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Datasheet for the decision of 1 December 2015

Case Number: T 1242/11 - 3.3.04

Application Number: 00203772.9

Publication Number: 1090642

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Language of the proceedings: EN

Title of invention:

Vaccines comprising a polysaccharide antigen-carrier protein conjugate and free carrier protein

Patent Proprietor:

GlaxoSmithKline Biologicals s.a.

Opponents:

Novartis Vaccines and Diagnostics, Inc. (opposition withdrawn)
Wyeth LLC
Sanofi Pasteur, Inc.

Headword:

Vaccine compositions/GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 56
EPC R. 115(2)
RPBA Art. 13(1), 15(3)

Keyword:
Inventive Step of all requests - (no)

Decisions cited:

Catchword:

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Case Number: T 1242/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 December 2015

Appellant: (Patent Proprietor)	GlaxoSmithKline Biologicals s.a. rue de l'Institut 89 1330 Rixensart (BE)
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Respondent III: (Opponent 3)	Sanofi Pasteur, Inc. 1 Discovery Drive, Knerr Building 1 Swiftwater, PA 18034 (US)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 April 2011 revoking European patent No. 1090642 pursuant to Articles 101(2) and (3)(b) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
M. Blasi

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division to revoke European patent No. 1 090 642. The patent has the title "*Vaccines comprising a polysaccharide antigen-carrier protein conjugate and free carrier protein*".

II. Three oppositions were filed against the patent invoking Article 100(a) EPC in combination with Articles 54 (novelty) and 56 EPC (inventive step), Article 100(b) and Article 100(c) EPC as grounds of opposition.

III. The decision under appeal dealt with a main request, *i.e.* the patent as granted and two auxiliary requests. The opposition division held that all the claims of the main and auxiliary request 1 lacked inventive step. Auxiliary request 2 was not admitted into the proceedings because the objections of lack of inventive step raised with regard to the two previous requests also applied to this request.

IV. With its statement of grounds of appeal the appellant submitted claim sets of a main and four auxiliary requests and described auxiliary requests 5 and 6 with reference to auxiliary requests 3 and 4. Claim sets of both auxiliary requests 5 and 6 were filed later on 25 November 2015. The main request and auxiliary request 3 corresponded to the main request and auxiliary request 1 of the impugned decision.

Claim 1 of the main request reads as follows:

"1. A combined vaccine comprising:
a) a polysaccharide antigen derived from *Streptococcus pneumoniae*, or *Neisseria meningitidis* A, B or C conjugated to a carrier protein, and
b) the carrier protein also present as free antigen, characterised in that the ratio of polysaccharide to carrier protein in the conjugate is from 1:0.3 to 1:2 (w/w)."

The respective claims 1 of the six auxiliary requests read as follows:

Claims 1 of auxiliary request 1 and 2 differ from claim 1 of the main request in that the ratio of polysaccharide to carrier protein in the conjugate is from 1:0.3 to 1:1.5 or from 1:0.5 to 1:1.5, respectively (emphasis by the board).

Claims 1 of auxiliary requests 3 and 4 differ from claim 1 of the main request in that the feature "and wherein the carrier protein is a Diphtheria or Tetanus antigen which is Diphtheria toxoid or Tetanus toxoid, or a non toxic derivative of a toxin from Diphtheria or Tetanus" is added at the end of the claim. Claim 1 of auxiliary request 4 additionally recites the feature "and further comprising antigens protective against Diphtheria, Tetanus, and pertussis infection" at the end of the claim.

Claim 1 of auxiliary request 5 differs from claim 1 of the main request in that the ratio of polysaccharide to carrier protein in the conjugate is from 1:0.5 to 1:1.5 (emphasis by the board) and the feature "wherein the carrier protein is a Diphtheria or Tetanus antigen which

is Diphtheria toxoid or Tetanus toxoid, or a non toxic derivative of a toxin from Diphtheria or Tetanus" is added at the end of the claim.

Claim 1 of auxiliary request 6 combines the features from auxiliary request 5 and the additional feature of auxiliary request 4 "and further comprising antigens protective against Diphtheria, Tetanus, and pertussis infection".

V. Only opponent 2 (hereafter "respondent II") filed a reply to the statement of grounds of appeal. Opponent 1 withdrew its opposition with the letter dated 10 March 2015 - its sole submission in the appeal proceedings.

VI. In response to the summons to oral proceedings the appellant and both respondents II and III informed the board that they would not be attending the oral proceedings. The appellant also withdrew its request for oral proceedings.

VII. In two communications pursuant to Article 15(1) RPBA, the board informed the parties of some of its preliminary views, *inter alia* that document D40 appeared to represent the closest prior art document, that documents D5, D55 and D57 (identified in section IX below) appeared to be relevant for assessing the obviousness of the subject-matter claimed, and that none of the claim requests on file appeared to be allowable.

VIII. Oral proceedings before the board were held on 1 December 2015 in the absence of the parties. At the end of the oral proceedings the chairwoman announced the board's decision.

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

D3: Scheifele et al., Vaccine, 10(7), 455-460, 1992

D5: Corbel M.J., Biologicals, 22, 353-360, 1994

D40: Peeters et al., Infect. Immun., 59(10), 3504-3510, 1991

D55: Insel R.A., Annals of the New York Academy of Sciences, 754, 35-47, 1995

D57: Becker R.S., Springer Semin. Immunopathol., 15, 217-226, 1993

X. The appellant's arguments submitted in writing may be summarised as follows:

Document D40 among others was not suitable as the closest prior art since it concerned "*monovalent conjugates rather than combined vaccines*"(see page 9, lines 5 and 6 of the statement of grounds of appeal).

The disclosure of document D5 represented the closest prior art since it related to the same purpose as the invention, *i.e.* combined vaccines, *inter alia* those comprising pneumococcal or meningococcal polysaccharide-protein conjugates. A combined vaccine comprising diphtheria, tetanus and pertussis antigens (DTP) and polysaccharides of *Haemophilus influenzae* serotype B (Hib) and *Neisseria meningitidis* serotype A and C (MenAC) was *inter alia* disclosed.

The claimed subject-matter differed from this disclosure in that the ratio of polysaccharide to carrier protein

was defined and in that the free carrier protein in the formulation did not reduce the immune response to the polysaccharide in the conjugate - an effect known as "carrier or epitopic suppression" or "immune interference". Thus, the technical problem underlying the invention was to be formulated as "*how to formulate the conjugate in an alternative combination vaccine against S. pneumonia or N. meningitidis also containing the carrier protein in free form thereby avoiding significant immune interference*" (see page 9, lines 34 to 41 of the statement of grounds of appeal).

The problem was plausibly solved by conjugates characterised by the claimed low polysaccharide to carrier protein ratio, as could be derived from the data of example 4 of the patent.

The solution was not obvious, although the suppression of the immune response to the polysaccharide antigens in conjugates by the free carrier protein in combination vaccines was a known phenomenon, since none of the available documents such as, D5 or D40 pointed to the claimed solution, *i.e.* a low carrier protein to polysaccharide ratio in the conjugated antigens as a means for avoiding suppression.

XI. Respondent II's arguments submitted in writing may be summarised as follows:

Document D40 represented the closest prior art, since it disclosed an immunisation scheme based on two separate vaccine formulations administered subsequently wherein the first comprised meningococcal and pneumococcal polysaccharide antigens conjugated to carrier proteins in a ratio falling within the claimed range and the second a free protein carrier. Alternatively, documents

D3 and D57 were suitable candidates to be the closest prior art. The technical problem could be considered as the provision of a "*childhood combination vaccine including meningococcal or pneumococcal polysaccharides*".

The skilled person had the motivation to combine the free protein carrier with the conjugates into a single formulation due to the known advantages of arriving at a simplified and more convenient immunisation scheme, in particular for children (see e.g. documents D5 and D55), and would thus have arrived at the claimed subject-matter in an obvious manner.

XII. Respondent III did not make any submissions relating to substantive issues in the appeal proceedings.

XIII. The appellant requested in writing that the decision under appeal be set aside and that the European patent be maintained as granted (main request), or alternatively, that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 4, all filed with the statement of grounds of appeal, or auxiliary requests 5 and 6, both filed with the letter of 25 November 2015.

Respondent II requested in writing that the appeal be dismissed.

Reasons for the Decision

1. As communicated to the board in their respective letters, none of the duly summoned and remaining parties was present or represented at the oral proceedings which, in accordance with Rule 115(2) EPC and Article 15(3) RPBA, took then place in their absence.

Admission of auxiliary requests 5 and 6

2. Claim sets for auxiliary requests 5 and 6 were not submitted with the statement of grounds of appeal. Instead, the appellant described in writing by reference to auxiliary requests 3 and 4 what the claims should be. In the board's view, this is not sufficient for these requests to be regarded as having been actually submitted. Hence, the admission of auxiliary requests 5 and 6, of which claim sets were then filed later, lies in the discretion of the board (Article 13(1) RPBA). Taking account of, in particular the fact that the statement of grounds of appeal had already described the two claim requests by reference to auxiliary requests 3 and 4, the board decided to admit auxiliary requests 5 and 6 into the proceedings

Main request - claim 1

Claim interpretation

3. The appellant took the view that certain documents were not suitable as the closest prior art "*because they concern monovalent conjugates rather than combined vaccines*". This seems to imply that the appellant interprets claim 1 as relating exclusively to

multivalent vaccines, *i.e.* to vaccines which comprise more than one conjugated bacterial polysaccharide antigen from either the same or different bacterial pathogens.

4. However, claim 1 reads: "A combined vaccine comprising: a) a polysaccharide antigen derived from *Streptococcus pneumoniae*, **or** *Neisseria meningitidis* A, B **or** C conjugated to a carrier protein, and b) the carrier protein also present as free antigen, [...]" (emphasis added by the board). Accordingly, the "or" indicates that the wording encompasses vaccine formulations which contain only a single conjugated polysaccharide antigen of either *Streptococcus (S.) pneumoniae* or *Neisseria (N.) meningitis* serotypes A, B or C. Thus, in the board's view, claim 1 does not relate exclusively to multivalent, but also to monovalent vaccines. The following considerations relate to this latter embodiment of claim 1.

Inventive step (Article 100(a) in combination with Article 56 EPC)

Closest prior art

5. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal of the EPO generally apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

The closest prior art is generally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, *i.e.*

requiring the minimum of structural modifications (see Case Law of the Boards of Appeal (CLBA), 7th edition 2013, I.D.3.1).

6. The present invention concerns vaccines for preventing bacterial infections of either *S. pneumoniae* ("pneumococcal" infections) or *N. meningitis* A, B or C ("meningococcal" infections).

7. The appellant considered the teaching of document D5, respondent II that of documents D3, D40 or D57, to represent the closest prior art.

7.1 Document D3 discloses the prevention of *Haemophilus influenzae* type B (Hib) and diphtheria, tetanus and pertussis (DTP) infections by immunising children with a vaccine comprising a polysaccharide antigen from Hib conjugated to diphtheria toxoid (DT) as a carrier protein and DTP antigens (see abstract).

7.2 Document D5 reports on combination vaccines *"currently in use", inter alia* for the prevention of DTP and Hib infections and suggests future combination vaccines comprising meningococcal A and C polysaccharide-carrier protein conjugates (see page 354, column 1, second paragraph to column 2, first paragraph).

7.3 Document D40 reports on monovalent bacterial polysaccharide-carrier protein conjugate vaccines inducing a protective immune response against a *S. pneumoniae* or *N. meningitis* infection in mice. In one conjugate, a pneumococcal polysaccharide is linked to tetanus toxoid (TT) as carrier protein in a ratio of 0.7:1, in other words, in a ratio of about 1:1.4. A second conjugate consisting of TT and a meningococcal polysaccharide is characterised by a ratio of 1:1 (see

abstract, page 3504, column 2, third paragraph to page 3505, column 1, first paragraph). Thus, both conjugate antigens have ratios which fall within the range defined in claim 1. The document further discloses that "*priming*" the mice, *i.e.* pre-immunising them with a low dose of free, *i.e.* non-conjugated TT carrier protein, increases the antibody response to the bacterial polysaccharides upon subsequent vaccination with conjugates of TT linked to these polysaccharides.

7.4 Document D57 is a review article about conjugate vaccines of different bacterial pathogens, including *Haemophilus influenzae* serotype B (Hib), *S. pneumoniae* and *N. meningitis* (see page 217, last paragraph to page 218, second paragraph).

8. The board notes that only documents D5, D40 and D57 relate to the same purpose as the invention, *i.e.* vaccines for the prevention of either pneumococcal or meningococcal infections.

Concerning the commonality of technical features, the board considers that in relation to the embodiment under consideration (see point 4 above) document D40 shares the highest number, because it discloses a polysaccharide to carrier protein ratio in the conjugate which falls within the claimed range and the administration of a free carrier protein - albeit prior to that of the conjugate. The combination vaccines of documents D5 and D57 disclose neither the claimed ratio in their conjugated antigens nor a free carrier protein.

Thus, document D40 represents the closest prior art.

Technical problem and solution

9. The technical problem to be solved is to be formulated in the light of the technical effects achieved by those features distinguishing the claimed invention from the closest prior art (see CLBA, 7th edition 2013, I.D. 4.3.1, second paragraph).

10. The difference between the embodiment of claim 1 relating to monovalent vaccines and the vaccines disclosed in document D40 is that the claimed vaccines relate to "combined vaccines", *i.e.* they comprise the polysaccharide-protein carrier conjugates and the free carrier protein in a single formulation. This has the advantage that the number of necessary vaccine injections to achieve a protective immune response is reduced, resulting in more convenient and comfortable vaccination schemes for patients. Hence, in the light of the disclosure in document D40 the technical problem to be solved is formulated as the provision of a monovalent vaccine for preventing infections by *S. pneumoniae* or *N. meningitides* with an improved comfort and convenience when administered to patients.

11. The appellant argued that the objective technical problem starting from document D5 as the closest prior art was "*how to formulate the conjugate in an alternative combination vaccine against S. pneumonia or N. meningitidis also containing the carrier protein in free form thereby avoiding significant immune interference*".

12. However, as noted in point 7.3 above, the closest prior art document D40 already discloses conjugate antigens with ratios of polysaccharide to carrier protein which are within the range defined in claim 1. Assuming

further that the subject-matter of claim 1 is a solution to the problem formulated by the appellant, then it is to be expected that a "*significant immune interference*" which is avoided by conjugates of the claimed ratio, also does not occur when using the vaccine according to document D40. Hence, concerning the issue of "*immune interference*" the board does not see any difference between the vaccines disclosed in document D40 and those presently claimed, so that this effect cannot be taken into account for the formulation of the technical problem (see point 9 above). In view of these considerations, the board is not convinced that the technical problem is to be formulated as suggested by the appellant.

13. The board is satisfied that the technical problem formulated in point 10 above is solved by the subject-matter of claim 1, since the combination of the conjugate antigen and the free carrier into a single formulation reduces the amount of injections necessary to achieve a protective immune response.

Obviousness

14. The issue to be assessed here is whether the skilled person, starting from the vaccines of document D40 and faced with the technical problem identified in point 10 above, would be motivated to provide the claimed vaccines.

15. At the priority date of the patent, the skilled person was certainly aware of the advantages offered by combination vaccines. Document D5, for example, discloses on page 353, left column: "*Vaccines consisting of a combination of protective antigens derived from different pathogenic organisms have some obvious*

attractions. In particular, they may greatly simplify immunization schedules and they offer increased ease of administration and greater comfort and convenience to the patient by reducing the number of injections required and possibly the number of attendances. They may also prove more economical to manufacture and administer because of savings on processing of combined bulk materials, containers, packaging, distribution and injection equipment."

16. In the context of infant immunisation programmes the development of combined vaccines was even considered "*mandatory*" (see documents D5, page 353, abstract and column 1, first paragraph). Document D55 reports along the same lines on page 35, lines 1 to 3 that "*One of the goals of the Children's Vaccine Initiative (CVI) is to reduce the number of contacts required to immunize a child fully. To meet this goal, new combination vaccines will need to be developed.*"

17. On the other hand, the skilled person was also certainly aware of potential problems that could be associated with the combination of formerly individual vaccine formulations into a single one, for example a "*sub-optimal immunogenicity*" or "*excessive batch-to-batch variation resulting from complex interactions of multiple components*" (see e.g. document D5, Table 4), or buffer or adjuvant incompatibilities (see e.g. document D55, page 36 and 37, under the heading "Interaction of vaccines"). It was furthermore known that the occurrence of any of these potential problems for a given combination vaccine was unpredictable, in particular whether or not the combined vaccine would generate an equivalent protective immune response to that when the vaccines were administered separately (see document D5, page 359, column 2, last paragraph). Also, document D5

as a whole highlights the necessity to monitor and control the quality of combination vaccines (see page 359, column 2, last paragraph to page 360, column 1, first paragraph, Tables 7 and 8).

18. Yet, document D55 discloses that "*The possibility of immunological interaction between different vaccine components of combination vaccines remains relatively unexplored. Interaction could either enhance or suppress the immune response to individual vaccine components. Overall, when tested, the theoretical possibility of enhanced reactivity or suppression of immune responses with vaccine combinations has rarely been observed*" (see page 37, third paragraph; emphasis added by the board).

19. Consequently, in the board's view the knowledge of potential risks when combining individual vaccine components - the occurrence of these risks being apparently very low - would not have discouraged the skilled person from combining the individual components into a single formulation. This is so because of their apparent need and in view of the attractive advantages offered by such a combination, including a reduced number of injections (see points 15 and 16 above).

20. Thus, the skilled person starting from the monovalent vaccines disclosed in document D40 and faced with the technical problem identified in point 10 above would have been motivated to provide the "combined" monovalent vaccines encompassed by claim 1.

21. Hence, in the board's judgment, the provision of a combined vaccine according to claim 1 is obvious for the skilled person in the light of the teaching of document D40 and documents D5 or D55. Consequently, the ground of opposition under Article 100(a) EPC in combination with

Article 56 EPC prejudices the maintenance of the patent as granted, *i.e.* the main request.

Inventive Step (Article 56 EPC)

Auxiliary requests 1 to 3 and 5 - claim 1

22. Claims 1 of auxiliary requests 1, 2 and 5 differ from claim 1 of the main request in that the ratio range of the polysaccharide to carrier protein in the conjugate is from 1:0.3 to 1:1.5 or from 1:0.5 to 1:1.5 respectively (emphasis added by the board). Claims 1 of auxiliary requests 3 and 5 in addition differ from claim 1 of the main request in that the carrier protein is defined as "a Diphtheria or Tetanus antigen which is Diphtheria toxoid or Tetanus toxoid, or a non toxic derivative of a toxin from Diphtheria or Tetanus".

23. The conjugate vaccines of document D40 have a polysaccharide to carrier protein ratio in the conjugates which falls within the range defined in claims 1 of all of auxiliary requests 1 to 3 and 5. Moreover, tetanus toxoid is the carrier protein of the conjugates and it is administered as a free carrier protein - albeit in a separate formulation (see point 7.3 above). Hence, the reasoning in points 8 to 21 above applies *mutatis mutandis* to claims 1 of auxiliary requests 1 to 3 and 5. Therefore, none of these requests is allowable since they do not fulfil the requirements of Article 56 EPC.

Auxiliary requests 4 and 6 - claim 1

24. Claims 1 of auxiliary requests 4 and 6 differ from previous auxiliary requests 3 and 5 respectively, in that they additionally recite the feature "and further comprising antigens protective against Diphtheria, Tetanus, and pertussis infection".

25. As regards this feature, the board notes that the incorporation of DTP antigens in combination vaccines is already highlighted in document D5 (see page 353, column 1, first paragraph) and document D55 (see page 35, lines 1 to 3). Also, the specific combination of DTP antigens with either meningococcal or pneumococcal conjugate antigens in a single vaccine formulation has been proposed in these two prior art documents (see documents D5, page 353, lines 3 to 5; and D55, page 35, lines 9 to 13).

26. It follows from the reasoning given in points 8 to 21 above that the subject-matter of claims 1 of auxiliary requests 4 and 6 is obvious for the skilled person in the light of the combined teaching of document D40 and either one of documents D5 or D55.

Consequently, also these two requests do not fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated