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Datasheet for the decision of 28 November 2013

Case Number: T 1074/09 - 3.3.04

Application Number: 00945494.3

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IPC: A61K39/116, A61P31/04

Language of the proceedings: EN

Title of invention:
Multi-component vaccine to protect against disease caused by Haemophilus influenzae and Moraxella catarrhalis

Patent Proprietor:
Sanofi Pasteur Limited

Opponent:
GlaxoSmithKline Biologicals SA

Headword:
Vaccine/ SANOFI PASTEUR LIMITED

Relevant legal provisions:
EPC Art. 123(2), 123(3), 83, 54, 56
RPBA Art. 13(1)

Keyword:
"Main request, auxiliary request 1 - added matter (yes)"
"Auxiliary request 2 - requirements of the EPC met (yes)"

Decisions cited:
T 0686/99, T 0727/00

Catchword:

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Case Number: T 1074/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 November 2013

Appellant: (Opponent)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
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Representative:	Bizley, Richard Edward avidity IP Kestrel House Falconry Court Baker's Lane Epping, Essex CM16 5DQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 April 2009 concerning maintenance of the European Patent No. 1200122 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Morawetz
M. Montrone

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter "appellant") lies against the decision of the opposition division whereby European patent No. EP 1200122 was maintained in amended form on the basis of auxiliary request 1 filed on 11 February 2009.

II. The patent at issue has the title "Multi-component vaccine to protect against disease caused by *Haemophilus influenzae* and *Moraxella catarrhalis*". It was granted on European application No.00945494.3 which originated from international application PCT/CA2000/000811 published as WO 2001/005424 (hereinafter "application as filed").

III. The patent was opposed under Article 100(a) EPC 1973 on the grounds of lack of novelty (Article 54 EPC 1973) and lack of inventive step (Article 56 EPC 1973), under Article 100(b) EPC 1973 and under Article 100(c) EPC 1973.

IV. The Opposition Division decided that claims 11 to 15, 17 and 19 of the main request before it (claims as granted) failed the requirements of Article 123(2) EPC (Article 100(c) EPC) but that claims 1 to 19 of the auxiliary request filed during the oral proceedings met all requirements of the EPC.

V. The appellant filed its statement of grounds of appeal on 26 August 2009 including new documents (D20) to (D39e) and substantial arguments why the claims upheld by the opposition division *inter alia* failed the requirements of Article 83 EPC.

VI. In reply the proprietor (hereinafter "respondent") filed its submissions on 11 January 2010, submitting the claims allowed by the opposition division as main request and filing an auxiliary request 1. Claims 1 to 10, 13 and 14 of the main request read:

"1. A multi-valent immunogenic composition for conferring protection in a host against disease caused by both *Haemophilus influenzae* and *Moraxella catarrhalis*, characterised by:

at least four different antigens comprising at least one antigen from *Haemophilus influenzae* and at least one antigen from *Moraxella catarrhalis*, at least three of which antigens are adhesins and at least one of which adhesins is from *Moraxella catarrhalis*.

2. The immunogenic composition claimed in claim 1, wherein one of said antigens which is an adhesin is a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae*, preferably a HMW1 or HMW2 protein of the non-typeable strain of *Haemophilus influenzae*, preferably produced recombinantly.

3. The immunogenic composition claimed in claim 2, wherein said HMW1 and HMW2 proteins are derived from the respective strain of non-typeable *Haemophilus influenzae* and possess respective molecular weights as set forth in the following table:-

Molecular Weight (kDa) non-typeable *H. influenzae* Strain

		12	JoyC	K21	LCDC2	PMH1	15
Mature Protein:	HMW1	125	125.9	104.4	114.0	102.4	103.5
	HMW2	120	100.9		111.7	103.9	121.9

4. The immunogenic composition claimed in claim 1 or 2, wherein another of the antigens which is an adhesin is a *Haemophilus influenzae* adhesin (Hia) protein of a non-typeable strain of *Haemophilus influenzae* or a *Haemophilus influenzae* surface fibril (Hsf) protein of a typeable strain of *Haemophilus influenzae* preferably produced recombinantly.

5. The immunogenic composition claimed in claim 4, wherein said recombinantly-produced Hia protein is an N-terminal truncation V38 rHia.

6. The immunogenic composition claimed in any one of claims 1 to 3, wherein an antigen of *Haemophilus influenzae* which is not an adhesin is a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae*, preferably an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than 10% of that of natural Hin47 protein.

7. The immunogenic composition claimed in claim 6, wherein said analog of Hin47 protein is one in which at least one amino acid of the natural Hin47 protein contributing to protease activity has been deleted or replaced by a different amino acid and which has substantially the same immunogenic properties as natural Hin47 protein.

8. The immunogenic composition claimed in claim 7, wherein said at least one amino acid is selected from the group consisting of amino acids 91, 121 and 195 to 207 of natural Hin47 protein, preferably Serine-197 is replaced by alanine, Histidine-91 is replaced by alanine, lysine or arginine, more preferably alanine, or Asp-121 replaced by alanine.

9. The immunogenic composition claimed in any one of claims 1 to 8, wherein one of said antigens which is an adhesin is an outer membrane protein of *Moraxella catarrhalis* having an apparent molecular mass of 200 kDa, as determined by SDS-PAGE, preferably produced recombinantly.

10. The immunogenic composition claimed in claim 9, wherein recombinantly-produced 200 kDa protein is an N-terminal truncation V56 r200kDa.

13. The immunogenic composition claimed in claim 11 or 12 comprising:

(a) 25 to 100 µg of the Hin47 protein analog, and
(b) 25 to 100 µg of the Hia protein,
(c) 25 to 100 µg of the HMW protein, and
(d) 25 to 100 µg of the 200 kDa protein.

14. The immunogenic composition claimed in any one of claims 1 to 13 further comprising an adjuvant, preferably aluminium hydroxide or aluminium phosphate."

VII. Claim 1 of auxiliary request 1 read (amendments vis-à-vis claim 1 of the main request indicated in bold by the board):

"1. A multi-valent **component vaccine** immunogenic composition for conferring protection in a host against disease caused by both *Haemophilus influenzae* and *Moraxella catarrhalis*, characterised by:

at least four different antigens comprising at least one antigen from *Haemophilus influenzae* and at least one antigen from *Moraxella catarrhalis*, at least three

of which antigens are adhesins and at least one of which adhesins is from *Moraxella catarrhalis*."

VIII. By a communication of 16 January 2013 the parties were summoned to oral proceedings to be held on 10 September 2013.

IX. On 9 August 2013 the appellant provided further written submissions and documents.

X. With letter of 9 August 2013 the respondent submitted auxiliary requests 2 and 3 to address the objections raised by the appellant in its grounds of appeal under Article 123(2) EPC and Article 54 EPC.

XI. On 3 September 2013 the respondent filed further observations in response to appellant's letter of 9 August 2013.

XII. With letter of 5 September 2013 the appellant filed further observations in response to respondent's letter of 3 September 2013.

XIII. On 6 September 2013 the parties were informed that the oral proceedings scheduled for 10 September 2013 were cancelled.

XIV. With a communication of 16 September 2013 the parties were summoned for oral proceedings on 28 November 2013.

XV. On 28 October 2013 the respondent filed further written submissions and auxiliary requests 4 to 15.

XVI. On 19 November 2013 the appellant filed comments in response to respondent's submission of 28 October 2013.

XVII. Oral proceedings before the board were held on 28 November 2013. All documents filed on appeal were admitted in the appeal proceedings by agreement of the parties. During the oral proceedings the respondent filed a new auxiliary request 2. Independent claims 1, 5 and 6 of auxiliary request 2 read:

"1. A multi-valent immunogenic composition for conferring protection in a host against disease caused by both *Haemophilus influenzae* and *Moraxella catarrhalis*, comprising at least four different antigens selected from:
(a) an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than 10% natural Hin47 protein,
(b) a *Haemophilus influenzae* adhesin (Hia) protein of a non-typeable strain of *Haemophilus influenzae*,
(c) a high molecular weight (HMW) adhesin protein of a strain of non-typeable *Haemophilus influenzae*, and
(d) an outer membrane adhesin protein of *Moraxella catarrhalis* having an apparent molecular mass of 200 kDa, as determined by SDS-PAGE.

5. A multi-valent immunogenic composition as claimed in any one of claims 1 to 4 for use in conferring protection in a host against disease caused by both *Haemophilus influenzae* and *Moraxella catarrhalis*.

6. The use of at least four different antigens as defined in any one of claims 1 to 4 in the manufacture of a multi-valent immunogenic composition for conferring protection in a host against disease caused by both *Haemophilus influenzae* and *Moraxella catarrhalis*."

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

(D5) Gu X-X. et al., Infection and Immunity, 1998, vol. 66, pages 1891-1897

(D30) WO98/28333

(D33) Barenkamp S.J., Infection and Immunity, 1996, vol. 64, pages 1246-1251

(D34) Barenkamp S.J. and J.W. St. Geme III, Molecular Microbiology, 1996, vol. 19, pages 1215-1223

(D35) Loosmore S.M. et al., Infection and Immunity, 1998, vol. 66, pages 899-906

(D36) WO96/34960

XIX. The relevant arguments of the appellant can be summarised as follows:

Main request
Amendments (Articles 100(c) and 123(2) EPC) - claims 4 to 10, 13 and 14

There was no basis in the application as filed for the combination of the features claimed in claims 4 to 10. A combination, unsupported by the application as filed, of one item from each of two lists of features meant that, although the application might conceptually comprise the claimed subject-matter, it did not disclose it in that particular individualised form (see T 727/00). There was no basis for any combination of the four antigens disclosed but only for a combination of all four antigens together or a generic composition comprising only one of the disclosed specific antigens. Looking at claim 9 by way of example, the paragraphs at page 7, lines 21 to 24 and at page 8, lines 1 to 3 could not be readily combined to provide basis for a specific combination of HMW and

a 200 kDa protein. The only basis for a combination of these proteins was the preferred embodiment in which all 4 antigens (HMW/Hia/Hin47/200kDa) were present. Page 8, lines 1 to 3 referred to "one of the antigens" and provided no basis for claim 9. The antecedent was the general statement of the invention on page 7, lines 14 to 20. The antecedent for all intervening paragraphs was the generic statement. There was no language in the application as filed disclosing that the composition of the invention might comprise any of the features in a combination other than in the preferred embodiment in which all four antigens needed to be present. The claims as filed supported this view. That the passages "could" be combined was not the standard for direct and unambiguous disclosure.

In a similar fashion all of claims 4 to 8 and 10 covered such undisclosed 2/3-specified-antigen combinations not individualised at the date of filing.

Claim 13 lacked a basis in the application as filed because the word "about" had been removed from each part of the claim.

Claim 14 lacked a basis in the application as filed because page 9, lines 3 to 4 disclosed the use of an adjuvant only in the context of the preferred embodiment.

Auxiliary request 1
Amendments (Articles 100(c) and 123(2) EPC)

No further objections were raised.

Auxiliary request 2

Admissibility

No objections were raised.

Amendments (Articles 123(2) and (3) EPC)

No objections were raised.

Sufficiency of disclosure (Article 100(b) and 83 EPC)

It was stated that the objections put forward previously were maintained for this request. Firstly, the skilled person had not been provided with a single way of putting the claimed invention into practice. It was the aim of the patent to avoid immunological interference (see paragraphs [0044], [0047] and [0108]). However, not a single embodiment had been provided in which no antigenic interference was observed. Secondly, the patent in suit provided four specific antigens, the provision of every other multi-valent immunogenic composition required undue burden.

Novelty

No objections were raised.

Inventive step

The statement in point 4.1.1 on page 21 of the statement of grounds of appeal was of relevance. Document (D30) did not represent the closest prior art.

XX. The relevant arguments of the respondent can be summarised as follows:

Main request
Amendments (Articles 100(c) and 123(2) EPC)

Page 7 to page 10 of the application as filed provided the basis for compositions wherein two or three antigens were defined. Only the preferred embodiment disclosed on page 8, lines 4 to 13 and the following paragraph on page 8, lines 14 to 17 were linked. From page 8, line 18 onwards a different language was used. The specific components were listed in a way that provided a basis for their combination. HMW was disclosed on page 7, lines 21 to 24 and Hia on page 7, line 25 to 28. The skilled person understood that these passages could be combined. Consistory clauses for claims 2 to 13 were to be found on pages 7 to 9. It was not accepted that deletion of the term "about" added matter. Page 9, lines 3 to 4 provided a basis for claim 14.

Auxiliary request 1
Amendments (Articles 100(c) and 123(2) EPC)

Since the component vaccine was the only difference, the respondent conceded that the objections to the main request had to apply to this request.

Auxiliary request 2
Admissibility

This request was admittedly filed at a late stage in the proceedings but it addressed the objections raised. Nothing had been added from the specification, the only amendments carried out consisted in the deletion of claims, and the request converged from the higher requests.

Amendments (Articles 123(2) and (3) EPC)

Claim 8 as filed provided a basis for claim 1. The scope of the amended claims did not exceed the scope of the claims as granted, see claim 11 as granted.

Sufficiency of disclosure (Article 100(b) and 83 EPC)

The composition of claim 1 had to be suitable to provide dual protection but claim 1 was silent as regards antigenic interference. Examples 7 and 8 fell within the scope of claim 1. Example 7 described the protective ability of a multi-component vaccine comprising H91A Hin47, rHMW, rHIA, and r200 kDa. The results of the protection study were shown in Figures 9 and 10. Example 8 illustrated the bactericidal properties of the composition. Paragraphs [109] and [0123] of the patent indicated that no interference was observed. Claim 1 identified the four antigens that provided dual protection and the patent in suit provided the necessary tests to ensure that the desired protection against the two organisms was not lost.

Inventive step

Document (D30) represented the closest prior art. Document (D30) was the only document that aimed at providing a vaccine capable of protecting against both organisms (i.e. it was functionally close) and actually investigated a combination of antigens for their combined protective effect (page 45, lines 10 to 15). The problem to be solved was the provision of a multi-valent vaccine which was protective against both *H. influenzae* and *M. catarrhalis*. The problem was not the avoidance of immunological interference altogether but rather the avoidance of immunological interference to

the extent that a protective effect against both organisms could be achieved. This problem was solved by the combination of antigens in claim 1. Document (D30) did not demonstrate dual protection, not least because it did not show protection against *H. influenzae*, see example VI, on page 109, line 10 onwards. In relation to HbO, the relevant data provided in document (D30) were immunogenicity data from mice immunised with the HbO-UspA2 conjugate wherein UspA2 served as the carrier (see Table XXV). These data were not a reliable indicator for implying a protective effect. Bactericidal data toward *M. catarrhalis* were reported in Table XXVII. Starting from document (D30) and attempting to create a vaccine which was protective against both *H. influenzae* and *M. catarrhalis* the skilled person would have been at a loss as to what to do next. There was no suggestion in document (D30) to include further antigens. In order to arrive at the invention a wholesale redesign of the vaccine of document (D30) was required. Firstly, it would have been necessary, either to abandon altogether the chosen *M. catarrhalis* antigen (UspA2) and replace it with an adhesin or to add a second *M. catarrhalis* antigen which was an adhesin. No motivation for making this change was provided by document (D30) or any other document. Secondly, it was necessary, in order to arrive at the multi-valent vaccine of the invention, to include three adhesins in total. No motivation for making this change was provided by document (D30) or any other document.

Document (D33) related to immunization with proteins HMW 1 and 2 of *H. influenzae* and discussed their possible inclusion in a multicomponent *H. influenzae* vaccine. Document (D34) disclosed the Hia protein of *H. influenzae*, its immunogenicity and suggested the possibility of including it in a vaccine in combination

with HMW1/HMW2-like proteins. Document (D35) disclosed that the H91A mutant of HtrA was found to be partially protective in animal protection models. Documents (D33), (D34) and (D35) were silent on *M. catarrhalis*.

Document (D36) investigated the role of the 200 kDa protein of *M. catarrhalis* as an antigen in its own right and mentioned in passing that another use of the protein was to act as a carrier for polysaccharide antigens of other organisms, including *H. influenzae*. However there was nothing in document (D36) that suggested that the glycoconjugates so formed were intended to be protective against both *M. catarrhalis* and *H. influenzae*. Document (D36) provided only immunogenicity data and nothing on the protective capability of the 200 kDa protein.

The partial problem approach was not appropriate for vaccine claims. The contribution of individual antigens could not be separated (see document (D15), summary, line 6). Contrary to a partial problem situation, additional components could not just be added in the expectation that protective ability would be maintained. The dual protection was effected by all antigens in claim 1.

XXI. The appellant requested that the decision under appeal be set aside and that the patent be revoked. The respondent requested that the appeal be dismissed or that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 1 filed with its reply to the statement of grounds of appeal dated 11 January 2011, or of its auxiliary request 2 filed during oral proceedings.

Reasons for the Decision

Main request
Amendments (Articles 100(c) and 123(2) EPC) - claims 4 to 10, 13 and 14

1. In the decision under appeal the opposition division considered that this request fulfilled the requirements of Article 123(2) EPC. The appellant contested this decision.

2. Claim 9, when read as referring back to claim 2, relates to a multi-valent immunogenic composition in which two antigens, the high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* (*H. influenzae*) and the outer membrane protein of *Moraxella catarrhalis* (*M. catarrhalis*) having an apparent molecular mass of 200 kDa, are specified in an otherwise generically defined multi-valent immunogenic composition.

3. It is undisputed that this combination of antigens is not explicitly disclosed in the application as filed. The relevant question to be answered is thus whether or not this combination of antigens is clearly and unambiguously derivable from the application as filed.

4. The application as filed discloses on page 7, lines 14 to 20 a generic composition as follows "*In accordance with one aspect of the present invention, there is provided a multi-valent immunogenic composition for conferring protection in a host against disease caused by infection with Haemophilus influenzae and Moraxella catarrhalis, which comprises at least four different antigens, comprising at least one antigen from Haemophilus influenzae and at least one*

antigen from Moraxella catarrhalis, at least three of which antigens are adhesins and at least one of which adhesins is from Moraxella catarrhalis." In the following paragraphs on page 7, line 21 to page 8, line 3, and page 8, line 18 to page 9, line 4 these various antigens of *H. influenzae* and *M. catarrhalis* are more closely defined. Thus, according to e.g. page 7, lines 21 to 24: "*One of the antigens which is an adhesin may be a high molecular weight protein (HMW) of a non-typeable strain of Haemophilus, particularly an HMW1 or HMW2 protein of the non-typeable strain, which may be produced recombinantly.*" Or according to page 8, lines 1 to 3: "*One of the antigens which is an adhesin may be an outer membrane protein of Moraxella catarrhalis having an apparent molecular mass of about 200 kDa, as determined by SDS-PAGE, and may be produced recombinantly.*"

5. The subject-matter of claim 9, when read as referring back to claim 2, results from the combination of the generic definition provided on page 7, lines 14 to 20 with the selection of the HMW protein provided on page 7, lines 21 to 24 and the selection of the 200 kDa protein provided on page 8, lines 1 to 3. In other words, it results from a combined selection from the list of possible antigens disclosed in the application as filed.

6. As to whether or not the particular combination of claim 9 contravenes Article 123(2) EPC, established case law of the Boards of Appeal (see decision T 686/99 of 22 January 2003, reasons, point 4.3.3) stipulates that: "*The content of the application as filed must not be considered to be a reservoir from which individual features pertaining to separate sections can be combined in order artificially to create a particular*

combination. In the absence of any ***pointer*** *to that particular combination, this combined selection of features does not, for the person skilled in the art, emerge clearly and unambiguously from the content of the application as filed (cf. T 727/00 of 22 June 2001, point 1.1.4 of the reasons).*" (Emphasis added by the board).(See also Case law of Boards of Appeal of the European Patent Office, 7th edition 2013, sections II.E.1.1.4 and II.E.1.7.1).

7. The application as filed lists the various antigens that can be used without any pointer regarding the possible combination of these antigens other than a composition comprising four defined antigens or a generic composition comprising only one of the disclosed specific antigens (see page 7, line 21 to page 9, line 2). The skilled person reading pages 7 to 9 would understand clearly and unambiguously that one of the antigens could be a HMW protein or a Hia protein or an analog of the Hin47 protein or the 200 kDa protein but not that the HMW and the 200 kDa should be combined in an otherwise generically defined composition. This combination has not been individualised in the application as filed. Also the claims as filed cover only combinations where a single antigen or all four antigens are defined.

8. It follows, that the combination of page 7, lines 14 to 20, page 7, lines 21 to 24 and page 8, lines 1 to 3 results in the skilled person being presented with a new combination of features and thus new technical information which he or she would not derive clearly and unambiguously, using common general knowledge, from the application as filed. The same argumentation applies *mutatis mutandis* to the subject-matter of

claims 4 to 8 and 10.

9. The respondent submitted that the skilled person understood that the passages on page 7, line 14 to page 8, line 3 could be combined. The board is not persuaded by this argument because the relevant question is not whether the passages "could be combined" but rather whether the application as filed provides a pointer to a particular combination. In the present case, the application lists the various antigens in an undifferentiated manner without any pointer to any particular combination thereof other than the combination of each individual antigen with the generic composition and a combination of 4 defined antigens, see page 8, lines 4 to 13.

10. Claim 13 specifies the amount of the various antigens being present in claims 11 or 12 as "25 to 100 µg". The appellant submitted that there was no basis in the application as filed for the specific range "25 to 100 µg".

11. The application as filed discloses in claim 25 and in the corresponding passage on page 9, lines 14 to 21 the amount as being "about 25 to about 100 µg". The board agrees with the opposition division (see decision under appeal, reasons, point 1.3.1) that the skilled person understands that the term "about" merely reflects the experimental accuracy with which values are determined and that deletion of the term neither creates a new value nor a new range and hence no new technical information. Accordingly, claim 13 is allowable under Article 123(2) EPC.

12. Claim 14 relates to the immunogenic compositions claimed in any one of claims 1 to 13 further comprising

an adjuvant. The appellant submitted that claim 14 lacked a basis because page 9, lines 3 to 4 disclosed the use of an adjuvant only in the context of the preferred embodiment.

13. Page 9, lines 3 to 4 discloses that "*The immunogenic composition of the invention may be further formulated with an adjuvant.*" In the board's judgement, the immunogenic composition of the invention is not only the preferred embodiment (with all 4 antigens being specified) but any immunogenic composition disclosed in the application as filed as being part of the invention. Accordingly, claim 14 is allowable under Article 123(2) EPC.

14. For the reasons set out above (see points 1 to 9), the subject-matter of claims 4 to 10 extends beyond the content of the application as filed and the main request is accordingly not allowable (Article 123(2) EPC).

Auxiliary request 1
Amendments (Articles 100(c) and 123(2) EPC) - claim 1

15. The claims of this request differ from the claims of the main request only in that the component nature of the vaccine has been specified in independent claims 1, 16 and 18 (see section VII above).

16. The respondent provided no further arguments for this request and conceded that the objections set out above for the main request also applied to this request.

17. Auxiliary request 1 is not allowable under Article 123(2) EPC for the same reasons as set out above for

the main request, see points 1 to 9.

Auxiliary request 2
Admissibility

18. This request was filed during the oral proceedings before the board and thus at a late stage in the proceedings. The independent claims of this request have been limited to an immunogenic composition in which all 4 antigens are defined (see section XVII above for the complete wording of independent claims 1, 5 and 6). The appellant has not contested the admissibility of this request. The board is satisfied that the amendments made in this request are straightforward, that they do not raise new issues, do not lead to any surprising turn of events or to subject-matter which diverges from the subject-matter of the higher ranking requests and accordingly, do not lead to a delay of the proceedings. Under these circumstances the board decides to admit this request into the appeal proceedings in the exercise of its discretion under Article 13(1) RPBA.

Amendments (Article 123(2) EPC)

19. The appellant did not raise any objections under Article 123(2) EPC. The board is satisfied that claim 1 finds a basis in claim 8 as filed, while claims 2 to 6 find a basis in claims 25, 26, 27 as filed and on page 9, line 12 to 13 of the application as filed. Therefore auxiliary request 2 complies with the requirements of Article 123(2) EPC.

Article 123(3) EPC

20. The appellant did not raise any objections under Article 123(3) EPC. The board is satisfied that claim 1 as amended corresponds to claim 11 as granted, while claims 2 to 6 correspond to claims 13, 14, 15, 17 and 19 as granted. Therefore the claims as amended do not extend the scope of protection vis-à-vis the claims as granted, such that the requirements of Article 123(3) EPC are satisfied.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

21. Claim 1 concerns a multi-valent immunogenic composition for conferring protection in a host against disease caused by both *H. influenzae and M. catarrhalis*, and comprising at least four defined antigens (see section XVII for the complete wording of claim 1). The mention of the grant of the present patent was published in the European Patent Bulletin on 7 February 2007. The version of the European Patent Convention revising that of the year 1973 (EPC 1973) entered into force on 13 December 2007. Hence, Article 54(5) EPC 2000 (for which no corresponding provision exists in the EPC 1973) does not apply, in accordance with Article 3 of the decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the EPC of 29 November 2000 (Special Edition No.1 OJ EPO 2007, 197). Accordingly, claim 1 is to be interpreted as a product claim, with the consequence that the multi-valent immunogenic composition has to be suitable for conferring protection against disease caused by both *H. influenzae* and *M. catarrhalis*.

22. According to established case law of the Boards of Appeal an invention is only disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art if at least one way of enabling the person skilled in the art to carry out the invention is disclosed, and if this allows the invention to be performed in the whole range claimed (Case law of Boards of Appeal of the European Patent Office, 7th edition 2013, sections II.C.4.2 and II.C. 4.4). The appellant submitted that neither requirement was fulfilled by the subject-matter of claim 1 (see section XIX above).

23. The patent in suit discloses (see example 7 and Figure 9) that a multi-component vaccine comprising the four antigens H91A Hin 47, rHMW, rHia and r200 kDa provides excellent protection in a chinchilla nasopharyngeal colonization challenge model, which is the relevant animal model for establishing protective efficacy against infection with *H. influenzae*. There is no relevant animal model for infection by *M. catarrhalis* but a bactericidal antibody assay has been developed as a surrogate assay. The patent in suit also discloses (see example 8, Tables III and IV) that antisera raised against the multi-component vaccine comprising the four antigens H91A Hin 47, rHMW, rHia and r200 kDa possess bactericidal antibody activity in this bactericidal antibody assay.

24. The board is satisfied that the evidence provided by examples 7 and 8 of the patent in suit shows that a multi-valent immunogenic composition falling within the scope of claim 1 is suitable for conferring protection in a host against a disease caused by both *H. influenzae* and *M. catarrhalis*. Therefore, in the board's judgement, the patent in suit provides at least

one way to carry out the invention.

25. Appellant's further argument that not a single embodiment had been provided by the patent in suit in which no antigenic interference was observed is not found persuasive. The board notes that claim 1 requires that the composition is suitable to provide dual protection but is silent as regards the avoidance of antigenic interference. In other words, claim 1 does not extend to compositions in which the components interfere to an extent that dual protection is no longer provided. Importantly, according to the patent in suit there was no apparent enhancing or inhibiting effect on the anti-r200 kDa response with the addition of the other vaccine components, i.e. H91A Hin47 + rHMW + rHIA (see paragraph [109]). Moreover, the patent in suit also discloses that the relative bactericidal antibody activity of anti-r200 kDa and an anti-4 component (H91A Hin47 + rHMW + rHia + r200 kDa) antisera was compared and found to be equivalent (see paragraph [0123]). Therefore, the board is satisfied that the patent in suit provides compositions which provide dual protection and in which the antigens are combined such that antigenic interference is avoided.

26. As regards the second requirement (see point 22 above), i.e. performance over the whole range claimed, the board notes that present claim 1 differs from claim 1 of the main request, for which the appellant had raised and substantiated its objection, in that all 4 antigens are now defined proteins. Extensive guidance regarding these proteins is provided in the patent in suit (see paragraphs [0005] to [0010] and [0012] to [0017]). The patent in suit provides moreover animal models which allow the skilled person to assess the protective ability of any multi-component composition comprising

these proteins (see examples 7 and 8).

27. In the board's judgement, it can therefore reasonably be assumed that a skilled person, following the guidance provided in the patent in suit, would be in a position to prepare appropriate immunogenic compositions, to test them and to select those which are suitable for conferring protection in a host against a disease caused by both *H. influenzae* and *M. catarrhalis* and, thus, that the skilled person could put the invention into practice over the whole scope of the claim without undue burden.

28. Accordingly, the board is satisfied that the requirements of Article 83 EPC are satisfied.

Novelty

29. The appellant has not raised any objection under Article 54 EPC and the board is satisfied that none of the documents on file anticipates the claimed subject-matter, such that the requirements of Article 54 EPC are satisfied.

Inventive step
Closest prior art

30. In the decision under appeal document (D5) was considered to represent the closest prior art. On appeal, the appellant failed to identify one single closest prior art document but submitted that "in general combinations of antigens from *M. catarrhalis* and *H. influenzae* to make *M. catarrhalis/ H. influenzae* vaccines were known at the priority date", while the respondent considered that document (D30) constituted

the closest prior art.

31. The present invention aims at providing a multi-valent immunogenic composition which confers protection in a host against a disease caused by both *H. influenzae* and *M. catarrhalis*. The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common.

32. Document (D5) relates to the synthesis and characterisation of lipooligosaccharide-based conjugates as vaccine candidates for *M. catarrhalis*. It discloses that the detoxified LOS (dLOS) was coupled to high-molecular weight proteins (HMP) from non-typeable *H. influenzae* and that the dLOS-HMP conjugate was immunogenic (see abstract). The HMP protein is used as a carrier and document (D5) neither mentions protection against *H. influenzae* nor aims at providing protection against both *H. influenzae* and *M. catarrhalis*.

33. Document (D30) aims at providing a vaccine capable of protecting against both *H. influenzae* and *M. catarrhalis* (see page 45, lines 10 to 15) and provides a conjugate in which the UspA2 of *M. catarrhalis* serves as a carrier for an *H. influenzae* type b oligosaccharide (HbO). Therefore, in the board's judgement, document (D30) qualifies as the closest prior art because it is directed to the same purpose as the invention, while document (D5) is not. The immunogenic and bactericidal effects of the HbO-UspA2 conjugate are reported in example VI of document (D30). The conjugate elicited antibodies against the pneumococcal oligosaccharide (see Table XXV) as well as

bactericidal antibodies to *M. catarrhalis* (see Table XXVII). While the immunogenicity data provided in Table XXV allow no conclusion as regards the protective ability of the antibodies against *H. influenzae,* the bactericidal activity indicates a protective effect against *M. catarrhalis*.

Technical problem to be solved

34. Starting from document (D30) as closest prior art the board considers the problem to be solved as the provision of a multi-valent vaccine which is protective against both *H. influenzae* and *M. catarrhalis*.

35. Claim 1 proposes as solution to this problem a composition comprising at least (a) an analog of *H. influenzae* Hin47 protein having a decreased protease activity which is less than 10% natural Hin47 protein, (b) a *H. influenzae* adhesin (Hia) protein of a non-typeable strain of *H. influenzae*, (c) a high molecular weight (HMW) adhesin protein of a strain of non-typeable *H. influenzae*, and (d) an outer membrane adhesin protein of *M. catarrhalis* having an apparent molecular mass of 200 kDa, as determined by SDS-PAGE. In the light of the experimental data provided in the patent in suit (see examples 7 and 8) the board is satisfied that the problem is solved by the subject-matter of claim 1.

Obviousness

36. It remains to be addressed whether the skilled person, when faced with the technical problem defined in point 34 above, would have modified the teaching in the closest prior art document (D30) - possibly in the light of other teachings in the prior art - so as to

arrive at the claimed invention in an obvious manner.

37. Document (D30) discloses the HbO-UspA2 conjugate and its ability to raise antibodies against the *H. influenzae* oligosaccharide in mice as well as bactericidal antibodies against *M. catarrhalis*. Document (D30) neither teaches nor suggests to include further proteins and in particular adhesins of *H. influenzae* or of *M. catarrhalis* to provide a multi-valent vaccine which is protective against both *H. influenzae* and *M. catarrhalis*. Accordingly, the claimed solution is not obvious from document (D30) alone.

38. Document (D36) investigates the role of the 200 kDa protein of *M. catarrhalis* as an antigen and mentions that another use of the protein is to act as a carrier for polysaccharide antigens of other organisms, including *H. influenzae* (see page 16, lines 1 to 12). However there is nothing in document (D36) that suggests that the glycoconjugates so formed are intended to be protective against both *M. catarrhalis* and *H. influenzae*. Finally, although document (D36) provides immunogenicity data (see examples 3, 5 and 6), it provides no data relating to a possible protective capability of the 200 kDa protein and in particular no experimental data regarding the bactericidal activity of antibodies raised against the protein. Therefore, in the board's judgement, the skilled person would not derive any motivation from document (D36) to include the 200 kDa protein in the combination known from document (D30), when faced with the problem of providing a multi-valent vaccine which is protective against both *H. influenzae* and *M. catarrhalis*.

39. Document (D33) discloses (see abstract) that immunisation with HMW of non-typeable *H. influenzae*

modifies experimental otitis media in chinchillas and concludes that although protection following immunization was incomplete, these data suggest that the high-molecular weight adhesion proteins are potentially important protective antigens which might represent one component of a multi-component non-typeable *Haemophilus* vaccine.

40. Document (D34) discloses the identification of a second family of high-molecular-weight adhesion proteins expressed by non-typeable *H. influenzae* and designated Hia protein. Document (D34) suggests the possibility of developing vaccines based upon a combination of HMW1/ HMW2-like proteins and Hia-like proteins which could be protective against diseases caused by most if not all non-typeable *H. influenzae* (see abstract).

41. Document (D35) discloses that a H91A mutant of HtrA (also known as Hin47, see paragraph [0012] of the patent) was found to be partially protective in animal protection models and therefore H91A HtrA may be a good candidate antigen for a vaccine against invasive *H. influenzae* disease and otitis media.

42. Documents (D33), (D34) and (D35) relate to *H. influenzae* antigens and none of these documents even mentions *M. catarrhalis* or the possibility of providing a vaccine affording dual protection against *H. influenzae* and *M. catarrhalis*.

43. In summary, the board concludes that none of the documents relied on by the appellant provides any hint that would have motivated the skilled person to modify the teaching of document (D30) to abandon altogether the chosen *M. catarrhalis* antigen (UspA2) and to replace it with the 200 kDa *M. catarrhalis* antigen or

even to add the 200 kDa *M. catarrhalis* antigen when faced with the problem of providing a multi-valent vaccine which is protective against both *H. influenzae* and *M. catarrhalis* so as to arrive at the claimed invention in an obvious manner.

44. The appellant submitted that each of the antigens disclosed in the patent, i.e. the HMW, Hia/Hsf, Hin47 from *H. influenzae* and the 200 kDa protein from *M. catarrhalis*, was known to be a vaccine candidate and that in general combinations of antigens from *M. catarrhalis* and *H. influenzae* to make *M. catarrhalis /H. influenzae* vaccines were known at the priority date. The combination of these antigens was a mere aggregation of antigens and each antigen represented a partial problem. The solution to each of these problems was obvious in view of documents (D33), (D34), (D35) and (D36).

45. According to established case law of the Boards of Appeal partial problems exist if the features or sets of features of a claim are a mere aggregation of those features or sets of features (juxtaposition or collocation) which are not functionally interdependent, i.e. do not mutually influence each other to achieve a technical success over and above the sum of their respective individual effects, in contrast to what is assumed in the case of a combination of features. What has to be established is whether each set of features is separately obvious in the light of the prior art (Case Law of the Boards of Appeal of the EPO, 7th edition, 2013, I.D.9.2.2).

46. As pointed out in the patent in suit (see paragraph [0044]): "*The composition of multi-component vaccines is important. The vaccine components must be compatible*

and they must be combined in appropriate ratios to avoid antigenic interference and optimize any possible synergies." Document (D15) relates to clinically relevant vaccine-vaccine interactions and confirms (see lines 6 to 10 of the summary on page 443) that "*Many vaccines should not be administered together because of adverse reactions known as vaccine-vaccine interactions, a phenomenon where one vaccine affects another vaccine, thus potentially causing loss of immunogenicity, loss of protective efficacy or induction of adverse reactions*". The skilled person thus knew that additional components could not just be added to vaccines in the expectation that the protective ability afforded by the individual components would be maintained. In the present case, the dual protection against diseases caused by *H. influenzae* and *M. catarrhalis* is effected by the combination of antigens recited in claim 1 and the contribution of the individual antigens can not be separated. In the board's judgement, the partial problem approach is therefore not appropriate for the subject-matter of present claim 1.

47. Moreover, the board notes that the appellant failed to establish that the inclusion of each antigen as defined in present claim 1 was separately obvious in the light of the prior art. Taking protein 200 kDa of *M. catarrhalis* as an example, document (D36) which is the sole document in these proceedings relating to this protein, does not disclose any data showing a protective activity of this protein. Therefore, the skilled person had neither a motivation nor any reasonable expectation of success that inclusion of that particular protein in the composition known from document (D30) would solve the problem formulated above

(see point 34).

48. The above considerations in respect of claim 1 also apply to the subject-matter of claims 2 to 6. For these reasons auxiliary request 2 complies with 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 on the basis of auxiliary request 2 filed on 28 November 2013 and the description and figures to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated