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D E C I S I O N
of 26 October 2005

Case Number: T 1010/01 - 3.3.04

Application Number: 90907222.5

Publication Number: 0471726

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Language of the proceedings: EN

Title of invention:
Acellular vaccine

Patentee:
MEDEVA B.V.

Opponents:
Chiron Corporation
Aventis Pasteur Limited/Aventis Pasteur Limitée

Headword:
Acellular vaccine/MEDEVA B.V.

Relevant legal provisions:
EPC Art. 83, 87(4), 54, 56

Keyword:
"Main request, first auxiliary request, second auxiliary request: inventive step (no)"
"Third auxiliary request: sufficiency of disclosure (yes); right to priority (yes); novelty (yes); inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1010/01 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 26 October 2005

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 27 April 2001 revoking European patent No. 0471726 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. European Patent No. 0 471 726 (application No. 90 907 222.5) claiming priority from GB 8910570 of 8 May 1989 (hereafter: "the priority document") was filed on 26 April 1990. The patent relates to an acellular vaccine and was granted on the basis of 9 claims for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL and SE and 5 claims for the Contracting State ES. Claims 1, 5 and 8 for all designated Contracting States except ES read as follows:

"1. An acellular vaccine comprising the 69kDa antigen of Bordetella pertussis and the filamentous haemagglutinin antigen of Bordetella pertussis in admixture with a saline solution, the 69kDa antigen and the filamentous haemagglutinin antigen being present in a weight ratio of between 1:10 and 10:1 so as to produce a synergistic effect in vaccine potency.

5. A vaccine as claimed in any one of claims 1 to 4 further comprising an adjuvant.

8. Use of a 69kDa antigen of Bordetella pertussis, the filamentous haemagglutinin antigen of Bordetella pertussis and a saline solution for the manufacture of an acellular vaccine for the prophylactic treatment of a mammal susceptible to B. pertussis infection, wherein the vaccine contains the 69kDa antigen and the filamentous haemagglutinin antigen in a weight ratio of between 1:10 and 10:1 so as to produce a synergistic effect in vaccine potency."

Claims 2 to 4 and 6 to 7 related to specific embodiments of the vaccine of claim 1. Claim 9 was addressed to a method for the preparation of the vaccine of claim 1. The claims for the Contracting State ES were drafted as corresponding method claims.

II. Notices of opposition were filed by opponents (01) and (02) both requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC. By a decision dated 27 April 2001 the opposition division revoked the patent on the grounds that the patent did not contain a sufficient disclosure to enable a skilled person to obtain the synergistic effect required by claim 1 of the main request and of the auxiliary request then on file.

III. The appellant (patentee) filed an appeal against the decision of the opposition division. Opponent (02) withdrew its opposition during the appeal phase.

IV. On 19 February 2004, the appellant filed inter alia a **Main Request** (claims 1 to 8 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES), of which claim 1 for the non-ES Contracting States read as follows:

"1. An acellular vaccine comprising the 69kDa antigen of Bordetella pertussis and the filamentous haemagglutinin antigen of Bordetella pertussis in admixture with a saline solution, the 69kDa antigen and the filamentous haemagglutinin antigen being present in a weight ratio of between 1:10 and 10:1 so as to

produce a synergistic effect in vaccine potency, the vaccine further comprising an adjuvant."

Claim 1 of this request for the Contracting State ES was drafted as a method claim.

V. In the oral proceedings held on 19 March 2004 only the issue of sufficiency of disclosure of the subject-matter of the claims of the Main Request was heard.

VI. On 26 September 2005, the appellant filed a **Second Auxiliary Request** (claims 1 and 2 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES), of which claim 1 for the non-ES Contracting States read as follows:

"1. Use of purified 69kDa antigen of Bordetella pertussis, purified filamentous haemagglutinin antigen of Bordetella pertussis and a saline solution for the manufacture of an acellular vaccine for the prophylactic treatment of a mammal susceptible to B. pertussis infection, wherein the vaccine contains the 69kDa antigen and the filamentous haemagglutinin antigen in a weight ratio of between 1:10 and 10:1 so as to produce a synergistic effect in vaccine potency and further comprises an adjuvant."

Claim 1 of this request for the Contracting State ES was drafted as a method claim.

VII. During further oral proceedings held on 26 October 2005 the appellant submitted a new **First Auxiliary Request** (claims 1 and 2 for the Contracting States AT, BE, CH,

DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES) and a new **Third Auxiliary Request** (claims 1 to 7 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 3 for the Contracting State ES). Claim 1 of the new **First Auxiliary Request** for the non-ES Contracting States read as follows:

"1. Use of the 69kDa antigen of Bordetella pertussis and the filamentous haemagglutinin antigen of Bordetella pertussis as individual components, and a saline solution, for the manufacture of an acellular vaccine for the prophylactic treatment of a mammal susceptible to B. pertussis infection, wherein the vaccine contains the 69kDa antigen and the filamentous haemagglutinin antigen in a weight ratio of between 1:10 and 10:1 so as to produce a synergistic effect in vaccine potency and further comprises an adjuvant."

Claim 1 of this request for the Contracting State ES was drafted as a method claim.

Claim 1 of the new **Third Auxiliary Request** for the non-ES Contracting States read as follows:

"1. An acellular vaccine comprising the 69kDa antigen of Bordetella pertussis and the filamentous haemagglutinin antigen of Bordetella pertussis in admixture with a saline solution, the 69kDa antigen and the filamentous haemagglutinin antigen being present in a weight ratio of between 1:10 and 10:1 so as to produce a synergistic effect in vaccine potency, the vaccine further comprising an adjuvant and being devoid of the B. pertussis toxin."

Claim 1 of this request for the Contracting State ES was drafted as a corresponding method claim.

VIII. The following documents are cited in the present decision:

(D1) De Magistris M. T. et al., J. Exp. Med., Vol. 168, pages 1351-1362 (1988);

(D6) Charles I. G. et al., Proc. Natl. Acad. Sci. USA, Vol. 86, pages 3554-3558 (1989);

(D8) Charles I.G. et al., Tokai J. Exp. Clin. Med. Vol. 15 (Suppl.), pages 227-234 (1988);

(D10) Declaration of Dr. R. Rappuoli dated 17 January 1997 with Exhibits RR-1 and RR-2;

(D11) Brennan M. J. et al., Tokai J. Exp. Clin. Med. Vol. 13 (Suppl.), pages 211-215 (1988);

(D25) Declaration of Dr. R. Rappuoli dated 26 June 1997 with Exhibits RR-1 to RR-3;

(D26) Abstract by Dr. Novotny et al., distributed at the International Workshop on Bordetella pertussis on 18-20 August 1988, at Rocky Mountain Laboratories, Hamilton, Montana (see declaration (D70));

(D28) Declaration of Prof. J. C. van Houwelingen (June 1997);

(D30) Declaration of Mr. P. A. Knight dated 14 September 1998;

(D31) Declaration of Prof. I. G. Charles dated 20 August 1998;

(D37) Weiss A. A. et al., Ann. Rev. Microbiol., Vol. 40, pages 661-686 (1986);

(D39) Munoz J. J. et al., Microbiol. Immunol. Vol. 33, No. 4, pages 341-355 (1989);

(D40) Physicians' Desk Reference, pages 1149-1151 (1994);

(D42) The Concise Oxford Dictionary of Current English, page 1237 (1990);

(D43) Sato Y. et al., The Lancet, pages 122-126 (21 Jan 1984);

(D59) Declaration of Mr P. A. Knight dated 2 November 2000;

(D60) Declaration of Prof. J. C. van Houwelingen dated 27 October 2000;

(D61) Declaration of Prof. J. Murphy received on 2 November 2000;

(D64) Kallings L. O. et al., The Lancet, pages 55-960, (30 April 1988);

(D70) Declaration of Dr. S. Loosmore dated 13 November 2000;

(D75) Submission of 10 February 1998 by Chiron in case T 780/95;

(D80) Roberts M. et al., Molecular Microbiology, Vol. 5, No. 6, pages 1393-1404 (1991);

(D81) Schematic representation of Bordetella pertussis (patentee);

(D85) Chazono M. et al., Journal of Biological Standardization, Vol. 16, pages 83-89 (1988).

IX. The submissions by the appellant (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Sufficiency of disclosure (Article 83 EPC)
All requests

- Sufficiency of disclosure had to be judged based on the patent as amended. The amended claims and the patent, not limited to the Examples, taught the use of an adjuvant as an essential requirement of the claimed invention.

- A skilled person could obtain the synergistic effect as set forth in claim 1 without undue burden by making an adjuvanted vaccine composition by combining the 69 kDa antigen and filamentous hemagglutinin (FHA) in a ratio between 1:10 and 10:1 so as to produce a synergistic effect in

vaccine potency. The observation of the effect required nothing more than applying a standard experimental test, the Kendrick test, which was the gold standard.

– The preliminary results in Example 4 of the patent in suit provided encouragement to the skilled person that the 69 kDa antigen and FHA in combination may be synergistic because the difference between the results for 69 kDa + FHA and those for the single antigens was so great.

– There were experimental tests which directly demonstrated synergy. These were the tests performed by the inventor Dr. Novotny that were recorded in his laboratory notebook and analysed in declaration (D30) and the tests performed by Dr. Nigel Connor and his colleagues at Medeva which were analysed in declaration (D59).

– Post-published document (D80) explained the mechanism by which synergy occurred between the 69 kDa antigen and FHA.

Priority rights (Article 87(4) EPC)
All requests

– Although the priority document did not expressly use the word "synergistic" as used in claim 1 of this request, it stated in the sentence bridging pages 3 and 4 that: "The present inventors have found, that a combination of 69kDa and FHA together is, surprisingly more potent than the aggregate effect of the individual components.".

This statement in the priority document corresponded perfectly to the ordinary meaning of the word "synergy" as set forth in dictionaries.

– There was no basis in the priority document for the respondent's interpretation that other antigens could not be present. There was nothing in the priority document to suggest that the "comprising" language was limited to encompass only the possibility of adjuvants and carriers.

– The fact that the priority document did not include Example 4 was not critical for obtaining synergy.

Novelty (Article 54 EPC)
All requests

– Document (D26) did not disclose any of the three features in claim 1, namely (i) combination of the 69 kDa antigen with FHA; (ii) the weight ratio between 1:10 and 10:1; and (iii) the presence of an adjuvant.

Inventive step (Article 56 EPC)
Main Request

– Document (D1) represented the closest prior art because it related to defined-component acellular pertussis vaccines and mentioned each of 69 kDa and FHA. The problem derivable from document (D1) was to produce a highly potent acellular vaccine, possibly as potent as the whole cell vaccine in the Kendrick test.

– The solution was provided by the inventor's entirely unexpected finding that selecting 69 kDa and FHA out of many possible candidates (see document (D31), paragraph 13; document (D39), page 351 and document (D81)) and combining them in the manner claimed produced a synergistic effect and consequently a highly potent vaccine. The solution was thus not obvious over document (D1).

– Documents (Dl) and (D26) did not suggest that a vaccine made with the 69 kDa antigen and FHA in a weight ratio between 1:10 and 10:1 and supplemented with an adjuvant would have exhibited a potency comparable with that of the whole cell vaccine.

– Document (D26) did not disclose (i) FHA; (ii) combining the 69 kDa antigen with FHA; (iii) the presence of an adjuvant; (iv) adding the 69 kDa antigen to FHA in a weight ratio of 1:10 to 10:1 and (v) the synergistic effect.

– The skilled person would not necessarily add the 69 kDa antigen to the Japanese type vaccines in the weight ratio of between 1:10 to 10:1 stated in claim 1 at issue since document (D40) showed that Takeda prepared a vaccine comprising 4% 69 kDa and 86% FHA, i.e., with a weight ratio outside the interval 1:10 to 10:1.

– Document (D26) (the Novotny abstract) was not the proper document to start from. This document merely made a vague reference to adding the 69 kDa

antigen to "Japanese type vaccines" but there was no information about the content of these vaccines and whether they contained FHA. Although some "Japanese type vaccines" contained FHA, other did not. For instance document (D64) related to two "Japanese type vaccines" one of which contained LPF alone and the other LPF + FHA. However, there were many more Japanese type vaccines. This was evident from D64 which described a clinical trial of Japanese vaccines called "JNIH-6" and "JNIH-7", i.e. the number 6 vaccine and the number 7 vaccine of the Japanese National Institute of Health.

– There were a great many antigens in the "Japanese vaccines". This is because the term "Japanese type vaccines" would have told a skilled person how the vaccines were made rather than what they contained. Japanese type vaccines were made by a process involving a step of sucrose density gradient ultracentrifugation whose purpose was to separate components to be included in the vaccine from those which were not. Where the vaccines contained more than one antigen, the antigens were co-purified. The composition of a given vaccine depended on which fraction was taken from the gradient.

– As for the respondent's contention that claim 1 encompassed low doses at which there was no synergy, i.e., compositions lacking an inventive step, the board already concluded that the patent did contain a sufficient disclosure in relation to the whole range covered by claim 1.

First Auxiliary Request

– In this request, claim 1 had been amended to specify that the 69 kDa antigen and FHA used to manufacture the vaccine were taken "as individual components", unlike the Japanese-type vaccines.

Second Auxiliary Request

– The claims of the Second Auxiliary Request emphasised a further difference between the claimed invention and the Japanese-type vaccines. The latters contained a great many contaminating antigens, as the antigens were co-purified (see document (D43), Fig. 2), rather than being "purified" and then mixed together.

Third Auxiliary Request

– In claim 1 of this request it had been made clear that the vaccine was "devoid of B. pertussis toxin" (i.e., LPF).

X. The submissions by the respondent (opponent (01)), insofar as they are relevant to the present decision, can be summarized as follows:

Sufficiency of disclosure (Article 83 EPC)
All requests

– The skilled person would not find any reliable guidance in the description as to how to proceed to find synergy and to measure it. The patent in suit failed to demonstrate the existence of a

synergistic effect, if any. Therefore, the skilled person could not succeed in finding a synergistic effect where the patent itself failed.

– If the presence of an adjuvant was an essential requirement of the claimed invention, the patent was insufficient for failing to disclose this "vital information".

– Examples 3 and 5 of the patent were not designed in such a way as to directly reveal synergy because there was no comparison of the two antigens in isolation with the two antigens in combination. Example 4 was designed in such a way as to be capable of showing synergy between the 69 kDa antigen and FHA. However, statistical analysis did not reveal any synergistic effect.

– The discrepancy between the data from the inventor's notebook (D30) and those in the patent in suit, despite the same dose range and ratio (1:1) having been used in both experiments, showed that synergy was elusive, in the sense that synergy was an artefact depending on the conditions used in the Kendrick test. Moreover, an adjuvant was used in the experiments of document (D30), contrary to the teaching in the patent.

– The test performed by Dr. Novotny reported in the notebook annexed to declaration (D30) did not allow a meaningful statistical analysis because the 69 kDa antigen alone had no measurable potency, while FHA alone had a very low potency, to the extent that the doses chosen did not "bracket" the

ED50, namely the dose which protected 50% of the mice.

– The data from Dr. Connor were either inconclusive (first series of experiments) or were obtained using methods which differed significantly from the teaching of the patent in that higher doses of antigen and an adjuvant had been used (second series of experiments).

Priority rights (Article 87(4) EPC)
All requests

– The sentence bridging pages 3 and 4 of the priority document ("The present inventors have found, that a combination of 69kDa and FHA together is, surprisingly more potent than the aggregate effect of the individual components") was not a clear and unambiguous disclosure of synergy, since the word "synergy" meant different things to different people and not everyone would interpret the statement as meaning synergy.

– In claim 1 of all requests synergy was linked to the ratio 69 kDa:FHA of between 1:10 and 10:1 and to the presence of an adjuvant, whereas no such teaching could be derived from the priority document.

– The priority document was even less sufficient than the patent in suit, since Example 4 of the patent was missing.

All requests other than the Third Auxiliary Request

– Whereas the vaccine now claimed could comprise other antigens such as PT (also known as LPF), the language used in the priority document did not encompass vaccines containing antigens in addition to 69 kDa and FHA, such as LPF. The open-ended meaning of "comprising" applied to the possibility of including adjuvants and carriers, but not other antigens.

Novelty (Article 54 EPC)
All requests other than the Third Auxiliary Request

In the absence of priority entitlement, documents (D10) and (D25) were novelty-destroying for claim 1.

– Claim 1 lacked novelty over the inventor's prior art abstract (D26), which instructed the skilled person to mix the 69 kDa antigen with "Japanese vaccines". According to document (D64), the "Japanese vaccines" contained LPF and FHA and aluminium phosphate as an adjuvant (see page 956, l-h column). Document D26 thus contained a direct disclosure of mixing a known LPF/FHA and adjuvant combination with the 69 kDa antigen.

Inventive step (Article 56 EPC)
All requests

– It was stated in document (D26) that "The 69KD protein is protective in the Kendrick test and when added to "Japanese vaccines" increases their potency over that of whole cell British reference.

The protective effect of this combination is independent on the concentration of the free LPF present". Therefore, it would have been obvious for the skilled person to add the 69 kDa antigen to any known vaccines comprising FHA and LPF in the expectation of providing an alternative acellular vaccine.

– It would have been obvious for the skilled person to add the 69 kDa antigen to **any** known acellular vaccines in the expectation of providing an alternative acellular vaccine.

– Claim 1 was not inventive across its whole scope since it was not limited to doses of antigen exhibiting the relevant technical effect but encompassed low doses (e.g. 20 µg), for which Dr. Connor did not find any synergy (see Exhibit 1 to document (D59)).

XI. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of

– claims 1 to 8 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES, filed on 19 February 2004 (Main Request)

or, in the alternative, on the basis of

– claims 1 and 2 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES filed during

the oral proceedings of 26 October 2005 (New First Auxiliary Request),

or

– claims 1 and 2 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 4 for the Contracting State ES, filed on 26 September 2005 (Second Auxiliary Request),

or

– claims 1 to 7 for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 3 for the Contracting State ES, filed during the oral proceedings of 26 October 2005 (Third Auxiliary Request).

The respondent (opponent 01) requested that the appeal be dismissed.

Reasons for the Decision

Sufficiency of disclosure (Article 83 EPC)
All requests

1. The relevant question to be decided, in the board's judgement, is whether the skilled person armed with the disclosure of the patent in suit is in a position to arrive at the claimed adjuvanted vaccine exhibiting synergy between the 69 kDa antigen and FHA.

2. A considerable portion of the parties' submissions indeed relates to a heavy dispute about whether or not the patent in suit provides sufficient information for the skilled person to arrive at the claimed synergistic compositions, and whether or not a synergistic effect actually takes place.

3. It has not been disputed by the parties that the first step toward the synergistic vaccine as claimed is making an adjuvanted vaccine composition by combining the 69 kDa antigen and FHA in a ratio between 1:10 and 10:1.

4. The respondent argues that the Examples of the patent in suit do not mention the use of any adjuvant, and that hence the patent is already insufficient for failing to disclose this "vital information".

5. However, sufficiency of disclosure has to be judged based on the claims as amended and their counterpart on page 3, line 34 of the description, which both relate to or teach the use of an adjuvant, bearing in mind that the disclosure of the patent is not limited to the Examples.

6. The respondent also maintains that the patent does not teach the skilled person how to measure synergy. However, the observation of this technical effect requires nothing more than applying a standard experimental test, the Kendrick test, a mouse challenge model wherein success is recorded as number of surviving mice out of the number of mice in the trial. The Kendrick test was the gold standard at the priority date of the patent in suit (see document (D37),

page 673, penultimate paragraph)) and indeed Example 3 of the patent in suit headed "Kendrick test" describes the protocols for performing this test.

7. The respondent further maintains that the patent in suit failed to demonstrate the existence of a synergistic effect.

8. Examples 3, 4 and 5 in the patent, which relate to Kendrick tests performed to measure the potency of vaccines, lack the information that an adjuvant should be used. Moreover, Examples 3 and 5 are not designed in such a way as to directly reveal synergy because there is no comparison of the two antigens in isolation (69 kDa alone; FHA alone) with the two antigens in combination (69 kDa + FHA). In spite of the above deficiencies, in the board's opinion, Example 3 shows that the 69 kDa antigen and FHA in combination are capable of giving at least as good protection in the Kendrick test than a whole cell reference vaccine (see page 5, lines 29-30, Table 1 on page 5 and Figure 1 of the patent). This experimental result would be an encouraging result to a skilled person because it suggests to use the combination 69 kDa + FHA as the basis for an acellular vaccine which would be as protective as whole cell vaccines, but which is expected to cause fewer adverse side-effects than a whole cell vaccine.

9. Moreover, unlike Example 3, Example 4 does relate to a comparison between the protection afforded at different dosage levels by a combination of 69 kDa + FHA versus that afforded by the two antigens in isolation. The results of Example 4 are shown in Table 2 on page 6 of

the patent. At the highest dose (20 µg) mice are not protected by either the 69 kDa antigen or FHA alone but 14 out of 18 mice are protected by the combination of these antigens.

10. The respondent criticizes the results of Example 4, arguing that the response to FHA alone is non-linear (at the 20 µg dose, FHA alone protects no mice, whereas 1/17, 4/18 and 6/18 mice are protected at the lower doses, respectively) and thus these data do not fit in with the "parallel line probit" method of statistical analysis commonly used to analyse the results of Kendrick tests (see declarations (D28) and (D60) and paragraph 12 of declaration (D71)).

11. Despite the low precision of the estimates of relative potency and the lack of information that an adjuvant should be used, in the board's view, the preliminary results in Example 4 of the patent in suit provide encouragement to the skilled person that the 69 kDa antigen and FHA in combination may be synergistic. This is because the difference between the results for 69 kDa + FHA and those for the single antigens is **so great** as to confer on the skilled person a strong impression of synergy, as the respondent himself admits in the submissions dated 22 January 1997 (see item 5.1.22: "In the application as filed, there were some data to support synergy (see Table 2 of the Opposed Patent)").

12. In summary, the results in the Examples in the patent in suit are merely suggestive of synergy between 69 kDa and FHA without being statistically conclusive.

13. However, it is common practice in proceedings before the EPO, in particular where the issue is sufficiency of a patent disclosure in relation to pharmaceutical compositions or vaccines, that a decision about the presence or absence of a given biological effect be made on the basis of all sorts of evidence, be it preliminary tests carried out to allow an initial assessment of the likelihood of success (and the Examples in the patent in suit fall within this frame), or data filed after the filing date of the application, provided that they render the intended effect credible.

14. Turning to this further evidence, only experiments in which an adjuvant was used, would be relevant, as the vaccine set forth in claim 1 contains an adjuvant.

15. One such experiment available to the board is a further Kendrick test performed by Dr. Novotny and his colleagues in February 1989. This test is recorded on pages 54 to 57 of Dr. Novotny's laboratory notebook, annexed to declaration (D30). Page 54 of this notebook shows that Dr. Novotny used Alhydrogel as an adjuvant. It can be seen (see paragraph 10 of declaration (D30)) that the potency of the combination 69 kDa + FHA is considerably greater than it would have been if the effect of the two antigens had been additive.

16. The respondent criticizes this test performed by Dr. Novotny because the 69 kDa antigen alone has no measurable potency and FHA alone has a very low potency, to the extent that the doses chosen do not "bracket" the ED50 to permit a meaningful statistical analysis.

17. A correct Kendrick test indeed requires that the probit lines be parallel and that the chosen doses should "bracket" the ED50, which is the dose which protects 50% of the mice. The ratio of the ED5O value for each antigen composition relative to a standard preparation provides an estimate of the relative potency of each composition. If the relative potency of the combination of 69 kDa + FHA is greater than the aggregate potency of the individual antigens to a statistically significant extent, synergy is demonstrated (see paragraphs 7-9 of declaration (D30)).

18. However, while it is desirable that the doses embrace the ED5O, the fact that the doses of an individual antigen fail to do so (FHA) or has no measurable potency at all (69 kDa) merely means that the precision of the estimate of relative potency is low, not that no synergy turns up between 69 kDa and FHA. This is because in the present situation the difference between the estimated potency for the combination of antigens is **very much greater** than the estimated potency for each antigen alone. In particular, the 69 kDa antigen alone does not give a measurable potency at any dosage (pure 69 kDa antigen has turned out to be non-protective in the Kendrick test; see document (D75), page 21, last line), while there is a substantial increase in potency of the 69 kDa + FHA combination. Once the common sense prevails over poor statistics, it becomes thus evident that said considerable increase in potency of the 69 kDa + FHA combination vis-à-vis the potency of FHA alone must be attributed to synergy.

19. The respondent also views the discrepancy between the data from the inventor's notebook (D30) and those in

the patent in suit, despite the same dose range and ratio (1:1) having been used in both experiments, as a demonstration that synergy is elusive, in the sense that synergy is merely an artefact following from the conditions used in the Kendrick test. However, the board observes that the only discrepant value relates to that for FHA at 20 µg: 0/17 (see patent, Table 2 on page 6) vs. FHA at 20 µg: 4/16 (see declaration (D30), page 4, under "Results of Dr Novotny experiment"), all the remaining data being fully consistent. Moreover, some variation is tolerable when testing new preparations possibly contaminated with trace antigens in different strains of mice and in a different laboratory environment. Therefore, no case has been made out that the data from the inventor's notebook (D30) and those in the patent in suit are contrasting, or that synergy is an artefact linked to the conditions used in the Kendrick test.

20. Further experiments involving an adjuvant are the Kendrick tests performed by Dr. Connor and his colleagues at Medeva Pharma Limited in Speke in the United Kingdom (see declaration (D59)). Exhibit 1, page 1 to this declaration shows that Dr. Connor used Alhydrogel as an adjuvant.

21. Dr. Connor carried out two series of experiments. The results of the first series of experiments are suggestive of synergy between the 69 kDa antigen and FHA (see declaration (D59), paragraph 5). In particular, the results for the 69 kDa antigen alone and FHA alone indicate that the maximum effect that would be expected from adding the effects of the isolated antigens would be protection of 2 out of 18 mice, but the combination

of 69 kDa + FHA in fact protects 5 out 18 and 6 out of 18 mice in duplicate assays (ibidem, page 7). However, these results are not statistically conclusive because in no assay does the test material protect more than 50% of the mice, the responses to all the materials being too low (on the grounds emphasized under point 26 infra) to allow a definitive conclusion to be reached.

22. Therefore, Dr. Connor carried out a second series of experiments in which the doses of the test materials had been increased. It can be derived (see Table 1 and paragraphs 10 and 11 of declaration (D59)) that the potency of the combination 69 kDa + FHA is in a statistically significant manner considerably greater than it would have been if the effect of the two antigens had been additive.

23. The respondent questions the data from Dr. Connor's second series of experiments arguing that they were obtained using methods which differed significantly from the teaching of the patent in that doses of antigen higher than the patent had been used.

24. However, the board firstly observes that the dose range used in Dr. Connor's second series of tests (4.5 to 286 µg/ml or 2.25 to 143 µg per 0.5 ml dose in the 69 kDa + FHA vaccine; see Exhibit 2 to declaration (D59)) overlaps both the range used according to Example 4 of the patent (0.65 to 40 µg per 0.5 ml dose in the 69 kDa + FHA vaccine) and the range of 0.01 to 5.0 mg/ml (i.e., 5 to 2,500 µg/0.5 ml) referred to in present claim 3 and in page 3, line 38 of the patent.

25. Secondly, when using a Kendrick test as suggested by the patent in suit, the skilled person would of necessity use a dose range wherein the ED50 falls within the range (see point 17 supra). If the selected doses do not fulfil the above requirements, the skilled person would be guided by the ED50 to fine tune (i.e., increase or decrease) the doses, so that said ED50 falls within the selected dose range. In the present case Dr. Connor had to increase the doses.

26. Finally, the doses also depend on the nature of the antigen, in the sense that the protective potency may be damaged upon treatment of the antigen with formalin or glutaraldehyde. The appellant's argument that Dr. Connor's first series of experiments involved a formalin-treated 69 kDa antigen from SmithKline Beecham (see declaration (D59), page 1), exhibiting a higher ED50 (shift to the right) and that, owing to this partial denaturation, Dr. Connor had to increase the doses to "catch" the ED50 in his second series of experiments, convinces the board, also because the possibility that the protective potency of the 69 kDa antigen be damaged by denaturating/cross-linking agents is stated expressis verbis in the patent in suit on page 6, lines 51-53.

27. The respondent also argues that the very high doses (286 µg/ml) used in Dr. Connor's second series of experiments have no relationship to the real word of human vaccines. However, the Kendrick test and the high doses used therein merely pertain to mice (see point 6 supra). Once the skilled person finds synergy at high (mice) antigen levels, it is common practice to reduce, by extrapolation, these levels to obtain a safe and

practical human vaccine. But the fact that these (mice) antigen levels have to be reduced does not mean that synergy vanishes at lower doses (see point 61 infra).

28. Finally, post-published document (D80), taken as expert opinion, represents, in the board's judgement, further evidence that synergy turns up between the 69 kDa antigen and FHA. This document (see page 1400, l-h column, second paragraph) proposes a plausible mechanism by which synergy between the two "adhesins" (i.e., antigens involved in adhesion of the bacterial cells to human cells) 69 kDa and FHA takes place. It would appear that if only one of the two adhesins (e.g. 69 kDa) is blocked, B. pertussis is still able to adhere to (and infect) human cells using the FHA antigen. Thus, the ability of the B. pertussis cells to infect human cells may not be reduced much, if at all, by blocking only one of the proteins. However, if both proteins are blocked, bacterial adhesion (and thus infectivity) may be reduced to a substantial extent because the bacterial cells cannot remediate the blocking of one adhesin (e.g. 69 kDa) via the other (FHA).

29. In view of the foregoing, the board concludes that the skilled person armed with the disclosure of the patent in suit is in a position to arrive at the claimed adjuvanted vaccine exhibiting synergy between the 69 kDa antigen and FHA. Therefore, no case of insufficiency of disclosure has been made out.

Priority rights (Article 87(4) EPC)
All requests

30. The respondent has disputed the right to priority on the ground that the priority document does not disclose "synergy" or a "synergistic effect".

31. However, the concept of synergy can directly and unambiguously be derived from the passage bridging pages 3 and 4 of the priority document ("FHA alone only provides minimal protection"; "69kd on its own is not as efficient as the whole cell vaccine"; "the present inventors have found, that a combination of 69kDa and FHA together, is surprisingly more potent than the aggregate effect of the individual components"). These statements taken together correspond to the ordinary definition of the word "synergy" (see e.g., document (D42): "the combined effect of drugs, organs, etc., that exceeds the sum of their individual effects."

32. The respondent argues that, in view of an absence of experimental data showing synergy in the priority document, the latter does not contain a sufficient disclosure of the invention as presently claimed.

33. However, the board has already decided that the patent in suit contains a sufficient disclosure as required by Article 83 EPC. Despite the priority document containing less experimental data than the patent, all what the skilled person needs to do is to combine 69 kDa and FHA in the given ratio in the presence of an adjuvant and check it in a Kendrick test. Therefore, the priority document is sufficient for essentially the same reasons as the patent in suit since the former

discloses all the elements necessary for the skilled person to obtain the claimed biological effect. It is true that Example 4 is missing. However, the Table on page 8 shows that the combination of 69 kDa + FHA can be more potent than a reference whole cell vaccine. A skilled person would conclude from this and from the fact that 69 kDa and FHA alone provides minimal or inefficient protection (see page 3, fourth and fifth full paragraph of the priority document) that there is likely to be synergy between 69 kDa and FHA.

34. The respondent further argues that in the priority document, synergy was linked to the LPF's absence (i.e., the priority document excluded vaccine compositions containing PT (= LPF)). As this limitation is not in claim 1, there can be no priority entitlement.

35. However, the priority document, when read as a whole, does not present the invention as a way to finally dispose of PT (= LPF). Rather, the priority document uses open-ended language of the form "comprising", which allows for the vaccine composition to include further components in addition to 69 kDa and FHA, be they adjuvants, excipients or antigens (e.g., LPF).

The vaccine preparation disclosed in the priority document may also be one in which "LPF is absent". This can be derived from page 4, first two lines of the priority document ("The synergistic combination of 69 kDa and FHA is advantageous since LPF is absent, and consequently the chances of adverse effects are minimised.").

36. The respondent also argues loss of priority rights on the basis that in claim 1 of all requests, synergy is linked to the ratio 69 kDa:FHA of between 1:10 and 10:1 and to the presence of an adjuvant, whereas no such teaching could be derived from the priority document. However, the ratio 69 kDa:FHA of between 1:10 and 10:1 and the presence of an adjuvant were already in the priority document (see page 4, third full and penultimate paragraph, respectively).

37. In conclusion, the claimed subject matter is entitled to priority rights insofar as the claims cover vaccines "comprising" other components, with the option that LPF may be absent. Therefore, documents (D10) and (D25) are no prior art.

Novelty (Article 54 EPC)
All requests

38. Document (D26) ("the Novotny abstract") is an abstract by the inventor distributed at the International Workshop on Bordetella pertussis on 18-20 August 1988, at Rocky Mountain Laboratories, Hamilton, Montana (see declaration (D70)). It is stated in document (D26) that "The 69KD protein is protective in the Kendrick test and when added to "Japanese type vaccines" increases their potency over that of whole cell British reference".

39. According to the respondent, claim 1 lacks novelty in view of the disclosure of document (D26), as this document contains a direct disclosure of mixing a combination of LPF and FHA ("Japanese vaccine") with the 69 kDa antigen. However, a combination as claimed

comprising the 69 kDa antigen and FHA in a weight ratio of between 1:10 and 10:1 and an adjuvant cannot be directly and unambiguously derived from this document **alone**, nor is there any pointer in document (D26) to this specific combination, bearing in mind that a "Japanese type vaccine" may also contain LPF only (see document (D64), page 956, l-h column, vaccine "JNIH-7" under the heading "Vaccines and Placebo").

40. In conclusion, the claimed subject-matter satisfies the requirements of Article 54 EPC.

Inventive step
Main Request
Closest prior art and problem to be solved

41. The appellant argues that document (D1) represents the closest prior art because it refers on page 1351, first paragraph, to various vaccines such as inactivated whole cell vaccines and Japanese vaccines including PT (=LPF) and FHA and it is concerned with an attempt to define the minimal antigenic structures that may be required for introduction into a "third generation" vaccine. A reference to the 69 kDa protein is also made on page 1360 of this document.

42. However, document (D26) states that "The 69KD protein is protective in the Kendrick test and when added to "Japanese type vaccines" increases their potency over that of whole cell British reference". Since a "Japanese type vaccine" may prima facie include LPF and FHA (see document (D1), lines 14-15), document (D26), which suggests mixing 69 kDa with LPF and FHA represents prior art closer to the claimed subject

matter than document (D1), which fails to suggest any 69 kDa/FHA association.

43. The vaccine of claim 1 differs from the teaching of document (D26) in that the claim recites the further features "in a weight ratio of between 1:10 and 10:1", "further comprises an adjuvant" and "synergistic effect". As regards the latter expression, the appellant never disputed in the context of sufficiency of disclosure that the synergistic effect is an implicit and inevitable consequence of mixing the antigens in the way recited in claim 1. This view is consistent with document (D26) stating that "The 69KD protein ...when added to "Japanese vaccines" increases their potency over that of whole cell British reference".

44. Therefore, the objective problem to be solved departing from document (D26) can be formulated as "fine tuning" the weight ratios of the 69 kDa/FHA/LPF mixture suggested by document (D26) and adding an adjuvant.

45. However, the feature "in a weight ratio of between 1:10 and 10:1" (9:91 to 91:9 in percentage terms) is the range that the skilled person would normally adopt, as the board can see no valid reasons for the skilled person to avoid this very broad range. As for the addition of an adjuvant, this measure is rendered obvious by document (D64), which discloses Japanese type vaccine "JNIH-6", made of 7.5 µg/ml of each the pertussis toxin (LPF) and FHA and further comprising aluminium phosphate as an adjuvant (see page 956, l-h column, under "Vaccines and Placebo").

46. In conclusion, claim 1 lacks an inventive step in view of document (D26) taken in combination with document (D64), which discloses Japanese vaccine "JNIH-6".

47. Departing from the acellular vaccine mentioned in document (D1) on page 1351, first paragraph, as closest prior art, as the appellant argues, would lead to the same negative conclusion. This is because the skilled person wishing to prepare an alternative acellular vaccine to that of document (D1) was motivated to add thereto the 69 kDa antigen, in view of document (D8) (see page 227, end of r-h column) and document (D11) (see page 212, l-h column, lines 1-2), which suggested that the "protective" 69 kDa antigen was worth being included in any acellular vaccine.

48. The appellant's argument that there were many more Japanese type vaccines possibly devoid of FHA, in addition to vaccine "JNIH-7", is not convincing because all the remaining prior art documents before the board disclose Japanese type vaccines including FHA (see document (D43), page 123, r-h column, under point (7) and document (D85), page 88, lines 8-9 from the bottom). This finding is in line with declaration (D31) filed by the appellant (see paragraphs 9 and 10).

49. As for the appellant's contention that document (D40) demonstrates that the skilled person would not necessarily add the 69 kDa antigen to the Japanese type vaccines in the weight ratio of between 1:10 to 10:1 stated in claim 1 at issue, this post-published document does not reflect the skilled person's knowledge before the priority date of the patent in suit.

50. The appellant also maintains that it was not obvious to select the 69 kDa antigen and FHA out of a great many many possible candidates (see document (D31), paragraph 13; document (D39), page 351 and document (D81)) and combining them in the manner claimed to produce a synergistic effect and consequently a highly potent vaccine.

51. In the board's opinion, when it comes to the production of a vaccine, it is important to include therein as few antigens as possible by identifying those which would be most protective, whilst ensuring that the vaccine is safe and effective. The board also agrees that there were many candidates suggested for making a pertussis vaccine, including, in particular, the fimbrial agglutinogens, adenylate cyclase-haemolysin (AC-HLY), and outer membrane proteins of a number of molecular weights (30 kD, 31 kD, 32 kD and 9l kD OMP's) (see document (D81) and document (D39), page 352, lines 19-22) and that selecting the binary combination "69 kDa + FHA" out of the many possible combinations was not obvious. Neither did the respondent dispute that said combination did not follow from the prior art in an obvious way.

52. However, owing to the open-ended wording "comprising", claim 1 at issue is not restricted to the combination "69 kDa and FHA" but covers further antigens, such as B. pertussis toxin" (i.e., LPF). This board's view is confirmed by present claim 2 for both the non-ES and ES Contracting States stating that the vaccine referred to in claim 1 "is devoid of B. pertussis toxin" (i.e., LPF). This of necessity implies that the vaccine

referred to in claim 1 (for both non-ES and ES) may include said B. pertussis toxin (LPF). Therefore, the claims are not restricted to the "sharp" selection argued by the appellant but also covers adding the 69 kDa antigen to Japanese vaccines, which does not involve any inventive step (see point 46 supra).

53. For these reasons claim 1 of the main request does not satisfy the requirements of Article 56 EPC. This request is thus rejected.

First Auxiliary Request
Inventive step

54. Claim 1 of this request for the non-ES Contracting States is drafted as referring to a second/further medical use, whereas claim 2 (non-ES) is a method claim. Both claims involve 69 kDa and FHA "as individual components".

55. However, it cannot be derived from the wording of these claims that the 69 kDa antigen and FHA are the sole "individual components", or that the presence of LPF is excluded. On the contrary, the fact that claim 2 for ES states that the vaccine referred to in claim 1 "is devoid of B. pertussis toxin" (i.e., LPF)" of necessity implies that the vaccine referred to in claim 1 (for ES) and in its exact copy claim 2 (for non-ES) may include said B. pertussis toxin (LPF). Therefore, the conclusion arrived at by the board in relation with the main request also applies to the First Auxiliary Request.

Second Auxiliary Request
Inventive step

56. Claim 1 of this request for non-ES is drafted as referring to a second/further medical use, whereas claim 2 (non-ES) is a method claims. Both claims involve the "purified" 69 kDa antigen and FHA.

57. However, it cannot be derived from these claims in their present version that the "purified" 69 kDa antigen and FHA are the sole antigens, or that the presence of LPF is excluded. On the contrary, the fact that claim 2 for ES states that the vaccine referred to in claim 1 "is devoid of B. pertussis toxin" (i.e., LPF)" of necessity implies that the vaccine referred to in claim 1 (for ES) and in its exact copy claim 2 (for non-ES) may include said B. pertussis toxin (LPF). Therefore, the conclusion arrived at by the board in relation with the main request also applies to the Second Auxiliary Request.

Third auxiliary request
Inventive step

58. The vaccines referred to in independent claims 1 and 6 for non-ES and in claim 1 for ES are "devoid of the B. pertussis toxin" (i.e., LPF). The board already expressed the view (see point 51 supra) that selecting the "sharp" combination "69 kDa + FHA" out of the many possible combinations was not obvious, inter alia in view of the plethora of possible candidates suggested. Neither did the respondent raise any objections under Article 56 EPC against claims directed to said "sharp" combination.

59. The only objection under Article 56 EPC still pending against the claims of this request is that claim 1 encompasses low doses of antigens at which no synergy turns up, i.e., compositions lacking an inventive step.

60. It is true that claim 1 encompasses such low doses, however, as emphasized under point 17 supra, in order to obtain valid results in the Kendrick test it is necessary to test a range of doses of antigen which embraces the ED5O. The Kendrick test provides a "window" through which synergy can be observed. The observation is only valid when looking squarely through the middle of the window (i.e., when the requirement of the ED50 being embraced by the dose range is fulfilled). If a lower dose is chosen, this lower dose of antigen will of course fall below the ED5O and therefore protect a smaller number of mice (see e.g., the value 4/15 for 0.74 µg 69 kDa + 0.74 µg FHA on page 4 of document (D30)). But protection of a smaller number of mice is not an indication of lack of synergy in the lower range covered by claim 1, but merely failure of "vision" of synergy on the left side of the "window".

61. Moreover, the board is not convinced that the mechanism by which synergy between the two adhesins 69 kDa and FHA turns up (see point 28 supra) would suddenly loose its validity at lower doses. Therefore, if synergy exists, it will exist over a wide range of doses gradually diminishing to nothing as the zero dose is approached.

62. In view of the foregoing the board concludes that the claims of the Third Auxiliary Request also satisfy the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

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 the claims of the Third Auxiliary Request filed during these oral proceedings and a description to be adapted thereto.

The Registrar: Chair:

P. Cremona U. M. Kinkeldey