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Datasheet for the decision of 6 September 2022

Case Number: T 3038/19 - 3.3.07

Application Number: 11757949.0

Publication Number: 2608805

IPC: A61K39/095, A61K47/02, A61K47/34, A61K47/44, G01N33/569

Language of the proceedings: EN

Title of invention:
STABLE FORMULATIONS OF NEISSERIA MENINGITIDIS rLP2086 ANTIGENS

Patent Proprietor:
Wyeth LLC

Opponent:
Sanofi Pasteur

Headword:
Stable formulations of Neisseria Meningitidis rLP2086 antigens / WYETH

Relevant legal provisions:
EPC Art. 56, 123(2), 83
RPBA 2020 Art. 12(4)

Keyword:
Late-filed evidence - admitted (yes)
Inventive step - main request, auxiliary requests 1-9 (no) - effect not made credible within the whole scope of claim - auxiliary request 10 (yes)
Amendment to appeal case - suitability of amendment to resolve issues raised (yes)

Decisions cited:
T 2514/16, T 0184/16

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Case Number: T 3038/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 6 September 2022

Appellant: (Patent Proprietor)	Wyeth LLC 235 East 42nd Street New York, NY 10017-5755 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Appellant: (Opponent)	Sanofi Pasteur 14 Espace Henri Vallée 69007 Lyon (FR)
Representative:	Nony 11 rue Saint-Georges 75009 Paris (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 20 September 2019 concerning maintenance of the European Patent No. 2608805 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 608 805 (hereinafter "the patent") was granted on the basis of 15 claims. Claim 1 of the patent read as follows:

"An immunogenic composition comprising a detergent, a LP2086 (fHBP) Subfamily B polypeptide, a LP2086 (fHBP) Subfamily A polypeptide and aluminum, wherein the molar ratio of detergent to protein is between 0.5:1 and 10:1 and wherein the concentration of aluminum is between 0.1 mg/ml and 1 mg/ml."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, and it was not sufficiently disclosed.

III. The appeals were filed by the patent proprietor (appellant P) and the opponent (appellant O) against the interlocutory decision of the opposition division finding that, on the basis of auxiliary request 5 filed during the oral proceedings on 13 May 2019, the patent met the requirements of the EPC.

The decision was based on the patent as granted as the main request, on auxiliary request 1 filed on 28 August 2018, auxiliary requests 2 and 3 filed (as auxiliary requests 1 and 2) on 12 March 2019, and auxiliary requests 4 and 5 filed during the oral proceedings.

The detergent was limited to a non-ionic detergent in claim 1 of auxiliary requests 1 and 2, to a polysorbate detergent in auxiliary requests 3 and 4, and to

polysorbate 80 (PS80) in auxiliary request 5. Claim 1 of auxiliary requests 4 and 5 additionally specified the presence of histidine at a concentration of between 5 mM and 15 mM.

IV. The appealed decision cited the following documents among others:

D1: WO 2010/109323
D5: WO 2004/032958
D6: FASTA query of SEQ ID NO. 10 of WO 2004/032958
D7: FASTA query of SEQ ID NO. 11 of WO 2004/032958
D8: FASTA query of SEQ ID NO. 12 of WO 2004/032958
D9: Wang et al. (2008, International Journal of Pharmaceutics, Vol. 347: 31-38
D15: WO 2007/127665

V. The opposition division decided that:

(a) The subject-matter of claim 1 of the main request and of each of auxiliary requests 1-3 lacked novelty over D1.

(b) Auxiliary request 4 was admitted into the proceedings.

Regarding inventive step, the closest prior art D5 disclosed a combination of LP2086 subfamily A and B polypeptides, aluminium in the amount of claim 1 and polysorbate as a detergent. D5 did not disclose the ratio of detergent to total protein. The objective technical problem was the provision of an alternative bivalent immunogenic composition comprising both subfamily A and B polypeptides. The claimed solution lacked an inventive step in view of D5.

(c) Auxiliary request 5 was also admitted into the proceedings. Taking D5 again as closest prior art, the problem was to provide a stable immunogenic composition comprising both subfamily A and B LP2086 polypeptides. The claimed subject-matter involved an inventive step.

VI. Appellant O submitted the additional document D25 with the statement setting out the grounds of appeal dated 20 January 2020, and document D26 on 22 May 2020 with their reply to appellant P's appeal.

D25: Garidel et al, Biophysical Chemistry, 2009, 143: 70-78
D26: "lipoprotein", Webster Dictionary website (https://www.merriamwebster.com/dictionary/lipoprotein)

VII. With the statement setting out the grounds of appeal dated 17 January 2020, appellant P defended their case on the basis of the patent as granted as main request, and filed auxiliary requests 1-23. Appellant P further filed auxiliary request 24 with their reply dated 1 June 2020.

VIII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA dated 24 May 2022.

IX. Oral proceedings were held before the Board on 6 September 2022.

At the beginning of the oral proceedings, appellant P withdrew their main request (patent as granted) and renumbered their requests as follows. The (new) main request corresponded to auxiliary request 2 filed with

the grounds of appeal dated 17 January 2020. Auxiliary request 1 was auxiliary request 1 filed with the grounds of appeal. Auxiliary requests 2-22 corresponded to auxiliary requests 3-23 filed with the grounds of appeal, and auxiliary request 23 to auxiliary request 24 filed with the reply dated 1 June 2020.

The present decision was therefore taken on the basis of the following requests:

Claim 1 was identical in the main request and in auxiliary request 1 and differed from claim 1 as granted (see point I above) in that the detergent was limited to a non-ionic detergent.

In claim 1 of auxiliary requests 2 and 3, the detergent was limited, respectively, to a polysorbate detergent and to polysorbate 80 (PS80).

Claim 1 of auxiliary requests 4 and 5 differed from granted claim 1 in that the molar ratio of detergent to protein was limited, respectively, to between 1:1 and 5:1 and between 1.4:1 and 4.2:1.

Auxiliary requests 6-8 combined the amendments of auxiliary request 4 with those of auxiliary requests 1-3. Auxiliary request 9 combined the amendments of auxiliary request 5 with those of auxiliary request 3.

Claim 1 of auxiliary request 10 read as follows:
"An immunogenic composition consisting of a detergent, a LP2086 (fHBP) Subfamily B polypeptide, a LP2086 (fHBP) Subfamily A polypeptide, aluminum as $AlPO_4$, 10mM histidine pH 6.0, and 150 mM NaCl, wherein the detergent is Polysorbate 80, wherein the molar ratio of

Polysorbate 80 to protein is 2.8:1 and wherein the concentration of aluminum as $AlPO_4$ is 0.5 mg/mL."

X. Appellant P's arguments may be summarized as follows:

(a) Admittance of D25

D25 was late filed with no good reason and not *prima facie* relevant. D25 was thus not to be admitted into the proceedings.

(b) Inventive step, main request and auxiliary requests 1-9

The present invention pertained to a vaccine that included two related forms of the lipoprotein LP2086 (also named fHBP). It addressed the issues of long-term stability of the LP2086 Subfamily B antigen (hereinafter LP2086 B) and of aggregation of LP2086 Subfamily A (LP2086 A) and B antigens upon agitation.

D5 only provided a generic disclosure of a composition comprising two fHBP antigens, and mentioned, though not in combination, the optional presence of a detergent (e.g. tween 80) and adjuvants including aluminium salt. The aim of D5 was not to develop stable formulations.

The subject matter of claim 1 of the main request differed at least by:
- the presence of both subfamilies A and B;
- the inclusion of both proteins in their respective lipidated form;
- the presence of aluminum at a concentration of 0.1-1 mg/mL;
- the presence of a non-ionic detergent; and
- a molar ratio of detergent to protein of 0.5-10.

The patent showed an improved stability associated with a ratio of detergent to protein below 10, both in the case of compositions comprising only LP2086 B and in the case of bivalent LP2086 A and LP2086 B compositions, despite their different detergent binding behaviors. Claim 1 of the main request covered compositions comprising additional antigens, which represented a reasonable extrapolation. The burden of proof was on appellant O to demonstrate the contrary.

The objective technical problem was to provide an improved composition to be used as a vaccine against *N. meningitidis* which was capable to elicit an immune response against both the subfamily A and subfamily B variants of the LP2086 antigen and that exhibits improved storage and transport stability. The claimed solution involved an inventive step.

Even if the problem was formulated as the provision of an alternative, D5 provided no incentive to combine the antigens and excipients as defined in claim 1 of the main request.

The limitations carried out in auxiliary requests 1-9 further strengthened the inventive step of claim 1.

(c) Auxiliary request 10

Auxiliary request 10 had already been filed as auxiliary request 9 during the proceedings before the opposition division. The later filing of new auxiliary requests 4 and 5 did not amount to a deliberate choice not to defend this request. Auxiliary request 10 was thus to be admitted into the appeal proceedings.

Claim 1 of auxiliary request 10 derived from claims 2 and 34 of the application as filed. The criteria of article 123(2) EPC were met.

Regarding sufficiency of disclosure, the term immunogenic had its normal meaning in claim 1. The compositions of claim 1 comprised known antigens and were immunogenic. The immunogenicity of the composition could be measured without undue burden.

As to inventive step, the alternative starting point D15 described a composition comprising rLP2086 antigen of undefined subtype at 120µg/mL or 400µg/mL, 150 mM NaCl, 0.02% PS80, 0.25 mg Al/mL of $AlPO_4$ in a 10 mM phosphate buffer at pH 7 or a 5 mM succinate buffer at pH 6. The differences between the subject matter of claim 1 and D15 were at least:
- the presence of LP2086 A and B in the composition, and
- the molar ratio of detergent to protein of 2.8:1.
The objection from appellant O was based on a combination of this embodiment of D15 with D5 and the replacement of the LP2086 of D15 with a combination of LP2086 A and B in amounts which had no basis.
The objective technical problem was to provide an improved composition to be used as a vaccine against *N. meningitidis* which was capable to elicit an immune response against both the subfamily A and subfamily B variants of the LP2086 antigen and that exhibited improved storage and transport stability. The claimed solution involved an inventive step.

XI. Appellant O's arguments may be summarized as follows:

(a) Admittance of D25

D25 was filed in response to the arguments set forth for the first time by appellant P during the oral proceedings before the opposition division, and supported arguments made during the first instance proceedings. Thus D25 was to be admitted into the proceedings.

(b) Inventive step, main request

D5 had for purpose to provide compositions with broad immunity against serogroup B meningococcus. D5 suggested combining lipidated A and B variants in the same composition (see page 4, lines 8-12). In addition, the composition of D5 could comprise a detergent, e.g. < 0.01% PS80, a histidine buffer, and an aluminum salt at 0.6 mg Al^{3+} / ml.

The molar ratio detergent to protein was devoid of technical effect over the whole scope of the claims, for the following reasons.

Examples 2-5 of the patent showed that the detergent PS80 interacted with LP2806 B antigen, which could result in a loss of potency. This problem could be considered to be solved in the examples of the patent only for compositions comprising in particular:
- only LP2806 A and B as proteins,
- both proteins being in same amount, and
- PS80 as detergent.
However, the claimed composition could comprise further protein antigens, and the molar ratio detergent to protein was calculated with respect to the whole

protein content. Different proteins had different capacity to bind PS80, and this property was not predictable (see D25). The addition of further proteins not binding to PS80 would mechanically and necessarily results in an increase of the relative amount of PS80 with respect to LP2086 A and B, thus leading to an effective molar ratio of detergent to LP2086 outside the range of the calculated ratio. Consequently, the technical problem set out by the patent was not solved for compositions comprising more proteins than only LP2806 A and B.

It would have been routine work for the skilled person to optimize the ratio of detergent to protein to reach the recited values. Accordingly, the main request did not meet the requirements of inventive step.

(c) Auxiliary request 10

Auxiliary requests 4-22 were to be refused as being not convergent. Furthermore, auxiliary request 10 had not been discussed before the opposition division or in the appealed decision, and thus was not to be admitted.

Claim 1 of auxiliary request 10 contravened Article 123(2) EPC. The expression "consisting" of claim 1 was only shown, in the application as filed, in combination with specific concentrations of the fHBP polypeptides.

The criteria of sufficiency of disclosure were not met. The skilled person was not provided with enough guidance on how to evaluate whether a composition as claimed was effectively immunogenic or not.

Regarding inventive step, starting from D5, the compositions of claim 1 of auxiliary request 11

differed by a detergent to protein molar ratio of 2.8:1, by the presence of 10 mM histidine, and by the concentration of $AlPO_4$ at 0.5 mg/ml. The molar ratio did not have a technical effect over the whole scope of the claims, and no specific technical effect was associated with those specific ratios. A skilled person would have without inventive effort adjusted the molar ratio to reach the values recited in the claims. No technical effect was associated with the 10 mM histidine or the 0.5 mg/ml $AlPO_4$ either.

Alternatively, D15 aimed at providing stabilized immunogenic compositions and described a composition comprising 400 or 120 µg/mL LP2086, 5 mM Succinate buffer pH 6.0, 150 mM NaCl, 0.02% PS80 and 0.25 mg Al/ mL of $AlPO_4$. On the other hand, D5 taught that for maximum cross-strain efficacy, a composition preferably included more than one variant of LP2086. Starting from D15, a skilled person would have been motivated to consider the teaching of D5 in order to broaden the immune response towards a larger group of *Neisseria meningitidis* bacteria, and would have prepared the same composition with 0.4 mg/mL LP2086 A and 0.4 mg/mL LP2086 A. This composition had a detergent to protein molar ratio of 5.4. Claim 1 of auxiliary request 10 differed by a detergent to protein molar ratio of 2.8:1, by the presence of 10 mM histidine and by the concentration of $AlPO_4$ at 0.5 mg/ml. No technical effect was associated with any of these features. A skilled person would have without inventive effort adjusted these parameters.

Accordingly, auxiliary request 10 did not meet the requirements of inventive step.

XII. Appellant P requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, filed as auxiliary request 2 with the statement of grounds of appeal dated 17 January 2020 or, alternatively, that the patent be maintained on the basis of auxiliary request 1 filed with the statement of grounds of appeal or one of auxiliary requests 2-22 filed as auxiliary requests 3-23 with the statement of grounds of appeal, or auxiliary request 23 filed as auxiliary request 24 with the reply dated 1 June 2020. Appellant P further requested that document D25 be not admitted into the proceedings

XIII. Appellant O requested that the decision under appeal be set aside and that the patent be revoked in its entirety. Appellant O further requests that auxiliary requests 5-23 be not admitted into the proceedings.

Reasons for the Decision

1. Admittance of D25

Appellant O filed D25 for the first time together with the grounds of appeal dated 20 January 2020. D25 represents an amendment to appellant O's case in the sense of Article 12(4) RPBA 2020, and its admittance is thus subject to the Board's discretion. The criteria for the exercise of this discretion are, *inter alia*, the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal, and the need for procedural economy (Article 12(4), 5th sentence, RPBA 2020).

D25 relates to the interaction of human serum albumins and immunoglobulins with the detergent polysorbate 80

(PS80). Appellant O relies on D25, both in their argumentation regarding insufficiency of disclosure and inventive step, to demonstrate that the interactions between proteins and PS80, and with detergent in general, vary greatly depending on the proteins.

D25 does not amount to bringing a fresh case in appeal, but is only filed to further support arguments already brought forward during the first instance proceedings, in particular with respect to the achievement of an effect over the whole scope of the claim, which issue crucially determined the rejection of auxiliary request 4 and the allowance of auxiliary request 5 by the opposition division. As such, D25 does not unduly introduce complexity into the proceedings.

Accordingly, the Board admitted D25 into the appeal proceedings.

2. Main request, inventive step

2.1 The claimed invention

The patent relates to immunogenic compositions comprising *Neisseria meningitidis* rLP2086 antigens. rLP2086 is a lipoprotein that induces cross-reactive bacterial antibodies against a number of *Neisseria meningitidis* strains (see paragraphs [0001] and [0002] of the patent). Two subfamilies of rLP2086 exist, namely the LP2086 Subfamily A and LP2086 Subfamily B antigens (hereinafter LP2086 A and LP2086 B).

The purpose of the invention is to address the issue of stability of the composition. According to paragraphs [0047] and [0048], high molar ratios of detergent to protein result in LP2086 B antigen instability.

Reducing the molar ratio of detergent to protein in monovalent (i.e. LP2086 B) and bivalent (i.e. LP2086 A and LP2086 B) formulations resulted in increased stability, as determined by maintenance of potency over time, of LP2086 B without affecting the stability of LP2086 A. However, this also resulted in aggregation of LP2086 A and B upon agitation. This aggregation was prevented by increasing aluminum concentration (see paragraph [0048]).

Accordingly, claim 1 of the main request relates to an immunogenic composition comprising LP2086 B, LP2086 A, a non-ionic detergent in a molar ratio of detergent to protein between 0.5:1 and 10:1, and aluminum in a concentration between 0.1 mg/ml and 1 mg/ml.

2.2 Closest prior art

2.2.1 The closest prior art D5 relates, like the patent in suit, to vaccines against meningococcal infections, such as compositions inducing an antibody response against *Neisseria meningitidis* (see the abstract).

2.2.2 The compositions of D5 comprise several antigens, including a 741 protein, which corresponds to the present LP2086 polypeptide. The general passage on page 4 (lines 3 and 8-11) teaches that, for "maximum cross-strain efficacy", the composition should preferably include more than one variant (or, in other words, at least two variants) of protein 741, and lists 3 variants represented by SEQ ID NO:10 (i.e. LP2086 B24, see D6), SEQ ID NO: 11 (i.e. LP2086 A19, see D7) and SEQ ID NO: 12 (LP2086 A124, see D8) in lipoprotein form. Accordingly, in one alternative, the composition of D5 comprises an LP2086 B lipoprotein and an LP2086 A lipoprotein. This conclusion is not modified by the

mention, in other passages of D5, of further embodiments, such as truncated or non-lipidated forms or analogues with low sequence identity of the protein(s) (see page 3, lines 23-27; page 4, lines 12-19). Likewise, the disclosure of D5 is not limited to the example of page 36 containing only one 741 protein. Irrespective of these further alternatives, the passage on page 4 (lines 8-11) discloses a combination of lipidated LP2086 A and B polypeptides.

2.2.3 The compositions of D5 will usually include an adjuvant (see page 14, line 32), aluminium phosphates being particularly preferred, particularly in compositions which include *H.influenzae* saccharide antigens. A typical adjuvant is amorphous aluminium hydroxyphosphate included at 0.6 mg Al^{3+}/ml (see page 15, lines 8-10). This statement expresses a general preference for the presence of such an aluminum adjuvant, i.e. "particularly" but not only in the case of *H.influenzae* saccharide antigens.

Thus D5 shows, in one embodiment, the combined presence of LP2806A, LP2806B and 0.6 mg/ml aluminium.

2.2.4 The compositions of D5 may additionally comprise a detergent such as Tween 80, generally at low levels e.g. <0.01% (see page 14, lines 22-23). The Board however concurs with appellant P that these further features are not disclosed together with the above embodiment. Furthermore, claim 1 of the main request mandates that the molar ratio of detergent to protein is between 0.5:1 and 10:1. It is undebated that this molar ratio is calculated based on the total amount of proteins (see paragraph [0035] of the patent). D5 does not disclose the total amount of the proteins in the

composition in the case of a combination of LP2806A and LP2806B.

2.3 Differentiating features

The subject-matter of claim 1 of the main request differs from the teaching of D5 by the presence of a non-ionic detergent in a molar ratio of detergent to protein between 0.5:1 and 10:1.

2.4 Technical effect and problem

2.4.1 In the Board's view, a molar ratio of detergent to protein below 10 is shown to result in increased stability of LP2086 B, as determined by the maintenance of its potency over time, in the case of formulations containing LP2086 B, or LP2086 A and LP2086 B, as sole proteins and PS80 as detergent.

This is demonstrated in the case of monovalent compositions containing LP2086 in figure 2 and paragraph [00134] of the patent.

In bivalent compositions comprising equimolar amounts of LP2086 A and LP2086 B as sole proteins, the patent shows that LP2086 B has a better stability at a molar ratio of PS80 to the total LP2086 proteins of 4.3 or 5.3 as compared with 10.7 (see figure 1 and paragraph [00133]; figures 5 and 6, and paragraph [0136]). This effect is also substantiated by the result exhibited in figures 23 and 24 and example 4 of the patent: after studying the binding of the particular detergent PS80 to LP2086 A and B respectively, the patent shows a drop in potency when the amount of this detergent exceeds the upper limit of 10:1 relative to the total LP2086 A+B proteins.

2.4.2 However, when defining the objective technical problem, this improvement in stability can only be retained if it is credible that the effect is associated with the claimed detergent to protein ratio throughout the claimed area.

The patent analyses the binding properties of LP2086 A and LP2086 B with PS80 (see example 2, figures 15 and 16, and example 4), and concludes that the stability of LP2086 B is inversely correlated to a binding property to PS80 (see figure 17).

Claim 1 is however not limited to bivalent LP2086 A / LP2086 B compositions, but allows for the additional presence of further proteins in any amounts. The parameter differentiating the compositions of claim 1 from those of D5, namely the molar ratio of detergent to proteins, is calculated with respect to the whole protein content, and not to the sum of LP2086 A and LP2086 B. The patent contains no data regarding compositions comprising other proteins in addition to LP2086 A and LP2086 B.

These further proteins may have a different capacity to bind PS80. This is shown in D25, which evaluates the stabilizing effect of PS80 on different proteins and studies their interactions (see the abstract). It is concluded that immunoglobulins interact very weakly with PS80, while albumin interacts strongly (see page 76, left column, first paragraph). There is no limitation in claim 1 as to the additional proteins present, their amounts or to their PS80 binding properties. Contrary to appellant P's view, the presence of immunoglobulins is not excluded by claim 1.

Appellant P did in any case not contest that even antigens may bind differently to detergents.

Consequently, claim 1 allows for the presence of undefined amounts of further proteins which may have negligible binding to PS80. The addition of such proteins will necessarily results in an increase of the relative amount of PS80 with respect to LP2086 A and B, thus leading to an effective molar ratio detergent to LP2086 above 10 and a loss of LP2086 B stability. For instance, claim 1 covers compositions comprising further weakly-binding proteins in addition to LP2086 B and LP2086 A, and PS80 in a molar ratio of detergent to the sum of all proteins close to 10:1. In such a composition, the ratio of PS80 to LP2086 A or B will exceed 10:1. Since the other proteins do not bind the detergent, this excess PS80 will inevitably interact with LP2086 A and LP2086 B. Considering the data in the patent and the relevance of LP2086 B - PS80 binding indicated therein, a stabilisation is not credible for such an embodiment, and a loss of potency is instead to be expected. Contrary to appellant P's view, the relevant question here is whether claim 1 covers embodiments lacking the alleged stability effect, and not whether the skilled person could, in such a case, modify this embodiment and add further protein or PS80 to restore stability.

In conclusion, the alleged improvement is not credibly obtained over the whole scope of claim 1. The invention achieves LP2086 B stability in bivalent LP2086 A and LP2086 B formulations using the range 0.5:1-10:1 in view of the PS80 binding capacities of LP2086 A and LP2086 B determined in the patent, but this range cannot be extrapolated to compositions comprising

further proteins of unpredictable PS80 binding capacity.

2.4.3 Appellant P submitted that they had discharged their burden of proving the effect by providing experimental data regarding bivalent compositions, which represented a substantial part of the claimed subject-matter. The burden would thus rest with appellant O to demonstrate the non-achievement of this technical effect.

The Board does not share this opinion for the following reasons.

It is established case law that, if the patent proprietor alleges the fact that the claimed invention improves a technical effect, then the burden of proof for that fact rests upon him (see the Case Law of the Boards of Appeal, 10th edition, 2022, I.D.4.3.1). Furthermore, when defining the objective technical problem, an effect cannot be retained if it is not credible that the promised result is attainable throughout the entire range covered by a claim (*ibid*, I.D.4.1).

In the present case where the claims result from a generalisation of the exemplified bivalent compositions, it is thus for appellant P to show that the alleged improvement is achieved not just for bivalent compositions, but over the whole breadth of the claim. It cannot be considered that appellant P discharged their burden by providing evidence in respect of only a subset of the claimed subject-matter (namely bivalent LP2086 A / LP2086 B compositions), if it has not been made credible that this effect can be extrapolated to the rest of the claimed area, in particular to compositions comprising further proteins.

Having regard to the considerations made in point 2.4.2 above, the Board also fails to see the logic behind such extrapolation. Finally, the Board does not accept that bivalent compositions would somehow constitute the most relevant part of the claimed subject-matter. The presence of further immunogenic proteins is explicitly considered in the patent (see paragraph [0058]) and is a feature of the multivalent compositions of the prior art D5.

2.4.4 Contrary to appellant P's view, neither T 2514/16 nor T 184/16 lead to the conclusion that evidence regarding only part of the claimed area is necessarily sufficient to shift the burden of proof to the opponent.

T 184/16 does not address issues of burden of proof in the context of inventive step. It states, in the context of sufficiency of disclosure, that, for plausibility of a claimed effect to be acknowledged, it is enough if there are no *prima facie* serious doubts that the effect can be obtained and conversely no *a priori* reason and indication in the common general knowledge that the effect cannot be obtained. This is unrelated to the present question of credibility of a non-claimed effect in the context of obviousness.

As to T 2514/16, the Board found that the respondent had demonstrated with D16 that an effect was achieved for at least part of the claim at issue and that the burden of proving that this effect was not achievable across the whole breadth of the claim thus lay with appellant 1. However the circumstances of this case differed in that the alleged effect was made credible by D16, and that the appellants had not presented any argument calling into question the plausibility of the effect (see points 3.3.5-3.3.7 of the decision). In

contrast, in the present case, appellant O presented convincing arguments supported by D25 that, for some compositions of claim 1, an improvement in stability is not credible (see point 2.4.2 above).

2.4.5 Finally, appellant P argued that the stabilisation effect might be caused by other factors than the binding to PS80, and referred to D25 for a discussion of the various mechanisms of detergent / protein interaction (see page 71, left column). Appellant P also referred, without substantiation, to a potential role of aluminum. These arguments cannot help appellant P's case, because they still do not justify why the effect observed for the claimed ratio range in bivalent LP2086 A / B compositions should also arise with the same range in composition comprising additional undefined proteins. These arguments additionally contradict the correlation established in the patent between binding and potency (see 2.4.2 above).

2.5 Consequently, the differentiating feature over D5, namely the presence of a non-ionic detergent in a molar ratio of detergent to protein between 0.5:1 and 10:1, is not associated with any technical effect arising over the whole claimed area. The objective technical problem is thus the provision of an alternative immunogenic composition comprising both LP2086 subfamily A and B polypeptides.

2.6 For the following reasons, the claimed solution does not involve an inventive step.

As explained above, D5 discloses immunogenic compositions inducing an antibody response against *Neisseria meningitidis*. In one embodiment, this composition comprises lipidated LP2806 A and LP2806 B,

and 0.6 mg/ml aluminium (see 2.2 above). The skilled person would consider such compositions as a reasonable starting point for developing alternative immunogenic compositions. Furthermore, D5 generally mentions that the compositions may additionally comprise a detergent such as Tween 80 (i.e. PS80) at low levels (see page 14, lines 22-23). In light of the teaching of D5, the skilled person would consider incorporating PS80 in amounts such as those defined by claimed detergent : protein molar ratio of between 0.5:1 and 10:1. Such an amount is not associated with any particular technical effect. The arbitrary selection of these amounts does not involve an inventive step.

According to appellant P, an inventive step should be acknowledged on the ground that D5 provides no incentive to combine the antigen and excipients as defined in claim 1. The Board does not agree. The skilled person does not require any hint or incentive to follow the instructions in D5, prepare an immunogenic LP2086 A and LP2086 B composition as described therein, and use the suggested low detergent amount, such as the amount defined in claim 1, in the expectation of solving the technical problem, which is merely to provide an alternative immunogenic composition. The fact that D5 suggests other potential routes to solve the technical problem, such as the preferred non-lipidated forms (see page 3, lines 23-27) or the exemplified monovalent composition (see page 36), does not change this fact.

2.7 In conclusion, the main request does not meet the requirements of inventive step.

3. Auxiliary requests 1-9, inventive step

The conclusion reached above for the main request is not changed by any of auxiliary requests 1-9.

In each of the auxiliary requests 1-9, claim 1 allows for the presence of additional undefined proteins, such that no technical effect can be attributed to the parameter of the detergent : protein molar ratio.

Claim 1 is identical in the main request and in auxiliary request 1, such that the same considerations apply.

The detergent specified in claim 1 of auxiliary requests 2 and 3, namely a polysorbate detergent or PS80, are explicitly suggested in D5.

The limited ranges defined in claim 1 of auxiliary requests 4 and 5, namely 1:1-5:1 and 1.4:1-4.2:1, remain, in the absence of associated technical effect over the whole claimed area, an obvious arbitrary selection from the low amounts suggested in D5.

Lastly, the same considerations also apply to auxiliary requests 6-9, which combine the above amendments.

Thus, none of the auxiliary requests 1-9 meets the criteria of inventive step. The question of their admittance is consequently moot.

4. Auxiliary request 10

4.1 Admittance

Appellant P filed auxiliary request 10 (as auxiliary request 11) with their grounds of appeal dated 17 January 2020. Appellant O challenges the admittance of this request into the appeal proceedings.

Appellant P had already filed the same request, as auxiliary request 9, during the first instance proceedings on 12 March 2019, i.e. before the final date for making submissions set by the opposition division under Rule 116 EPC. Appellant P then filed (new) auxiliary requests 4 and 5 during the oral proceedings before the opposition division. Since the opposition division allowed this higher-ranking auxiliary request 5, auxiliary request 10 does not belong to the requests on which the decision under appeal is based (see Article 12(2) RPBA 2020). Nevertheless, the Board accepts appellant P's argument that this does not amount to a deliberate choice not to defend auxiliary request 10 before the opposition division, let alone to a withdrawal of this request.

In any case, it can be left undecided whether this request was admissibly raised and maintained in the proceedings leading to the decision under appeal, in the sense of Article 12(4) RPBA 2020. This is because the Board considers that the criteria for admitting this request are met even if auxiliary request 10 is considered to represent an amendment to appellant P's case.

Claim 1 of auxiliary request 10 is limited to a single specific composition. The filing of this request does

not modify the framework of the appeal proceedings to the point that it should be regarded as a fresh case. Furthermore, as explained below, this limitation suitably addresses the objections considered without introducing new issues. Lastly, auxiliary request 10 is convergent in the sense that it is more limited than any of the higher raking requests, so that its filing is not detrimental to procedural economy.

Accordingly, the Board admitted auxiliary request 10 into the appeal proceedings.

4.2 Article 123(2) EPC

During the oral proceedings, appellant O raised a new objection under Article 123(2) EPC against claim 1 of auxiliary request 10. According the appellant O, the expression "consisting" of claim 1 was only shown, in paragraphs [0009] and [0023] of the application as filed, in combination with specific concentrations of the fHBP polypeptides, namely 200ug/mL for each of the Subfamily A and B polypeptides.

It is not necessary to assess whether appellant O's objection of added subject-matter should be admitted into the proceedings, since the Board finds this objection not convincing.

The limitations, in claim 1 of auxiliary request 10, regarding $AlPO_4$, histidine, NaCl, PS80, together with their respective concentrations, derives directly and unambiguously from the application as filed, in particular from a combination of claims 2 and 34 as filed. These limitations are not associated with any specific concentrations for the A and B polypeptides. Additionally, the amendment to a composition consisting

of (instead of comprising) both polypeptides and the stated detergent and adjuvants is also supported by the exemplified compositions containing exactly these components in the application as filed.

Accordingly, auxiliary request 10 meets the requirements of Article 123(2) EPC.

4.3 Sufficiency of disclosure

Claim 1 specifies that the claimed composition is immunogenic, i.e. that the composition as a whole is effective in eliciting an immune response. Appellant O had raised objections of insufficiency of disclosure against higher-ranking requests based on the possibility in claim 1 to include proteins other than LP2086 A and B, or to include detergents other than PS80. None of these objections apply to auxiliary request 10, which is limited in both respects. Considering that it contains LP2086 A and B, which are known to induce an immune response in the body, there is no reason to doubt that the claimed composition is immunogenic.

Furthermore, claim 1 does not require the composition to achieve any quantitatively defined level of immunogenicity nor the selection of one particular test. The fact that the composition is immunogenic (to any extent) may be tested using any suitable immunoassay (see paragraph [0038] of the patent), such as the Serum Bactericidal Assay (SBA) using as bacteria strain the MnB strains expressing LP2086 subfamily A and B proteins, as in example 8 of the patent.

The criteria of sufficiency of disclosure are thus met.

4.4 Inventive step

4.4.1 Starting from D5

The subject-matter of claim 1 of auxiliary request 10 differs from the teaching of D5 discussed above (see 2.2) at least by the presence of PS80 in a PS80 to protein molar ratio of 2.8:1.

As explained in the context of the main request (see 2.4.1 above), the selection of a detergent to protein molar ratio below 10 leads to an improved stability of LP2086 B in the claimed compositions. As a result of the limitation of claim 1 to binary compositions comprising LP2086 A and B and excluding the presence of further proteins, PS80 as detergent and with the claimed amount of aluminum, this technical effect credibly arises aver the whole area claimed. None of appellant O's objections to the contrary, based on the potential presence of further proteins or the use of other detergents, apply to this request.

Accordingly, the objective technical problem is the provision of an improved composition to be used as a vaccine against *N. meningitidis* which is capable to elicit an immune response against both the subfamily A and subfamily B variants of the LP2086 antigen and that exhibits improved storage and transport stability.

The claimed solution involves an inventive step because the prior art does not give any hint that the selection of the claimed low amounts of detergent would improve the stability of LP2086 B. In particular, neither a PS80 : protein molar ratio below 10:1, nor the technical effect associated therewith, are disclosed in any of D5 of D15 (as shown in 4.4.2 below).

4.4.2 Starting from D15

D15 relates to stable immunogenic compositions (see page 1, lines 13-15). D15 describes (see page 40, example 5 and table 8) stabilised meningococcal compositions comprising in particular an LP2086 polypeptide (at 120 or 400 µg/ml), 0.25 mg/ml aluminium as $AlPO_4$, 0.02% PS80 and a buffer.

D15 does not disclose the presence of a second LP2086 protein, i.e. the presence of both A and B subfamilies. The subject-matter of claim 1 of auxiliary request 10 additionally differs from the composition of D15 at least by the detergent to protein molar ratio.

Appellant O calculated a detergent to protein molar ratio of 5.4 for a hypothetic embodiment ("composition 2") derived from a combination of D15 and D5, and containing, in place of the 0.4 mg/ml LP2086 polypeptide of D15, 0.4 mg/ml LP2086 A and 0.4 mg/ml LP2086 B. However, such an embodiment, resulting from the combination of separate documents and the arbitrary selection of the replacing amounts of LP2086 A and B, is not part of the prior art. A detergent to protein molar ratio below 10:1, e.g. of 2.8:1 as in present claim 1, is disclosed neither in D15 nor in D5.

Accordingly, D15 does not come closer to the claimed invention than D5 and does not modify the conclusions as to inventive step: the differentiating feature pertaining to the PS80 to protein molar ratio of 2.8:1, leading to the demonstrated improvement in stability in the context of the composition of auxiliary request 10, establishes an inventive step for the same reasons as when starting from D5.

4.4.3 Accordingly, auxiliary request 10 meets the requirements of inventive step

Order

For these reasons it is decided that:

The decision under appeal is set aside

The case is remitted to the opposition division with the order to maintain the patent on the basis of auxiliary request 10, filed as auxiliary request 11 with the statement of grounds of appeal, and a description to be adapted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated