.04

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Title of invention:
Meningococcal conjugate vaccination

Patent Proprietor:
GlaxoSmithKline Biologicals SA

Opponents:
Pfizer Inc.
Sanofi Pasteur, Inc. (opposition withdrawn)

Headword:
Meningococcal conjugate vaccination/GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request, auxiliary requests 1 to 6: inventive step - (no)

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T 1285/13

Catchword:

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Beschwerdekammern

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Case Number: T 0787/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 February 2019

Appellant: (Patent Proprietor)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Dalton, Marcus Jonathan William GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Opponent 1)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 18 March 2014 revoking European patent No. 1740217 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietor ("appellant") lies against the opposition division's decision revoking European patent No. 1 740 217, entitled "*Meningococcal conjugate vaccination*" (the patent).

II. Two oppositions were filed against the patent. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.

III. In the course of the opposition proceedings opponent 2 withdrew its opposition.

IV. The opposition division decided *inter alia* that the subject-matter of the main request and of auxiliary requests 1 and 3 to 7 did not meet the requirements of Article 56 EPC and that the subject-matter of auxiliary request 2 did not meet the requirements of Article 123(2) EPC. Auxiliary request 3', submitted during the oral proceedings, was not admitted into the proceedings.

V. With the statement of grounds of appeal, the appellant filed sets of claims of a main request and of auxiliary requests 1 to 6. The set of claims of the main request corresponded to the set of claims of the main request underlying the decision under appeal; the sets of claims of auxiliary requests 1, 2 and 5 corresponded to those of auxiliary requests 1, 2 and 3' underlying the decision under appeal. The sets of claims of auxiliary requests 3, 4 and 6 were newly filed.

Claim 1 of the main request reads as follows:

"1. A composition that comprises: (a) a conjugate of (i) the capsular saccharide of serogroup A *N.meningitidis* and (ii) a diphtheria toxoid or CRM197; (b) a conjugate of (i) the capsular saccharide of serogroup C *N.meningitidis* and (ii) a diphtheria toxoid or CRM197; (c) a conjugate of (i) the capsular saccharide of serogroup W135 *N.meningitidis* and (ii) a diphtheria toxoid or CRM197; and (d) a conjugate of (i) the capsular saccharide of serogroup Y *N.meningitidis* and (ii) a diphtheria toxoid or CRM197, for use in a method for immunising a human patient against a disease caused by *Neisseria meningitidis* comprising the step of administering to the human patient the composition, wherein the patient has been pre-immunised within 1 year of the patient's birth with a conjugate of (i) a capsular saccharide of an organism other than *N.meningitidis* and (ii) a diphtheria toxoid or CRM 197, and wherein the patient was pre-immunised at least six months before the method."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that it specifies that each of the capsular saccharides of *N.meningitidis* referred to in the claim is conjugated to CRM197.

Claim 1 of auxiliary request 2 reads as follows:

"1. A composition that comprises: (a) a conjugate of (i) the capsular saccharide of serogroup A *N.meningitidis* and (ii) CRM197; (b) a conjugate of (i) the capsular saccharide of serogroup C *N.meningitidis* and (ii) CRM197; (c) a conjugate of (i) the capsular saccharide of serogroup W135 *N.meningitidis* and (ii) CRM197; and (d) a conjugate of

(i) the capsular saccharide of serogroup Y *N.meningitidis* and (ii) CRM197, for use in a method for immunising a human patient against a disease caused by *Neisseria meningitidis* comprising the step of administering to the human patient the composition, wherein the patient has been pre-immunised within 1 year of the patient's birth with (a) a diphtheria toxoid or CRM197 and/or(b) a conjugate of (i) a capsular saccharide of an organism other than *N.meningitidis* and (ii) a diphtheria toxoid or CRM197, and wherein the patient was pre-immunised at least six months before the method; the conjugates are mixed to give a 2:1:1:1 ratio (measured as mass of saccharide); each meningococcal antigen per dose is between 2 and 10 µg per serogroup (measured in terms of saccharide); and the meningococcal conjugates comprise an adipic acid linker."

Claim 1 of auxiliary request 3 is based on claim 1 of auxiliary request 2 but the reference to the adipic acid linker has been deleted.

Claim 1 of auxiliary request 4 is based on claim 1 of auxiliary request 2 but the references to the adipic acid linker and to the dose range have been deleted.

Claim 1 of auxiliary request 5 is based on claim 1 of auxiliary request 2 but the reference to an adipic acid linker has been deleted and the claim has been limited to specify that the patient has been pre-immunised with a conjugate.

Claim 1 of auxiliary request 6 corresponds to claim 1 of auxiliary request 5, except that the reference to the dose range has been deleted.

VI. In response to the statement of grounds of appeal, opponent 1 ("respondent") submitted arguments *inter alia* as regards lack of inventive step of the subject-matter of all the claim requests.

VII. The board issued a summons to oral proceedings accompanied by a communication pursuant to Article 15(1) RPBA.

VIII. The appellant and the respondent informed the board that they would not attend the oral proceedings. The appellant also withdrew their request for oral proceedings.

IX. Oral proceedings before the board were held on 14 February 2019. At the end of the oral proceedings, the chair announced the board's decision.

X. The following documents are referred to in this decision:

D1 WO 03/094834 (2003)

D3 Burrage M. et al., Infection And Immunity (2002), vol. 70, pages 4946 to 4954

D4 Dagan R. et al., Infection And Immunity (1998), vol. 66, pages 2093 to 2098

D5 Buttery J.P. et al., JAMA (13 April 2005), vol. 293, pages 1751 to 1758

D7 WO 03/007985 (2003)

D10 Rennels M. et al., The Pediatric Infectious Disease Journal (2002), vol. 21, pages 978 to 979

D14 CHMP assessment report for Menveo (2009)

D15 CDC, Morbidity and Mortality Weekly Report (2000), vol. 49, pages 35 to 38

D18 CDC, Morbidity and Mortality Weekly Report (2002), vol. 51, pages 31 to 33

D19 Excerpts from CDC website (2012)

D23 Schutze M.P. et al., The Journal of Immunology (1985), vol. 135, pages 2319 to 2322

D24 Di John D. et al., The Lancet (1989), vol. 2, pages 1415 to 1418

D25 Barington T. et al., Infection and Immunity (1993), vol. 61, pages 432 to 438

D26 WO 00/56360 (2000)

D30 Knuf M. et al., Vaccine (2010), vol. 28, pages 744 to 753

D31 Rennels M. et al., Abstracts of the 2001 Annual IDSA Meeting, Abstract 368

D32 FDA approval details for Prevnar (2011)

D34 Australian Public Assessment Report for Meningococcal Conjugated Vaccine (Menveo), 2010, extract

D35 Arguedas A, et al., Vaccine (2010), vol. 28, pages 3171 to 3179

XI. The appellant's arguments that are relevant to the present decision may be summarised as follows:

Inventive step (Article 56 EPC)

Main request

Closest prior art

The closest prior art document should be one having the same purpose, which was the treatment of meningococcal disease resulting from an infection with *Neisseria meningitidis* (*N. meningitidis) in* patients who had been pre-immunised with diphtheria toxoid (DT) or CRM197.

The opposition division was wrong to identify document D10 as the closest prior art on the basis that the composition used for immunisation was structurally similar to the composition recited in the claims.

Document D10 was published in October 2002, but the clinical trial it reported was completed before this date; see document D31. The relevant vaccination schedules were from 2000 and earlier. The schedule of 2000 did not include a pneumococcal conjugate vaccine. Therefore, it was very unlikely that any of the patients specified in document D10 would have received a pneumococcal-CRM197 conjugate vaccine.

Three different Hib conjugate vaccines were licensed for use in 2000, but only one of these vaccines (HbOC) was a CRM197 conjugate; see document D19.

Document D10 did not discuss the pre-immunisation status of its patients, did not discuss the problem of carrier suppression, and did not identify the patients defined in the claims. Therefore, document D10 could not be directed to the same purpose as the claims.

Document D26 was closer than document D10 because it related to the same purpose as the invention, i.e. the treatment of patients who had been pre-immunised with diphtheria toxoid or CRM197 as the conjugated (so-called carrier) protein; see page 7, lines 5 to 15 and the passage bridging pages 7 and 8. Document D26 disclosed immunisation against all four *N. meningitidis* serotypes A, C, W and Y on page 24, lines 23 to 29, and, importantly, it aimed to address the problem of the suppression of the immune response by the presence of pre-existing antibodies directed against the carrier protein ("carrier suppression") and thus the difficulty of using conjugate vaccines to immunise patients who had been pre-immunised with the carrier protein. Conjugate vaccines containing polysaccharides from *N. meningitidis* serotypes A and C (MenA and MenC) were tested in Examples 7 to 9.

Even if document D10 was nonetheless taken as the closest prior art, the solution was not obvious.

Objective technical problem and solution

The difference between the subject-matter of claim 1 and the disclosure of document D10 was the specific medical use claimed and in particular the patient subgroup specified.

The effect of the above difference was that the subject-matter of the claim provided for the boostable

immunisation against *N. meningitidis* serotypes A, C, W and Y of patients who had been pre-immunised with conjugates comprising diphtheria toxoid or CRM197.

In contrast to the opposition division's assertions, the patent did show evidence for this technical effect. The patent reported that infants immunised in Finland and Germany during the V59P2 clinical trial mounted a boostable response to the meningococcal ACWY conjugate vaccines; see paragraph [0117] of the patent and document D34, which was published after the filing date of the patent. The inventor recognised that these data indicated that the multivalent meningococcal conjugate vaccines of the invention could be administered to patients who had been pre-immunised with diphtheria toxoid or CRM197 or conjugates comprising diphtheria toxoid or CRM197.

Furthermore, the principle underlying the invention had been confirmed in studies that post-dated filing; see document D35.

The problem to be solved by the invention was the provision of a vaccine that induced a boostable immune response against meningococcal serotypes A, C, W and Y in patients who had been pre-immunised with a conjugate comprising diphtheria toxoid or CRM197.

Obviousness of the solution

The claimed solution was not obvious because the skilled person would have been aware of the risk of carrier suppression for patients who had been pre-immunised with conjugate vaccines, so the skilled person would not have considered treating patients pre-immunised with conjugates comprising a diphtheria

toxoid or CRM197 by administering a multivalent conjugate vaccine comprising the same carrier.

The problem of carrier suppression was well known in the art for conjugate vaccines, see paragraphs [0007], [0009],[0011] and [0013] of the patent, which discuss documents D23, D24, D25 and D3 respectively.

The fact that carrier suppression was particularly a problem for multivalent conjugate vaccines was evidenced by document D4.

The known risk of carrier suppression was confirmed by a trial carried out shortly before the priority date of the patent; see document D5.

In light of the teaching of documents such as D3, D4, D23, D24 and D25, the skilled person would have been concerned about the risk that carrier suppression would reduce the response to tetravalent MenACWY conjugate vaccines comprising diphtheria toxoid or CRM197 in patients who had been pre-immunised with non-meningococcal conjugate vaccines comprising diphtheria toxoid or CRM197 at least 6 months beforehand.

Instead, the skilled person would have adopted one of the approaches taught in the art for avoiding carrier suppression, and would have considered using either an alternative carrier protein (as suggested in document D26) or a mixture of different carrier proteins (as suggested in documents D6, D27 and D28).

In addition, the claimed medical use was not obvious from document D10, because document D10 did not include any relevant information or guidance that would have indicated to the skilled person that multivalent

meningococcal conjugate vaccines comprising diphtheria toxoid or CRM197 could be administered effectively to patients who had been pre-immunised with conjugates comprising the same carriers.

Auxiliary request 1

Claim 1 included a narrower definition of the composition, and corresponded more closely to the composition tested in the V59P2 trial reported in the patent at paragraphs [0114] to [0117] by specifying that each conjugate comprised the diphtheria toxoid derivative CRM197. Thus, claim 1 was further removed from document D10, which disclosed the use of conjugate vaccines comprising diphtheria toxoid protein as a carrier.

If document D10 was taken as the closest prior art document, then there were two differences from the claimed subject-matter: the definition of the patient sub-group, and the carrier used in the conjugates of the composition.

The effect of these differences was the same as for the main request, and the problem to be solved could therefore be formulated in the same way as for the main request.

Starting from document D10 and attempting to treat the patients specified in claim 1, the skilled person would have been concerned about the risk of carrier suppression; see the respective submissions in relation to the main request.

Moreover, the subject-matter of claim 1 was inventive because the skilled person would not have considered

replacing each of the carrier proteins to which the meningococcal capsular saccharides A, C, W and Y were conjugated, as disclosed in document D10, by CRM197. Firstly, there was no motivation in document D10 to replace any of the carrier proteins. Moreover, contrary to the opposition division's assertion, none of the documents on file said that diphtheria toxoid and CRM197 were "interchangeable". Finally, even if the skilled person had considered replacing a carrier protein, they would not have selected CRM197, because they would have been concerned about carrier suppression.

Auxiliary requests 2 to 4

In relation to auxiliary request 1, claim 1 of this request included an even narrower definition of the composition of the invention.

Firstly, it specified the ratio in which the conjugates were mixed. When discussing the V59P2 trial, the patent disclosed, in paragraph [0114], that a 2:1:1:1 ratio (measured as mass of saccharide) of MenA:C:W:Y was particularly effective, and this was confirmed in the analysis of document D14, which post-dated filing. In the V59P2 trial, the 2:1:1:1 ratio induced a more potent response in Group 3 than the 1:1:1:1 ratio in Group 4 at 19 of the 24 data points (see Table 1 of the patent).

The composition specified was the one tested in the examples in the patent, and corresponded to the authorised product Menveo.

Secondly, claim 1 specified that the conjugates comprised an adipic acid linker. The presence of a

linker provided additional advantages, as shown by the clinical trial that is disclosed in the examples, and in the course of which conjugates with adipic acid linkers were used; see paragraph [0114] and document D7. The patent showed that the tetravalent mixture of these conjugates induced a boostable immune response against the meningococcal saccharides A, C, W and Y contained in the vaccine. Subsequent work showed that the use of linkers improved this response compared to conjugates that did not contain linkers; see document D30.

Accordingly, the use of a ratio of 2:1:1:1 and the use of adipic acid linkers in the compositions of claim 1 significantly improved immune responses against all of the serogroups.

The technical problem vis-à-vis document D10 was thus the provision of an improved composition, with a better immune response to each of the serogroups.

The solution was not obvious. There was nothing in document D10 to motivate the skilled person to vary the ratio of the conjugates or to use adipic acid linkers. There was no suggestion in the cited prior art that a 2:1:1:1 ratio was particularly advantageous, or that linkers would have this effect in conjugate vaccines containing capsular saccharides of meningococcal serogroups A, C, W135 and Y.

The subject-matter of auxiliary requests 3 and 4 was inventive for the same reasons as those given in relation to auxiliary request 2.

Auxiliary requests 5 and 6

Moreover, the subject-matter of auxiliary request 5 was inventive because the composition benefited from the advantages achieved by using a 2:1:1:1 MenA:C:W:Y ratio, and because it specified that the composition was for use in patients pre-immunised with a conjugate comprising diphtheria toxoid or CRM197.

The subject-matter of auxiliary request 6 was inventive for the same reasons as those given in relation to the subject-matter of auxiliary request 5.

XII. The respondents' arguments that are relevant to the present decision may be summarised as follows:

Admissibility of auxiliary requests 3 to 6 and of document D35

Auxiliary requests 3 to 6 and document D35 were all filed late. Moreover, document D35 was not relevant to the claims of the patent.

Inventive step (Article 56 EPC)

Main request

Closest prior art

Document D10 could be selected as the closest prior art. Document D10 and the patent had the common purpose of successfully vaccinating children against infection with *N. meningitidis*, thus avoiding meningococcal disease, while allowing for the continued application of existing childhood vaccines. Neither the patent nor document D10 addressed any question of an immune

suppression by the carrier protein, that might or might not become apparent when tested in a respective subpopulation of children. In fact, both the patent and document D10 were concerned with protecting all children at risk of meningococcal infection. Only once a common purpose was established could the number of common features be considered.

Document D26 was not the closest prior art because it had fewer features in common with the vaccine claimed than document D10. The generally worded passage on page 24, lines 23 and 24, of document D26 mentioned a *N. meningitidis* vaccine of unknown composition. Document D26 did not report any immunisations of patient populations and did not provide data for any MenACWY combination vaccine, unlike document D10, which disclosed an actual vaccine used in a trial.

There were no data in the patent that made it possible to compare the vaccination efficacy of pre-immunised and non-pre-immunised patients.

The opposition division was correct that it was not possible to find a technical effect in the patent on which inventive step could have been based.

Obviousness

Most of appellant's submissions related to an assertion that the patent had overcome a prejudice to do with "carrier suppression".

Specifically, it was alleged that the skilled person would not administer vaccines including diphtheria toxoid (DT) or the CRM197 protein to patients who had previously received DT or CRM197 (or DT-conjugated or

CRM197-conjugated vaccines), i.e. the "pre-immunised" population.

However, there was no evidence in the art that the skilled person had any such prejudice that would have prevented their using these vaccines in "pre-immunised" patients, or, more specifically, in patients who had been pre-immunised with CRM197/DT-conjugate vaccines, as the main request specifically stated.

Prior art document D10 did not take into account the CRM197/DT immunisation status of the tested individuals. Thus, given that children at the relevant time were routinely immunised with a diphtheria toxoid as part of childhood vaccination (for example with childhood combination vaccines containing Diphtheria, Tetanus and Pertussis (DTP) antigens, the *Haemophilus influenzae* Type B (Hib) conjugate vaccine or even the heptavalent vaccine PCV7-CRM197 (Prevnar®)), it was apparent that the skilled person was fully prepared to immunise such children, irrespective of whether they had been "pre-immunised" with DT or CRM197 antigens. Thus, there was evidently no prejudice against such use - a prejudice which would have led the skilled person to use the respective vaccines solely on "non-pre-immunised" patients.

In fact, a skilled person who had conducted the study in document D10 acted no differently from a skilled person who had conducted the studies reported in the patent. The study neither tested nor actually reported any difference in immunological responses between "pre-immunised" and "non-pre-immunised" patients, a fact that clearly showed a lack of concern in this regard, rather than a prejudice.

The appellant had not provided any evidence that the V59P2 trial reported in the patent was more likely to have included a pre-immunised subpopulation that was materially different from that of document D10, e.g. a subpopulation that had received pneumococcal vaccinations (in addition to DTP and Haemophilus vaccinations), or any evidence of how the skilled person could have concluded such difference from the disclosure of said V59P2 trial provided by the patent.

It was technically irrelevant whether such pre-immunisation with DT or CRM197 was part of a vaccination with conjugate or non-conjugate vaccines.

Claim 1 of the main request specified that the patient had been pre-immunised within one year of the patient's birth. In routine vaccination schedules, the DTP vaccine - which includes diphtheria toxoid - was given to patients at 2 months in three separate doses (see document D15). Thus, this feature too was entirely conventional. In any case, the skilled person was given no teaching as to the relevance of this feature, as the V59P2 trial did not distinguish a pre-immunised patient subgroup, in which the patients had been pre-immunised within 1 year of birth, from non-pre-immunised patients.

Auxiliary requests 1 to 6

None of the auxiliary requests included any limitation that provided an advantage that was demonstrated in the patent with regard to the claimed patient population.

All requests related to the same patient population as the main request, i.e. a population that had not been tested by the patent. Thus, it was not possible to base

inventive step on any "particular efficacy" of the claimed vaccination with a MenACWY conjugate vaccine.

The difference between auxiliary request 1 and the main request was that the vaccine employed was restricted to CRM197 as the carrier of the A, C, W and Y saccharides in the vaccine.

The tetravalent MenACWY-CRM197 composition was already disclosed in document D1 on page 16; in document D7 on page 6, lines 11 to 12; and in document D20 on page 5.

Document D10 could be combined with any of documents D1, D7 or D20.

The difference between auxiliary request 2 and the main request was that the MenACWY vaccine employed was further restricted by the ratio of the individual serotypes, the dose (measured in terms of polysaccharide content), and the use of an adipic acid linker in the individual conjugates.

The considerations of inventive step applied in the same manner to auxiliary request 2 as to auxiliary request 1 and the main request. The patent did not teach any relationship between ratio, dose and use of a linker and the results obtained upon vaccination in the claimed pre-immunised patient population. Therefore, the choice of ratio, dose and use of a linker were merely arbitrary and could not contribute to inventive step.

The appellant asserted that MenACWY compositions having this ratio, dose range and linker were "*particularly effective*". However, there was no explanation of what was meant by "*particularly effective*". Efficacy in the

claimed population had not even been measured in the patent.

In addition, the requirements that the conjugates were mixed to give a 2:1:1:1 ratio, that each meningococcal antigen per dose was between 2 and 10 mg per serogroup, and that the meningococcal conjugates comprised an adipic linker had already been disclosed in the prior art; see document D1, page 2, lines 26 to 27, page 5, first paragraph and page 6, fifth paragraph and document D7, page 6, lines 11 to 12, page 12, lines 13 to 16 and page 5, lines 8 to 10.

The reasoning given in relation to the subject-matter of auxiliary request 2 also applied to the respective subject-matter of auxiliary requests 3 and 4, which in each case was broader.

XIII. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request and an adapted description, or alternatively on the basis of the set of claims of one of auxiliary requests 1 to 6 and an adapted description. It further requested that documents D31 to D35 be admitted into the appeal proceedings.

The respondent requested in writing that the appeal be dismissed, and that auxiliary requests 3 to 6 and document D35 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

2. The duly summoned parties were neither present nor represented at the oral proceedings. The board decided to continue the proceedings without the parties in accordance with Rule 115(2) EPC, and treated them as relying on their written case in accordance with Article 15(3) RPBA.

Admissibility of auxiliary requests 3 to 6 and of document D35

3. The respondent had requested that auxiliary requests 3 to 6 not be admitted into the appeal proceedings. The board considered the substance of all these claim requests.

4. The respondent had further requested that document D35 not be admitted into the appeal proceedings. The board decided not to exclude document D35 from the appeal proceedings.

5. In the circumstances of the present case - the board decided to dismiss the appeal - the board sees no need to provide justification for having admitted auxiliary requests 3 to 6 into and not excluded document D35 from the appeal proceedings.

Main request and auxiliary requests 1 to 6

Inventive step (Article 56 EPC) - claim 1

Closest prior art

6. In the decision under appeal, document D10 was considered to represent the closest prior art (see Reasons, point 1.3). The appellant maintains that document D26 rather than document D10 is the closest prior art.

7. In accordance with established jurisprudence, the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, section I.D.3.1).

8. The invention concerns vaccines against *Neisseria meningitidis* (*N. meningitidis*) (also referred to hereinafter as "meningococcal vaccines" or "meningococcal conjugates"), in particular vaccines based on conjugated capsular saccharides from multiple meningococcal serogroups (see paragraph [0001] of the patent). The patent states that meningococcal conjugates are well known, including mixtures of conjugates from serogroups A, C, W135 and Y, but that meningococcal conjugates have not yet been fitted into existing paediatric immunisation schedules, which for developed countries typically involve: "*hepatitis B vaccine at birth; and, starting at 2 months, all of diphtheria/tetanus/pertussis (DTP), H. influenzae*

type b (Hib) conjugate, inactivated poliovirus and pneumococcus conjugates at 2 months" (see paragraph [0005] of the patent).

9. Document D10, entitled "*Dose escalation, safety and immunogenicity study of tetravalent meningococcal polysaccharide diphtheria conjugate vaccine in toddlers*", was published in the year 2002 and states that, in areas with widespread use of the heptavalent conjugate pneumococcal vaccine, meningococcus will likely become the most common cause of meningitis and sepsis in young children, and that for these reasons glycoconjugate technology has been utilised to develop conjugate meningococcal vaccines. A tetravalent (serogroups A, C, Y and W-135) meningococcal polysaccharide vaccine in which the saccharides were conjugated to diphtheria toxoid (TetraMenD) was given to 30 toddlers aged 12 to <23 months, at dosages of 1, 4 and 10 µg/ml polysaccharide of each serogroup, i.e. in a 1:1:1:1 ratio. The children were given 2 injections of TetraMenD, separated by 6 to 12 weeks. No concomitant immunisations were given.

All four serogroup saccharide conjugates contained in the vaccine were found to be immunogenic, and for each serogroup a second dose of vaccine enhanced both the serum bactericidal antibody (SBA) titres and the amount of IgG antibody. While the immune reaction was acceptable at all dosages, antibody responses were highest in children given 4 µg of polysaccharide per serogroup (see page 978, abstract; paragraph bridging left- and right-hand columns; second and third paragraphs, right-hand column; page 979, first to third paragraphs and Table 1).

The trial was carried out in Maryland (see page 978, right-hand column, third full paragraph).

Document D10 thus provides a tetravalent meningococcal polysaccharide-diphtheria toxoid conjugate vaccine which induces a boostable immune response in toddlers.

10. As regards the pre-immunisation status of the patients of document D10, the board agrees with the appellant that it can be determined on the basis of the relevant vaccination schedule from the year 2000 for the United States of America (USA). This schedule did not include a pneumococcal-CRM197 conjugate vaccine, but did include DTP, given at 2, 4, and 6 months of age (see document D15, Figure 1).

The board also agrees with the appellant that, although document D10 mentions the use of a heptavalent pneumococcal conjugate vaccine (see point 9 above), it is unlikely that the patients who took part in the Maryland trial disclosed in document D10 had been pre-immunised with a pneumococcal-CRM197 conjugate vaccine, because such a vaccine was not approved in the USA until 2000 (see document D32, page 1, lines 18 to 20), and was not integrated into the US immunisation schedule until 2001 (see document D18, Figure 1).

11. Document D26 relates to bacterial polysaccharides conjugated to protein D from *Haemophilus influenzae (H. influenzae)*. It discloses that polysaccharide antigen vaccines are well known in the art and that (poorly immunogenic) bacterial capsular polysaccharides are linked to highly immunogenic protein carriers, which provide bystander T-cell help. According to document D26, examples of these carriers include diphtheria toxoid (DT or the CRM197 mutant), tetanus

toxoid (TT), Keyhole Limpet Haemocyanin (KLH), and the purified protein derivative of tuberculin (PPD). Document D26 also states that it is known that an antigen-specific immune response may be suppressed ("*epitope suppression*") by the presence of pre-existing antibodies directed against TT as a carrier and that, in the population at large, a very high percentage of people will have pre-existing immunity to both DT and TT as people are routinely vaccinated with these antigens.

12. Document D26 thus provides a different carrier, protein D from *H. influenzae,* for use in the preparation of polysaccharide-based conjugates in order to avoid epitope suppression (see page 6, line 21, to page 8, line 11).

Although document D26 discloses (on page 24, lines 23 to 29), that in a further embodiment a *N. meningitidis* vaccine, in particular comprising polysaccharides of serotypes A, B, C, W-135 and Y, is provided, it does not disclose - contrary to the submission by the appellant - immunisation with this tetravalent *N. meningitidis* vaccine and certainly not in a patient group as defined in the claims. Indeed, in the pertinent Examples 7 to 9, *N. meningitidis* polysaccharides from serotype C or A conjugated to protein D were tested in Balb/c mice. In the board's view, the disclosure in document D26 is thus further removed from the claimed invention than that in document D10.

13. Thus, neither document D10 nor document D26 discloses vaccination of a patient who was "pre-immunised at least six months previously and within 1 year of the patient's birth with a conjugate of a capsular

saccharide of an organism other than *N.meningitidis* and a diphtheria toxoid or CRM197". However, in the board's judgement, document D10 relates to the same purpose as the patent, namely successfully vaccinating children against meningococcal disease while allowing for the continued application of existing childhood vaccines, and shares more technical features with the invention than document D26. Therefore, document D10 represents the closest state of the art for the purpose of the assessment of inventive step.

Objective technical problem and its solution

14. One embodiment falling within claim 1 of all the claim requests is a composition that comprises conjugates of the four capsular saccharides of serogroups A, C, W-135 and Y of *N. meningitidis* and CRM197 as the carrier protein, wherein the conjugates are mixed to give a 2:1:1:1 ratio (measured as mass of saccharide); each meningococcal antigen per dose is between 2 and 10 µg per serogroup (measured in terms of saccharide); and the meningococcal conjugates comprise an adipic acid linker, for use in a method for immunising a human patient against a disease caused by *N. meningitidis* comprising the step of administering the composition to the human patient, wherein the patient was pre-immunised at least six months previously and within 1 year of the patient's birth with a conjugate of a capsular saccharide of an organism other than *N.meningitidis* and a diphtheria toxoid or CRM197.

It is this embodiment that will be considered by the board in the following.

15. The embodiment differs from the disclosure of document D10 as regards the composition used, namely in

that the conjugates comprise an adipic acid linker, in that the ratio of the polysaccharides is 2:1:1:1, in that the diphtheria toxoid carrier is the mutant CRM197 and further in that the patient has been pre-immunised at least six months previously and within 1 year of the patient's birth with a conjugate of a capsular saccharide of an organism other than *N. meningitidis* and a diphtheria toxoid or CRM197.

16. As to the effect of these differences, the appellant submitted that they resulted in the provision of an improved composition, which induces a better immune response to each of the serogroups. In this context, the appellant relied on clinical trial V59P2 as reported in the patent and post-published documents D14, D30, D34 and D35.

17. The patent discloses that in clinical trial V59P2, conducted in Finland and Germany with 620 subjects aged 12 to 16 months, five formulations were tested. The vaccines used the CRM197 carrier and an aluminium phosphate adjuvant. Various doses of each serogroup saccharide were tested. Subjects received an injection at time zero, and 25% of the subjects then received a second dose of the vaccine 4 weeks later. Sera of the patients were collected and tested in a SBA assay. The results are shown in Table 1. The patent concludes that "*the trivalent and tetravalent vaccines were both immunogenic in toddlers. The conjugates are immunogenic at saccharide doses as low as 2.5 µg per conjugate. The immune responses are boostable, with large SBA titre increases after the second dose. No evidence of carrier suppression was seen in this trial*" (see paragraphs [0114] to [0117]).

18. However, the board notes that the patent is silent on the pre-immunisation status of the patients enrolled in the clinical trial V59P2 and also on the year(s) in which the trial was carried out.

19. Thus, from the information provided in the patent for clinical trial V59P2, the skilled person cannot conclude that the patients were pre-immunised at least six months previously and within 1 year of the patient's birth with a conjugate of a capsular saccharide of an organism other than *N. meningitidis* and a diphtheria toxoid or CRM197, i.e. that they represented the subgroup of patients to be treated according to the embodiment under consideration.

20. Accordingly, any advantageous effect of the composition that may be seen in clinical trial V59P2 cannot be taken into account in assessing inventive step. Nor can the appellant rely on post-published documents D14, D30, D34 and D35: The assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. The verification of whether or not the claimed solution actually solves the problem, i.e. whether the claimed subject-matter actually provides the desired effect, must be based on the data in the application in order to avoid that an invention is based on knowledge available after the effective date only. Post-published evidence to support that the claimed subject-matter solves the underlying technical problem can only be taken into account if it is already credible from the disclosure in the patent that the

problem is indeed solved (see decision T 1285/13, Reasons, point 10 and Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.4.6).

21. The board concludes from the above analysis that the problem to be solved cannot be defined as put forward by the appellant, namely as the provision of an improved composition, which induces a better immune response to each of the serogroups.

22. As explained above, the skilled person cannot conclude from the information provided in the patent on clinical trial V59P2 that the claimed composition induces a boostable immune response in patients pre-immunised at least six months previously and within 1 year of the patient's birth with a conjugate of a capsular saccharide of an organism other than *N.meningitidis* and a diphtheria toxoid or CRM197.

23. Notwithstanding this, in the board's view the skilled person would have no reason to doubt that the claimed composition also induced a boostable immune response in these patients, since there was no prejudice in the art that pre-immunisation with diphtheria toxoid or CRM197 would result in carrier suppression, as will be explained in more detail below (see points 27 to 29).

24. Therefore, the board accepts as the problem to be solved the less ambitious problem put forward by the appellant, i.e. the provision of a vaccine that induces a boostable immune response against meningococcal serogroups A, C, W and Y in patients who have been pre-immunised with a conjugate comprising diphtheria toxoid or CRM197.

Obviousness of the solution

25. The question to be answered is whether the skilled person, aware of the teaching of document D10 and faced with the technical problem defined in point 24 above, would have modified the teaching of the closest prior art document D10 - possibly in the light of other prior art teachings - in such a way as to arrive at the embodiment under consideration (see point 14) in an obvious manner.

26. The appellant submitted that the skilled person, aware of the risk of carrier suppression in patients who have been pre-immunised with conjugate vaccines, would not have considered treating patients pre-immunised with conjugates comprising a diphtheria toxoid or CRM197 by administering a multivalent conjugate vaccine comprising the same carrier.

27. As evidence of the fact that the problem of carrier suppression was well known in the art for conjugate vaccines, the appellant relied on paragraphs [0007], [0009],[0011] and [0013] of the patent and on documents D23, D24, D3, D25, D4, and D5.

27.1 The patent explains that when adding conjugated vaccines to existing immunisation schedules, the issue of carrier-induced epitopic suppression ("carrier suppression") must be addressed, particularly suppression arising from carrier priming. Carrier suppression is said to be "*the phenomenon whereby pre-immunisation of an animal with a carrier protein prevents it from later eliciting an immune response against a new antigenic epitope that is presented on that carrier*" (see paragraphs [0004] to [0006]). In paragraphs [0007], [0009], [0011] and [0013] the patent

refers to prior art studies on the phenomenon of carrier suppression as reported *inter alia* in references 15, 18, 24, and 21, which are documents D23, D24, D3 and D25 in these proceedings.

27.2 However, the board notes that the patent does not report any trials in which carrier suppression has been shown to exist or has been shown to be overcome (see also points 17 to 19 above).

28. The board has also considered the disclosures of documents D3, D4, D5, D23, D24 and D25.

28.1 Document D3 reports that, in order to plan for the wide-scale introduction of meningococcal C conjugate (MCC) vaccine in the United Kingdom for children up to 18 years, phase II clinical trials were undertaken to investigate whether there was any interaction between the MCC vaccines conjugated to either TT or a derivative of diphtheria toxin (CRM197) and diphtheria-tetanus vaccines given for boosting at school entry or leaving.

Children received a diphtheria-tetanus booster 1 month before, 1 month after, or concurrently with MCC vaccines conjugated to CRM197 or TT. It was found that all of the MCC vaccines induced high antibody responses to the serogroup C polysaccharide that were indicative of protection. While the immune response to the MCC-TT vaccine was reduced as a result of prior immunisation with a tetanus-containing vaccine, prior or simultaneous administration of a diphtheria-containing vaccine did not affect the response to the MCC-CRM197 vaccine.

Thus, carrier-induced epitopic expression was only seen with the MCC-TT vaccine (see abstract and page 4953, left-hand column, fourth paragraph).

28.2 Document D4 reports an interference with the immune response of several co-administered vaccines containing the same protein component, TT. Infants simultaneously receiving either a tetravalent pneumococcal vaccine conjugated to TT and a diphtheria-tetanus-pertussis-poliovirus-*H. influenzae* type b-tetanus conjugate vaccine showed significantly lower anti-*H. influenzae* type b polysaccharide antibody concentrations than those receiving either a tetravalent pneumococcal vaccine conjugated to diphtheria toxoid or placebo.

28.3 Document D23 reports that the immune response against synthetic epitopes conjugated to TT can be suppressed by pre-existing immunity against this same carrier and that, because most humans have been exposed to this antigen, this effect may have important implications for the development of synthetic vaccines (see abstract).

28.4 Document D24 reports that mice pre-immunised with either TT or bovine serum albumin (BSA) displayed decreased antibody responses to those synthetic peptides conjugated to TT or BSA carriers, respectively (see paragraph bridging columns, page 1415) and that a prospective study was undertaken in which a largely tetanus-toxoid naive Venezuelan population was compared with a control group of North Americans who were well immunised against tetanus (see page 1415, right-hand

column, third paragraph). The authors concluded that the data suggested that the suppression might be overcome by providing higher doses of the haptenic antigen.

28.5 In document D25 non-epitope-specific suppression was observed. Thus, pre-immunisation with one conjugate (HibCP-DT) reduced the subsequent response to the carrier portion of the other conjugate (HibCP-TT).

28.6 Document D5 is a scientific paper published after the priority date and thus cannot have influenced the expectations of the skilled person before the priority date. The document needs not therefore be considered.

28.7 In summary, documents D3, D4, D23, and D24 report carrier suppression in those instances where TT was used as a carrier of conjugated vaccines in patients who had been pre-immunised with tetanus toxoid. The sole document looking at carrier suppression in the context of pre-immunisation with diphtheria toxoid, document D3, does not report any carrier suppression. Indeed, document D26 also explicitly mentions carrier suppression only for TT but not for diphtheria toxoid (DT or CRM197 mutant) as carrier (see above, point 11).

29. The board is thus not persuaded that the skilled person would have been concerned about the risk that carrier suppression would reduce the response to tetravalent MenACWY conjugate vaccines comprising diphtheria toxoid or CRM197 in patients who had been pre-immunised with non-meningococcal conjugate vaccines comprising diphtheria toxoid or CRM197 at least 6 months beforehand.

30. As explained above, document D10 reports that the TetraMenD vaccine induced a boostable immune response in the immunised children (see point 9). In the board's view, the skilled person reading document D10 would have been aware that most if not all of the children had previously been immunised with a diphtheria toxoid as part of their childhood vaccination with DTP at the age of 2, 6, and 8 months (see above, point 10). Notwithstanding this, the study reported in document D10 neither tested nor reported any differences in immunological responses between "pre-immunised" and "non-pre-immunised" patients. The board agrees with the respondent that this is further evidence of a lack of concern in this regard, rather than of a prejudice.

31. The board also agrees with the respondent that it is technically irrelevant, and thus would not have influenced the skilled person, whether the patients were pre-immunised with DTP rather than with a conjugate comprising diphtheria toxoid or CRM197, since the relevant point is that the patient's immune system, having been exposed to the carrier protein before - here a diphtheria toxoid - still raises an immune response against the polysaccharide antigen presented on that same carrier.

32. In the board's view, faced with the problem formulated above and aware of the teaching of document D10, the skilled person is thus motivated to provide a tetravalent ACWY meningococcal polysaccharide vaccine conjugated to a diphtheria toxoid as carrier for use in the population specified.

33. The skilled person starting from the teaching of document D10 will generate vaccines in line with the

recommendations in the prior art for the production of polysaccharide antigen conjugated vaccines. The skilled person is well aware that an alternative carrier to diphtheria toxoid is the mutant CRM197 diphtheria toxoid (see for example document D1, page 16, first table; document D7, page 4, lines 15 to 16), that linkers, such as adipic acid linkers, can be used to conjugate the saccharide to the carrier protein (see document D1, page 5, lines 1 to 3; document D7, page 5, lines 8 to 10) and that the ratio for saccharides from serogroups A:C:W135:Y can be varied (see document D1, page 2, lines 26 and 27; document D7, page 5, lines 24 to 27, and page 6, lines 11 to 12).

34. The board has no reason to doubt that any of the vaccines that would be obtained by following the teaching in the prior art is suitable for inducing a boostable immune response in the patient group specified, i.e. that the skilled person would have considered any of them as a solution to the technical problem at issue here.

35. The specific vaccine considered here by the board (see point 14 above) would be one of these vaccines. However, no surprising technical effect is linked to this vaccine in the specified patient population. Thus, in terms of its technically relevant effects, this vaccine is not distinguished from any of the other possible vaccines, i.e. it is a selection of one of several equally available alternative solutions to the problem formulated. Such a situation is referred to in the jurisprudence as an "arbitrary selection". Arbitrary selections are considered to be obvious (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, I.D.9.18.7).

36. In conclusion, the embodiment under consideration is obvious. Thus, one embodiment falling within the scope of claim 1 of all the claim requests lacks an inventive step. Therefore, the subject-matter of claim 1 as a whole of all the claim requests must be considered to fail to meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated