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Datasheet for the decision of 28 June 2007

Case Number: T 0602/05 - 3.3.04

Application Number: 96922871.7

Publication Number: 0833662

IPC: A61K 39/39

Language of the proceedings: EN

Title of invention:
A vaccine composition comprising a polysaccharide conjugate antigen adsorbed onto aluminium phosphate

Patentee:
SmithKline Beecham Biologicals S.A.

Opponent:
Novartis Vaccines and Diagnostics, Inc.

Headword:
Polysaccharide conjugate vaccine/SMITHKLINE BEECHAM

Relevant legal provisions:
EPC Art. 54, 56, 123(2)

Keyword:
"Main request - added subject-matter (yes)"
"First auxiliary request - added subject-matter (no), novelty, inventive step (yes)"

Decisions cited:
G 0001/03, T 0019/90, T 0939/92, T 0727/00

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0602/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 28 June 2007

Appellant: (Patent Proprietor)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 28 February 2005 concerning maintenance of the European Patent No. 0833662 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietor (Appellant) against the decision of the Opposition Division, according to which the European patent No. 0 833 662 could be maintained in amended form pursuant to Article 102(3) EPC.

II. The Opposition Division had decided that the claims of the main request and of "auxiliary request 4" before them contained subject-matter which extended beyond the content of the application as filed contrary to the requirements of Article 123(2) EPC. However, they decided that the claims of "auxiliary request 5" before them met all requirements of the EPC. No other requests were maintained by the Patent Proprietor at the oral proceedings before the Opposition Division.

III. The Board expressed its preliminary opinion in a communication dated 15 January 2007.

Oral proceedings were held on 28 June 2007.

IV. The Appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the main request filed with the grounds of appeal or, in the alternative, the first auxiliary request filed at the oral proceedings.

The Opponent (Respondent) requested that the appeal be dismissed.

V. Claims 1, 2, 6, 7, 8 and 14 of the main request read as follows:

"1. A combination vaccine comprising:

i) a capsular polysaccharide of Haemophilus influenzae B conjugated to a carrier protein characterised in that the conjugate is adsorbed onto aluminium phosphate; and

ii) other antigens which afford protection against diphtheria, tetanus and pertussis disease.

2. A combination vaccine as claimed in claim 1 wherein the conjugate is admixed with one or more other antigens which afford protection against a disease selected from the group: Hepatitis A, Hepatitis B and Polio.

6. A combination vaccine as claimed in any one of claims 1 to 5 wherein the adsorbed conjugate has been freeze dried prior to its combination with the other antigens.

7. A combination vaccine according to claim 6 wherein the other antigens are in a liquid form.

8. A kit for making a combination vaccine comprising a container of a freeze-dried vaccine comprising a capsular polysaccharide of Haemophilus influenzae B conjugated to a carrier protein and adsorbed onto aluminium phosphate, and a second container with a vaccine which affords protection against diphtheria, tetanus and pertussis disease.

14. The combination vaccine of claim 2 wherein the capsular polysaccharide of Haemophilus influenzae B is conjugated to tetanus toxoid, and wherein the vaccine comprises the following antigens: diphtheria toxoid, tetanus toxoid, whole-cell pertussis and Hepatitis B surface antigen."

Dependent claims 3 to 5 and 13 refer to preferred embodiments of the combination vaccine of claims 1 and 2, claims 9 and 10 refer to a method of producing the combination vaccine, claims 11 and 12 relate to the vaccine for use in medicine, respectively to its use in the manufacture of a medicament for the treatment of Haemophilus influenzae B infection.

Claims 1 to 12 of the first auxiliary request correspond to claims 1 to 6 and 8 to 13 of the main request, with claims 7 and 14 thereof being deleted.

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

(2) EP-A-0 594 950

(5) Pediatr. Infect. Dis. J., Vol.10, 1991, pages 758 to 761

(10) Vaccine, Vol.13, No.6, 1995, pages 525 to 531

(11) Can. Med. Assoc. J., Vol.149, No.8, 1993 pages 1105 to 1112

(18) Pediatr. Infect. Dis. J., Vol.12, 1993, pages 632 to 637

(22) Pediatr. Infect. Dis. J., Vol.12, 1993, pages 638 to 643

(32) WO 02/00 249

(44) European Medicines Agency, EMEA/H/C/000556, submitted by the Appellant with letter dated 18 June 2007, pages 1/2 to 2/2

VII. The submissions by the Appellant, as far as they are relevant to the present decision, may be summarised as follows:

The claims of the main request, and in particular claims 1, 7, 8 and 14, were based on the application as published (WO 97/00697) and met the requirements of Article 123(2) EPC.

None of the prior art documents on file disclosed adsorption of capsular polysaccharide (PRP, a polymer of ribose, ribitol and phosphate) from Haemophilus influenzae B (Hib) conjugated with a carrier protein onto aluminium phosphate. The claims are therefore novel within the meaning of Article 54 EPC.

Combination vaccines providing protection against diphtheria, tetanus and pertussis infections (DTP) were known in the art. These vaccines comprised a whole cell (Pw) or acellular (Pa) pertussis component. It would have been desirable to add PRP from Hib conjugated with a carrier protein to such combination vaccines, but simple mixing of the components resulted in a reduction of antibody titres to the PRP component. This drawback

was known in the art as interference. The problem underlying the patent in suit was to reduce interference between the antigens in a combination vaccine comprising a PRP conjugate and a DTP vaccine.

This problem had been solved by adsorbing the PRP conjugate onto aluminium phosphate before bringing it into contact with the other components of the combination vaccine. Example 2 of the patent proved the increased immunogenicity of PRP-tetanus toxoid conjugate pre-adsorbed on aluminium phosphate and combined with DTPa or DTPa-Hepatitis B. The Respondent has not provided any data to substantiate his argument that the problem had not been solved with regard to vaccines comprising Pw. Appellant's product comprising PRP-tetanus toxoid conjugate pre-adsorbed onto aluminium phosphate, DTPw and Hepatitis B surface antigen, designated Quintanrix^{RTM}, had been approved by the European Medicines Agency (EMEA).

The subject-matter of the claims could not be derived in an obvious way from the disclosure in the prior art documents on file.

The patent disclosed the invention in a manner sufficiently clear and complete for it to be carried out over the whole scope of the claims. No evidence had been provided that the claims embraced non-working embodiments.

VIII. The submissions by the Respondent, as far as they are relevant to the present decision, may be summarised as follows:

Claims 1, 7, 8 and 14 of the main request had no basis in the application as published, contrary to the requirements of Article 123(2) EPC.

Documents (2), (10) and (11) disclosed mixing of aluminium phosphate adsorbed DTPw vaccines with unabsorbed PRP conjugate. As a certain amount of PRP-conjugate was expected to have been adsorbed onto free aluminium phosphate at the mixing stage, the disclosure in these documents anticipated the novelty of the subject-matter claimed (Article 54 EPC).

No objection as to lack of inventive step was raised with regard to DTP-Hib combination vaccines. However, claim 1 was not restricted to this embodiment. Due to the word "comprising" used in the opening phrase of the claim, it covered also combination vaccines containing additional antigens.

Document (32), an international patent application of the Appellant, published almost seven years after the priority date of the patent in suit, disclosed a DTPw-HepB vaccine extemporaneously mixed with Hib-TT pre-adsorbed onto aluminium phosphate. Tests showed that surprisingly the Geometric Mean Titre (GMT) of a quarter dose Hib-TT formulation was higher than the titre of a full dose or half dose formulation. It was concluded that "this effect should be even greater if the Hib-TT vaccine is unadsorbed." Accordingly, the problem underlying the invention, namely reduction of Hib interference with other antigens was not solved by a combination vaccine comprising DTPw-HepB-Hib-TT, which was an embodiment of claim 1.

Moreover, as Pw not only acted as an antigen, causing the formation of specific antibodies, but also was a strong adjuvant, increasing the potency of other antigens given at the same time, the problem which the Appellant alleged to have been solved by providing the vaccine according to claim 1, did not exist in vaccines comprising Pw. A possibly existing interference of Hib with other antigens was masked by the strong adjuvant activity of Pw.

As the scope of the claims covered non-working examples also the requirements of Article 83 EPC were not met.

Reasons for the Decision

Main Request

Amendments - Article 123(2)

1. Claim 1 refers to a combination vaccine comprising a PRP conjugate adsorbed onto aluminium phosphate and other antigens which afford protection against diphtheria, tetanus and pertussis disease.

The application as published describes on page 1, line 26 to page 2, line 3, that combination vaccines providing protection against diphtheria, tetanus and Bordetella pertussis infections are known in the art. These vaccines comprise either a whole cell (Pw) or an acellular (Pa) pertussis component, and are accordingly referred to as DTPw or DTPa.

Page 2, lines 4 to 5 reads: "It would be desirable to add polysaccharide conjugate vaccines to **such a combination**." (emphases added by the Board).

The description continues that simple mixing of the components, namely DTPw or DTPa and a polysaccharide conjugate vaccine, results in a reduction of antibody titres to the polysaccharide component, but that it were the present inventors who found that this interference can be inhibited if the polysaccharide component (preferably PRP from Hib) conjugated with a carrier protein is adsorbed onto aluminium phosphate (page 2, lines 6 to 14).

Contrary to the argumentation brought forward by the Respondent, who considered that the part of the invention referring to DTPw and DTPa vaccines was merely describing the prior art and had not to be connected with the present invention, the Board is convinced that these passages from the description of the application as published refer to the subject-matter of the presently claimed invention. The sentence starting with the words "It would be desirable to.." on page 2, line 4, is considered to lay down the technical field of the present invention, namely DTPw or DTPa vaccines additionally comprising a polysaccharide conjugate vaccine. The following lines describe a problem occurring when manufacturing such vaccines, namely interference between the different antigens, and defines the problem underlying the patent in suit, namely to reduce interference. Finally the claimed solution to this problem is indicated.

Consequently, the Board decides that claim 1 is based on the disclosure on page 1, line 26 to page 2, line 14 of the application as published.

2. Claims 2 to 6 and 13, referring to preferred embodiments of the combination vaccine of claim 1, are based on claims 3 to 5, 7 and 8, and on page 3, line 14 to 15 and lines 30 to 31 of the application as published.

3. Claim 7 refers to a combination vaccine wherein the aluminium phosphate adsorbed PRP conjugate has been freeze dried prior to its combination with the other antigens, which are in liquid form.

According to the Appellant, the application as published contains a basis for claim 7 on page 4, lines 17 to 22 and on page 7, lines 8 to 12.

The cited passage on page 4 describes "... a method of producing **the vaccine** comprising adsorbing the conjugate antigen on to aluminium phosphate ... at a pH of between 5 and 6, preferably at about 5.4. In an embodiment **the vaccine** is freeze dried after standing for more than 24 hours. **Alternatively, the vaccine** of the invention may be combined with other antigens in a liquid form." (emphases added by the Board).
This disclosure does not form a basis for a vaccine containing a freeze dried conjugate antigen adsorbed onto aluminium phosphate **and** other antigens in liquid form. Rather these two features are defined as alternative embodiments of the claimed invention.

Also the statement on page 7, that freeze dried pre-adsorbed PRP-TT is mixed with DTPa or DTPaHB one hour before injection into baby rats, does not disclose that the "other antigens" are in liquid form.

Claim 7, therefore, contains subject-matter extending beyond the content of the application as published.

4. Claim 8 refers to a kit comprising two separate containers, one comprising freeze dried vaccine comprising PRP from Hib conjugated to carrier protein and adsorbed onto aluminium phosphate, the other containing a DTP vaccine.

The claim finds a basis in claim 10 when read in combination with page 1, line 26 to page 2, line 14 of the application as published (see point (1) above).

5. Claims 9 and 10 refer to a method for producing the claimed combination vaccine and are based on claim 11 and example 2 of the application as published.

6. Claims 11 and 12 refer to the combination vaccine for use in medicine and to its use for the manufacture of a medicament for the treatment of Hib infection and are based on claims 12 and 13 of the application as published.

7. Claim 14 refers to a vaccine comprising PRP-TT, DTPw and Hepatitis B surface antigen. The individual components of the claimed vaccine are disclosed in different lists contained in the application as published.

A specific combination - unsupported by the application as published - of one item from different lists of features means that although the application as published might conceptually comprise the claimed-subject-matter, it does not however disclose it in that particular individual form. For this reason, claim 14 is not supported by the description of the application as published (cf decision T 727/00 of 22 June 2001; point (1.1) of the reasons for the decision).

8. Consequently, as claims 7 and 14 contain subject-matter extending beyond the content of the application as filed, Appellant's main request does not meet the requirements of Article 123(2) EPC.

First auxiliary request

Amendments - Article 123(2) and (3) EPC

9. The claims of the first auxiliary request are distinguished from the claims of the main request only in so far as claims 7 and 14 have been deleted.

The claims as granted refer to a combination vaccine comprising a PRP conjugate and one or more other antigens. In the claims of the first auxiliary request these "other antigens" are defined as affording protection against diphtheria, tetanus and pertussis disease. Thus, the scope of protection of the claims has been restricted.

Consequently, the claims have not been amended during opposition proceedings in such a way as to extend the protection conferred.

Claims 1 to 12 of the first auxiliary request meet the requirements of Article 123(2) and (3) EPC.

Novelty - Article 54 EPC

10. Document (2) discloses a combination vaccine comprising a mixture of non-adsorbed PRP conjugate with diphtheria toxoid and tetanus toxoid, both adsorbed onto aluminium phosphate, and inactivated B. pertussis cells (Pw) suspended in a solution (see claims 1 to 3).

Document (11) investigates the possibility of combined administration to infants of an aluminium phosphate adsorbed DTP vaccine and a non-adsorbed PRP conjugate vaccine. It reports the manufacture of a combination vaccine by mixing the two vaccines (see page 1107, left column, second paragraph).

Document (10) deals with the development of a guinea pig model to assess immunogenicity of PRP conjugate vaccines. It reports the preparation and administration of a combination vaccine comprising aluminium phosphate adsorbed DTP vaccine and non-adsorbed PRP conjugate (see page 526, right column, first full paragraph). Table 6 on page 530 refers to an adsorbed HibT-1a conjugate eliciting a high antibody titre.

11. The Respondent has argued that by mixing aluminium phosphate adsorbed DTP vaccine and non-adsorbed PRP conjugate, inevitably small amounts of PRP conjugate vaccine must have been adsorbed onto free aluminium phosphate. As claim 1 does not contain a definition of the required degree of adsorption, the disclosure in

documents (2), (10) and (11) anticipated the claimed subject-matter.

12. Claim 1 refers to a combination vaccine comprising a PRP conjugate, characterised in that **the conjugate is adsorbed onto aluminium phosphate**. Further clarification that adsorption as mentioned in the claims is not an accidental and marginal effect which takes place during the mixing of non-adsorbed PRP conjugate and another vaccine adsorbed onto aluminium phosphate, but efficient and stable adsorption obtained in a separate working step, can be found throughout the patent specification and especially in example 2, having the title: "Immunogenicity of PRP-TT conjugate **preadsorbed** on aluminium phosphate and combined with DTPa and DTPa-HB" (emphases added by the Board).

In addition, no evidence, for example in the form of experimental data, has been provided by the Respondent from which it could be concluded that merely mixing of aluminium phosphate adsorbed DTP vaccine and non-adsorbed PRP conjugate, inevitably resulted in the adsorption of small amounts of PRP conjugate vaccine onto free aluminium phosphate.

Accordingly, Respondent's argument, which is based on an assumption only, must fail. The subject-matter of claims 1 to 12 of the first auxiliary request is novel over the disclosure in documents (2), (10) and (11) and in all other prior art documents on file. The requirements of Article 54 EPC are met.

Inventive step - Article 56 EPC

13. In accordance with the problem and solution approach, the Boards of Appeal in their case law have developed certain criteria for identifying the closest prior art providing the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be 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 (cf Case Law of the Boards of Appeal of the European Patent Office, 5th Edition 2006, chapter I.D.3.1).

14. In the present case the closest state of the art is represented by a group of documents which like the patent in suit disclose combination vaccines comprising PRP from Hib conjugated to a carrier and a DTP vaccine. Documents (2), (10) and (11), whose disclosure is described in point 10 above, belong to this group of documents.

A number of documents are on file which also refer to this subject-matter. Examples of this group of documents are:

Document (5) discloses a combination vaccine produced by mixing a DTPw vaccine adsorbed onto aluminium hydroxide and a PRP-TT conjugate (page 759, left column).

Document (18) reports the mixing of a DTP vaccine adsorbed onto aluminium potassium sulphate and a PRP-OMPC conjugate (Outer Membrane Protein Complex of *Neisseria meningitidis*) on page 633, right column.

Document (22) discloses mixing of an aluminium potassium sulphate adsorbed DTPw vaccine and PRP-TT conjugate (pages 638 and 639).

15. All of the above documents, each of which can be considered to represent the closest state of the art, investigate the effect of mixing the DTP vaccine with the PRP component on the anti-PRP response. The antibody titres elicited to the PRP component upon separate administration of the DTP vaccine and the PRP conjugate are compared with the antibody titres obtained upon mixing the components before administration.

16. The prior art documents arrive at different results with regard to the interference between the antigens, i.e. the reduction of antibody titres to the Hib component.

A first group of documents reports that the response to the PRP conjugate was reduced upon mixed administration together with a DTP vaccine (see document (5), page 762, passage bridging left and right column); document (18), page 636, right column; document (22), page 638, abstract).

However, document (2) reports an opposite effect on page 4, lines 23 to 24 ("The response to Hib polysaccharide after each of three immunizations was higher in the subjects receiving the combined vaccine..."). The same is said by document (10) which discloses that PRP antibody responses were similar or

enhanced with DTP-Hib-T compared to Hib-T given alone (page 530, end of left column).

The authors of document (11) report on page 1111, right column, lines 9 to 12 that that they observed no effect on the anti-PRP response after three doses of mixed product (DTP-PRP-T) when compared with responses to separately injected vaccines. However, they also mention that their results contrast with those from a recent study in Chile in which responses to PRP-T vaccine were reduced by more than 50% after three doses of mixed vaccines as compared with separately injected vaccines (page 1111, lines 16 to 20), and that PRP-T vaccines combined with a DTP vaccine made in France resulted in weaker responses to PRP and pertussis than separately injected vaccines (page 1106, passage bridging left and right column).

17. The problem to be solved by the patent in suit is the provision of a combination vaccine comprising a PRP conjugate from Hib and a DTP vaccine, wherein the interference between the Hib component and the other antigens contained in the vaccine is reduced.

The subject-matter of present claim 1 is distinguished from the disclosure in each of documents (2), (5), (10), (11), (18) and (22), which have been analysed above, in so far as the PRP conjugate is adsorbed onto aluminium phosphate before bringing it into contact with the other antigens.

18. The Respondent did not dispute that example 2 of the patent in suit convincingly shows that the problem formulated above has been solved by the subject-matter

of claim 1 with regard to vaccines comprising Pa as pertussis component.

However, he argued that no data has been provided showing that the subject-matter of claim 1 can overcome the problem of interference in DTP-PRP-conjugate vaccines comprising Pw. In fact the technical problem underlying the patent in suit did not even exist for such combination vaccines. Pw not only acted as an antigen, causing the formation of specific antibodies, but also was a strong adjuvant and as such increased the potency of other antigens given at the same time. Thus, if there was interference between the PRP compound and the other antigens, this effect would have been masked by the strong adjuvant activity of Pw.

He referred in this respect to document (32), a post-published International patent application of the Appellant. Example 6, on page 20, disclosed the results of a randomized trial for assessing the immunogenicity of Hib-TT adsorbed onto aluminium phosphate mixed at various doses with a DTPw-HepB vaccine. Surprisingly it was found that the highest anti-PRP titer was obtained with a formulation having the lowest dose of Hib-TT. The last sentence on page 20 read: "This effect should be even greater if the Hib-TT vaccine is unadsorbed."

The Respondent concluded that even the Appellant in later publications was aware that adsorbing Hib-TT onto aluminium phosphate was not helpful to overcome the drawback of reduced anti-PRP titers in combination vaccines comprising DTPw. Accordingly, he argued that the subject-matter of claim 1 encompassed non-working embodiments.

19. If a claim comprises non-working embodiments, this may have different consequences, depending on the circumstances. If a technical effect, in the present case the reduction of interference, is expressed in a claim and thereby constitutes a real technical feature, there may be lack of sufficient disclosure. Otherwise, if the effect is not expressed in a claim but rather is part of the problem to be solved, like in the present case, it may be a question of whether a given problem is solved by all embodiments falling under the claim which results in a problem of inventive step (cf decision of the Enlarged Board of Appeal G 1/03, OJ EPO 2004, 413, point (2.5.2) and T 939/92, OJ EPO 1996, 309).

20. Thus, the question whether or not a combination vaccine comprising PRP-TT adsorbed onto aluminium phosphate and a DTPw vaccine shows reduced interference between the Hib component and the other antigens contained in the vaccine, is a question that has to be answered when examining the requirements of Article 56 EPC.

21. It is not disputed between the parties that Pw is a strong vaccine adjuvant which increases the potency of a vaccine. However, contrary to the Respondent, who argued that the adjuvant effect of Pw inevitably masks an interference between the Hib component and the other antigens comprised in the vaccines according to claim 1, so that no beneficial effect of adsorbing PRP-TT to aluminium phosphate could be detected, the Appellant argued that the adjuvant-effect of Pw, respectively its influence on PRP interference and possible masking thereof, was not present in each and every case and

depended on the antigens actually used for the manufacture of a vaccine. In other words, while a specific lot of Pw when used for the production of a vaccine according to claim 1 may be able to mask the reduction of antibody titers to the PRP component, another lot may not.

22. Upon careful consideration of the disclosure in prior art documents (2), (5), (10), (11), (18) and (22), and in particular of the differing results of comparative tests described in points 15 and 16 above, the Board comes to the conclusion that PRP interference is not masked in each and every case by mixing a DTP vaccine comprising Pw with a PRP conjugate.

This is supported by a statement in document (11), page 1111, right column, lines 20 to 22, which reads: "The differing results most likely reflect compositional differences between the DTP products used."

23. Example 6 on page 20 of document (32), referred to by the Respondent to show that the Appellant himself does not consider that the problem underlying the patent in suit has been solved for the embodiment of a DTPw containing combination vaccine, does not contain any experimental data showing that higher anti-Hib-TT titers can in fact be obtained if the PRP-TT vaccine is unadsorbed.

24. Decision T 19/90 (OJ EPO 1990, 476), in point (3.3) of the reasons for the decision, decided on the quality of evidence required by a Board in order to decide that embodiments falling with the scope of a broad claim do

not work. The competent Board came to the conclusion that serious doubts substantiated by verifiable facts have to be required. Although decision T 19/90 in this point was concerned with the examination of the requirements of Article 83 EPC, the present Board, bearing in mind that the question if a claim comprises non-working embodiments may have different consequences, depending on the circumstances (see point (19) above), is of the opinion that the criteria elaborated in decision T 19/90 have to be applied also in the present case.

25. The subject-matter of claim 1 covers combination vaccines comprising PRP conjugate adsorbed on aluminium phosphate and a DTP vaccine, wherein the pertussis component may either be Pa or Pw. In example 2 of the patent it is shown that the problem underlying the invention, namely to inhibit the reduction of antibody titers to the PRP component in DTP-PRP-TT vaccines has been solved in an embodiment wherein the combination vaccine comprises Pa. Moreover, the Appellant has submitted post published document (44) from which it can be deduced that a PRP-TT-DTPw-HepB vaccine according to claim 1 has been approved by the European Medicines Agency (EMEA).

26. For the reasons set out in points 22 and 23 above, the Board comes to the decision that the evidence provided by the Respondent in order to substantiate the argument that claim 1 embraces non-working embodiments, does not meet the criteria established by the case law of the Boards of Appeal (cf decision T 19/90 supra) in that it fails to demonstrate serious doubts substantiated by verifiable facts.

The Board therefore has to reach the conclusion that the problem underlying the patent in suit has been solved over the scope of claims 1 to 12 of the first auxiliary request.

27. Within the requirements of Article 56 EPC it remains to be examined if this solution involves an inventive step.

As already mentioned in point 14 above, the closest state of the art is represented by a group of documents which each, like the patent in suit, disclose combination vaccines comprising PRP from Hib conjugated to a carrier and a DTP vaccine.

The subject-matter of claims 1 to 12 is distinguished therefrom in so far as the PRP conjugate is adsorbed onto aluminium phosphate before mixing it with other vaccine components.

28. The only document on file which mentions a PRP conjugate from Hib adsorbed on aluminium phosphate, albeit not as part of a combination vaccine comprising other antigens, is document (10) (see page 529, left column and table 6 on page 530).

Document (10) is concerned with the development of a guinea pig model to assess immunogenicity of Hib-PRP conjugate vaccines.

The utility of the guinea pig model to study immunogenicity of a Hib-T vaccine combined with DTPw vaccine is discussed on page 529, left column. It is found that the antibody response to PRP in guinea pigs

was unaffected when HibT-1 was mixed with DTP at the time of injection. Data substantiating this are given in the upper part of table (6) on page 530. The second part of table (6) shows the antibody response to PRP in guinea pigs obtained upon administration of different mixed vaccine formulas stored 1 month at 4°C. The antibody response to PRP elicited by two combination vaccines comprising HibT-1a and different lots of a DTPw vaccine are enhanced compared with the response to HibT-1a alone. The highest response is obtained by administering a vaccine containing HibT-1a adsorbed onto aluminium phosphate as the sole antigenic compound.

29. The authors of document (10) summarise "... that the PRP antibody responses were similar or enhanced with DTP-Hib-T compared to Hib-T given alone." Therefore, since "... In infants, a combination of Hib conjugate vaccine with DTP vaccine did not have important effects on the immunogenicity of PRP, tetanus and diphtheria components..." they reach the conclusion "... that the guinea pig model of Hib conjugate vaccine immunogenicity may be useful as a control test as well as for pre-clinical evaluation of new vaccine combinations containing diphtheria, tetanus, pertussis and Hib components." (see page 530, passage bridging left and right column).

30. Document (10) is not concerned with the problem underlying the patent in suit, namely the provision of a combination vaccine comprising a PRP conjugate from Hib and a DTP vaccine, wherein the interference between the Hib component and the other antigens is reduced. The tests carried out according to the experimental design of document (10) show that in the disclosed

guinea pig model no interference existed between the Hib component and the other antigens contained in the tested combination vaccine (PRP antibody responses were similar or enhanced with DTP-Hib-T compared with Hib-T alone).

Thus, despite the high antibody response obtained in guinea pigs upon administering Hib-T adsorbed onto aluminium phosphate, the skilled reader trying to solve the problem underlying the patent in suit, would get no incentive to modify the combination vaccines disclosed in document (10) and in many other documents (see points (11) and (14) above) and to arrive at the claimed subject-matter in an obvious way.

Accordingly, the subject-matter of claims 1 to 12 involves an inventive step and meets the requirements of Article 56 EPC.

Sufficiency of disclosure - Article 83 EPC

31. For the reasons outlined in points 19 and 20 above, Respondent's arguments, that the claims encompass non-working embodiments, have been dealt with in the part of the decision referring to the requirements of Article 56 EPC. No other objections or arguments have been presented by the Respondent in the appeal procedure.

The Board is satisfied that the patent discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, according to the requirements of Article 83 EPC.

Order

Reasons for the decision:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of claims 1 to 12 of the first auxiliary request filed at the oral proceedings and a description still to be adapted thereto.

Registrar: Chair:

P. Cremona U. Kinkeldey