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Datasheet for the decision of 1 October 2021

Case Number: T 0465/18 - 3.3.07

Application Number: 12157010.5

Publication Number: 2457590

IPC: A61K47/10, A61K47/12, A61K9/00, A61K38/47

Language of the proceedings: EN

Title of invention:
Protein formulation

Patent Proprietor:
Arecor Limited

Opponent:
GlaxoSmithKline Biologicals S.A.

Headword:
Protein formulation/Arecor Limited

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 100(b), 100(c), 54, 56

Keyword:

Admission of documents
Main request - Extension of subject-matter (No)
Main request - Sufficiency of disclosure (Yes)
Main request - Novelty (Yes)
Main request - Inventive step (Yes)

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Case Number: T 0465/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 1 October 2021

Appellant: (Opponent)	GlaxoSmithKline Biologicals S.A. P.O. Box rue de l'Institut 89 1330 Rixensart (BE)
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Respondent: (Patent Proprietor)	Arecor Limited Chesterford Research Park Little Chesterford Saffron Walden CB10 1XL (GB)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 December 2017 rejecting the opposition filed against European patent No. 2457590 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 457 590 was granted on the basis of a set of 15 claims.

Independent claim 1 as granted read as follows:

"1. An aqueous composition for use in therapy comprising a polysaccharide-based vaccine susceptible to hydrolytic cleavage of a polysaccharide moiety from a carrier protein, wherein the ionic strength of the composition is less than 20 mM said ionic strength being calculated using the formula:

$$I = \sum_{X=1}^{n} c_x z_x^2$$

in which C_x is molar concentration of ion x (mol L^{-1}), Z_x is the absolute value of the charge of ion x and the sum covers all ions (n) present in the composition."

II. An opposition was filed on the grounds that the subject-matter of the patent lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division to reject the opposition.

IV. The documents cited during the opposition proceedings included the following:

D1: Berti F. et al.: "Water accessibility, aggregation, and motional features of polysaccharide-protein conjugate vaccines", Biophysical Journal, 2004, vol. 86, pages 3-9
D2: WO 2005/089794
D3: WO 2003/007985
D4: Corbel MJ et al., "Reasons for instability of bacterial vaccines", New approaches to stabilisation of vaccines potency, 1996, col. 87, pages 113-124
D5: Egan W. et al.: "Structural studies and chemistry of bacterial capsular polysaccharides. Investigations of phosphodiester-linked capsular polysaccharides isolated from Haemophilus influenzae types a, b, c and f: NMR spectroscopic identification and chemical modification of end groups and the nature of base-catalyzed hydrolytic depolymerization", J. Am. Chem. Soc., 1982, vol. 104, ages 2898-2910
D17: Data filed by the patent proprietor on 5 May 2016
D17a: D17 reworked with addition of figures 1-5 and example 5
D18: Weber EJ et al., "Reaction mechanisms in environmental organic chemistry", Lewis publishers, 1994, Chapter 2
D19: Optimization of the Lowry Method of Protein Precipitation from the H. influenza Type b Conjugate Vaccine Using Deoxycholic Acid and Hydrochloric Acid", by Kim et al., published in 2016
20: A Customer Medicine Information Leaflet for GSK's HIBERIX product dated 5 July 2005
D21: "Pentacel" on www.rxlist.com on 27 November 2008
D22: "Dosage Form Design and Development", by Loyd V. Allen Jr published in 2008
D23: Schneerson et al., "Quantitative and qualitative Analyses of Serum Antibodies Elicited in Adults by Haemophilus Influenzae Type b and Pneumococcus Type 6A

Capsular Polysaccharide-Tetanus Toxoid Conjugates", 1986
D24: WO 96/40242
D25: Ronald A. Rader, "Biopharmaceuticals Products in the U.S. and European Markets", 6th Edition
D26: "Tripedia" on www.rxlist.com on 27 November 2008.

V. According to the decision under appeal, D22 and D17a were admitted into the opposition proceedings, while D19-D21 and D23-D26 were not admitted.

Claims 1-15 as granted met the requirements of Articles 76(1) and 123(2) EPC.

The opposition division found that the claimed invention was sufficiently disclosed as regards the terms "for use in therapy", "optimized pH", and "susceptible to hydrolytic cleavage". Moreover there was sufficient disclosure as to the hydrolytic cleavage of a polysaccharide moiety from a carrier protein, as to the ways of calculating the ionic strength, the amphiphilic excipient, the non-ionic excipient, and the fact that the factor 0.5 was not present in the claims. The alleged difference in values of ionic strength was not objectionable as it only concerned the rounding rather than the calculation itself. The technical effect claimed in claim 13 was credible in view of example 3 of the patent in suit and D17a.

The independent claims of the patent as granted were novel in view of documents D1-D3 and D17.

As regards inventive step, D3 was the closest prior art, since it related to the stabilization of polysaccharide conjugate vaccines and thus to the same problem as that addressed by the patent. The difference

between the claimed subject-matter and the disclosure of D3 was that the ionic strength was lower than 20mM, which involved a lower rate of hydrolysis. The objective technical problem was formulated as the provision of a formulation of Hib conjugate vaccine formulation with reduced hydrolytic cleavage. The solution was not obvious in view of D3, D4, D5 and D18.

VI. The opponent (hereinafter the appellant), filed an appeal against said decision. With the statement setting out the grounds of appeal the appellant submitted the following items of evidence:
D27: Yoo et al., "Measurement of Free Polysaccharide in Tetanus Toxoid-conjugate Vaccine Using Antibody/ Ammonium Sulfate Precipitation"
D28: WO 2018/020046, page 142, Examples H1 and H2

The appellant also requested that document D17a not be admitted into the proceedings, and that documents D19-D21 be admitted into the proceedings.

VII. With a letter dated 6 September 2018, the patent proprietor (hereinafter the respondent), filed auxiliary requests 1 to 6.

The respondent also requested that documents D27 and D28 not be admitted into the proceedings.

VIII. A communication from the Board, dated 24 April 2020, was sent to the parties. In this, it was considered in particular that the main request met the requirements of Article 76(1) and 123(2) EPC, and was novel.

IX. With a letter dated 15 September 2020, the respondent filed a main request and auxiliary requests 1-10. The main request request and auxiliary requests 1-5 and 10

corresponded respectively to the main request and auxiliary requests 1-5 and 6 already on file. Auxiliary requests 6-9 were new requests.

X. With a letter dated 27 September 2021, the appellant informed the Board and the respondent that it decided not to attend the oral proceedings.

XI. Oral proceedings took place on 1st October 2021.

XII. The written arguments of the appellant may be summarised as follows:

Admission of D17a into the appeal proceedings

D17a was based on previously filed D17 with Figures 1 to 5 and Example 5 added. These additions were rectifications of shortcomings in the data of D17. The late-filing of D17a could not be considered as reasonable as the document could and should have been filed earlier.

Inadmissibility of D19

The opposition division refused to admit documents D19 into the proceedings. D19 was prima facie relevant to novelty of the claimed invention because it disclosed aqueous compositions of polysaccharide-based vaccines in water for injection and having an ionic strength of around O mM.

Inadmissibility of D20 and D21

D20 and D21 were prima facie relevant for novelty and should have been admitted by the opposition division.

Main request - Amendments

There was no support in the original application for the claimed ionic strength in isolation. The feature of "minimal ionic strength" appeared in the parent application as filed only in combination with other features, such as optimised pH, that were deemed to be essential in order to reduce the rate of hydrolysis. In contrast, claim 1 of the patent was directed to an aqueous composition comprising a polysaccharide based vaccine and having an ionic strength of less than 20mM not including features identified as being essential.

The correction of the equation of ionic strength in claim 1 had no basis. The equation present in the parent application as filed contained a number of errors and was corrected by the patentee during the examination proceedings. However, the decision of the opposition division finding that the correction of the formula was allowable was flawed in many respects leading to an incorrect conclusion.

Main request - Sufficiency of disclosure

The claimed invention was not sufficiently disclosed in view of the claimed features "for use in therapy", "optimised pH", "susceptible to hydrolytic cleavage" and in view of the fact that the technical effect was not achieved over the whole scope of the claims.

Main request - Novelty

The subject-matter of the claims of the patent as granted was not novel in view of documents D19, D20, D21, D27 and D2.

Main request - Inventive step

The alleged technical problem was not plausible from the application as filed. Moreover, the further data supplied by the patentee in documents D17 and D17a did not demonstrate that there was any technical effect associated with the invention.

The difference between the disclosure of D3 and the composition of claim 1 of the patent was that the composition of the patent has an ionic strength which is lower than 20 mM, instead of 21,16 mM in formulation 2 of D3.

The technical problem solved by the invention was therefore the provision of an alternative composition.

The solution was obvious in view of D3 alone. The skilled person would have considered to change the concentration of the components of formulation 2 on page 23. Therefore, one modification that would be considered by the skilled person would be a reduction in the amount of phosphate buffer. A simple change in the phosphate buffer concentration from 5 mM to 4 mM would have produced a composition with an ionic strength within the claimed range.

The solution was obvious in view of D3 and common general knowledge. A skilled person simply looking at the chemical structure of the conjugates would have been able to identify bonds susceptible to hydrolysis and would have been aware that an increased ion concentration would make the bonds more susceptible to hydrolysis. Therefore, a skilled person would have known that, in order to reduce the amount of hydrolysis and improve the stability of a composition containing

polysaccharide conjugates, they would have needed to reduce the ionic strength of the composition.

The solution was obvious in view of D3 and D5 or D18. It was clear from D5 that the presence of any metal ion in the solution catalysed the hydrolysis of the phosphodiester linkage in the Hib capsular polysaccharide. A skilled person looking to reduce the hydrolysis of the capsular polysaccharide would have clearly reduced the number of metal ions in solution as a result of this disclosure. For D3, the skilled person would have done this by reducing the concentration of the phosphate buffer. It was also obvious from D18 that the effect of the ionic strength on the stability of a polysaccharide such as the Hib polysaccharide was well known. Therefore, in order to reduce the amount of hydrolysis, the skilled person would have reduced the number of ions in the composition of D3 by reducing the buffer concentration.

XIII. The arguments of the respondent may be summarised as follows:

Admission of documents

D17a was correctly admitted into the proceedings, since the OD exerted its discretionary power correctly.

D19 was not relevant for novelty, since the conjugate disclosed therein was not characterized.

D20 and D21 were neither prima facie relevant and should not be admitted.

D27 was late-filed, not relevant, could have been file earlier and should not be admitted into the appeal proceedings.

Main request - Amendments

The decision was correct on this point, and the basis for claim 1 was mentioned in said decision.

Main request – Sufficiency of disclosure

D11 provided evidence that the formula used in the patent, which only differs from the routinely used ionic strength formula in that it lacks the factor 1/2, is not applied to the protein when considering a composition containing a protein.

Main request - Novelty

The main request was novel over all cited documents.

Main request - Inventive step

D3 was the closest prior art, in view of the formulation on page 23, which had an ionic strength of at least 21.16 mM. The technical effect was that the lower ionic strength resulted in a lower rate of hydrolysis of the polysaccharide moiety from the carrier protein. This technical effect was credible in view of the patent and of D17/D17a, which were also evidence that the problem was solved over the whole scope of the claims. The problem to be solved was seen to be the provision of a formulation of a conjugate vaccine aqueous formulation with reduced hydrolytic cleavage. The claimed solution was inventive.

XIV. Requests

The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked. They also requested that the following requests and documents not be admitted into the proceedings:
- auxiliary requests 1-5 filed with the reply to the grounds of appeal, auxiliary requests 6-9 filed with letter dated 15 September 2020, and auxiliary request 10 which had been filed as auxiliary request 6 with letter dated 6 September 2018,
- D17a which had been admitted by the opposition division

The appellant furthermore requested that documents D19-D21, which had not been admitted by the opposition division, be admitted into the proceedings.

The respondent requested that the appeal be dismissed or, as an auxiliary measure, that the patent be maintained on the basis of one of auxiliary requests 1-5 filed with letter dated 6 September 2018, or one of auxiliary requests 6-10 filed with letter dated 15 September 2020 (whereby auxiliary request 10 had been filed as auxiliary request 6 with letter dated 6 September 2018).

The respondent also requested that documents D27-D28, filed with the statement setting out the grounds of appeal, not be admitted into the proceedings.

Reasons for the Decision

1. Admission of D17a into the appeal proceedings

This document was submitted by the respondent during the opposition procedure with letter dated 2 November 2017 and thus after expiry of the Rule 116 EPC time limit. It was admitted by the opposition division, since it contained additional experimental data to D17 in response to arguments on inventive step submitted for the first time by the appellant on 20 September 2017. Said document was furthermore discussed in the decision of the opposition division and is mentioned by the appellant in its statement of grounds of appeal in support of its assessment of inventive step, and discussed again by the respondent in its reply to the statement of grounds of appeal.

The Board considers this document to form part of the appeal proceedings as the decision of the opposition division is based in part on that document. Furthermore, in the Board's view, the opposition division appears to have exercised its discretionary power according to the right principles and in a reasonable way.

2. Admission of documents D19-D21 into the appeal proceedings

The appellant had filed documents D19-D21 during the opposition proceedings in response to document D16 and argued that they were *prima facie* relevant for novelty.

The opposition division noted in its decision that none of D19-D21 disclosed a detailed composition of the solution before lyophilization. None of D19-D21 could

be *prima facie* relevant for novelty. They could also not have been filed as a response to D16 which did not deal with a novelty objection. The opposition division thus decided not to admit D19-D21 into the proceedings.

As regards D19, this document appears to disclose compositions of bulk vaccine conjugates dissolved in water for injection (see page 216, Materials and Table 2, the "original" composition, without precipitation treatment). D19 does not disclose the exact composition and the ionic strength of the bulk solution comprising the conjugate that is diluted in water. In particular, there is no detail of how the bulk solution comprising the conjugate was prepared. Consequently, there is no evidence that the diluted bulk solution of D19 has an ionic strength inferior to 20 mM and this document cannot be considered to be *prima facie* relevant for novelty. Again, the opposition division correctly exercised its discretion not to admit D19 and the Board does not see any reason to deviate from this decision.

The Board notes that D20 and D21 explicitly mention the presence of excipients and do give the ionic strength, which is probably much higher than 20 mM (see D20, Product description and D21 3rd par.). It appears that the opposition division correctly exercised its discretion not to admit D20-D21. Hence, the Board does not see any reason to deviate from this decision.

Consequently, documents D19-D21 are not admitted into the appeal proceedings (Article 12(4) RPBA 2007).

3. Admission of documents D27 and D28 into the appeal proceedings

D27 was submitted by the appellant in the appeal proceedings as a new novelty-destroying document. This document constitutes a new fact which could and should have been filed earlier in the opposition proceedings. Moreover, as for D19, D27 provides no further indication of how the bulk solution containing the conjugate disclosed therein was produced and is silent as to the ionic strength of the bulk solution containing the conjugate when diluted with water (see page 470). Hence, there is no direct and unambiguous disclosure of the claimed subject-matter in D27, which does not appear *prima facie* relevant for the novelty of the claimed subject-matter. Consequently, this document is not admitted into the appeal proceedings (Article 12(4) RPBA 2007).

D28 has been filed by the appellant in support of its argumentation as regards insufficiency of disclosure. It was filed to demonstrate the stability of a Hib PRP polysaccharide vaccine in water and that it is hydrolysed within 2 and 7 days (see D28, page 142). In its communication pursuant to Article 15(1) RPBA, the Board observed that said passage relates to a vaccine solubilised in aluminium hydroxide, hence with a high ionic strength, and appears to be irrelevant for the claimed invention. The appellant did not submit any argument in reply to this remark. Consequently, this document is not admitted into the appeal proceedings (Article 12(4) RPBA 2007).

4. Main request - Amendments

The appellant objected the claims of the main request under Article 76(1) and 123(2) EPC as regards:
(i) the feature of "minimal ionic strength", which appears in the parent application only in combination with other features,
(ii) the correction of the claimed equation.

With regard to point (i), the ionic strength as claimed is disclosed directly and unambiguously as such in claim 2 of the parent application and claim 3 of the patent application.

With regard to point (ii), i.e the formula of ionic strength of claim 1, the parent application referred to the molar concentration. Said molar concentration was however expressed as $mol.L^{-3}$ in the parent application, as well as in the patent application, which is obviously wrong. The skilled person would have known that said molar concentration is mol/L, namely $mol.L^{-1}$. Consequently, there was an obvious mistake in the original formula, and the correction is obvious in view of the common general knowledge and is therefore allowable.

The main request meets the requirements of Articles 76(1) EPC and 123(2) EPC.

5. Main request – Sufficiency of disclosure

5.1 The appellant objected a lack of sufficient disclosure as regards the following features present in claim 1 of the main request:
(a) “for use in therapy”
(b) “optimised pH”

(c) “susceptible to hydrolytic cleavage”

In addition, the appellant argued that the technical effect was not achieved over the whole scope of the claim (d).

5.2 As regards more specifically point (a), the claimed invention relates to compositions comprising vaccines, and claim 1 is in particular directed to "an aqueous composition for use in therapy". The opposition division mentioned in its decision that “the present patent is directed to compositions comprising well known therapeutic substances, namely polysaccharide based vaccines, therefore there is no need to provide proof of a therapeutic activity, since such activity is well known”. The Board does not see any reason to deviate from these conclusions.

5.3 With regard to point (b), the Board notes that the claimed invention does not refer to the pH. This point appears to relate rather to the assessment of inventive step. The same conclusion appears to apply to point (d), since there does not appear to be any reference to a technical effect in claim 1. Claim 13 relates to a method for reducing hydrolitic cleavage of a polysaccharide moiety from a carrier protein in a polysaccharide-based vaccine. The Board agrees with the opposition division (point 3.4 of the decision) that this effect appears credible on the basis of the data disclosed in example 3 of the patent.

5.4 The skilled person appears also to know what is an hydrolytic cleavage, and to determine which molecules are susceptible to be cleaved. This point appears to relate to a clarity issue, which is not a ground of opposition.

5.5 Consequently, the claimed invention is sufficiently disclosed.

6. Main request – Novelty

6.1 The appellant mentioned documents D2, D19, D20, D21 and D27 as novelty-destroying documents. As set out above, D19-D21 as well as D27 are not part of the appeal proceedings.

6.1.1 D2 does not disclose directly and unambiguously a composition of vaccine with a low amount of excipients; the compositions disclosed on pages 17 and 18 show in particular a high amount of excipients, which excludes that the ionic strength be less than 20 mM.

The appellant cited in particular the disclosure on page 14, lines 21-25, of D2 to justify its objection of lack of novelty:
"Vaccines of the invention may include free phosphate ions in solution (e. g. by the use of a phosphate buffer) in order to favour non-adsorption of antigens. The concentration of free phosphate ions in the composition of the invention is generally between 0.1 and 10.0 mM, preferably between 1 and 5 mM, and more preferably about 2.5 mM.".

This sentence has however been taken in complete isolation from the remaining disclosure of D2, such as the remaining disclosure on page 14, which also mentions the addition of aluminium phosphate, sodium chloride, preservatives and detergents into the vaccine composition, which would contribute to the final

composition having an ionic strength of more than 20 mM.

This document is therefore not relevant for novelty.

6.2 Consequently, the main request is novel (Article 54 EPC).

7. Main request - Inventive step

7.1 The invention relates to the stability of polysaccharide-based vaccines susceptible to hydrolytic cleavage of the polysaccharide moiety from the protein carrier.

7.2 D3 was considered as the closest prior art in the decision of the opposition division, in particular the example of a polysaccharide vaccine conjugate given on page 23 of D3. This passage mentioning that the lyophilised form gives the following composition after reconstitution into a unit dose:

Component	Concentration
CRM-MenA	20µg saccharide/ml
Potassium phosphate buffer	5 mM
Mannitol	15 mg/ml

This vaccine composition is formulated at an ionic strength of at least 21.16 mM as calculated with the formula of claim 1 of the patent in the experiments D16. This value of 21.16 mM appears to be the minimum possible ionic strength of the lyophilised composition reconstituted in water for injection. As explained and demonstrated in D16, the ionic strength of this

composition depends indeed on its method of preparation and if prepared differently, the ionic strength would be higher than 21.16 mM (see Tables 3 and 4 of D16). The calculation done in D16 does also not account for any ionic strength contribution provided by the bulk solution comprising the vaccine conjugate, which is usually prepared in a relatively high ionic strength environment. In this regard, D3 indicates on page 16 lines 9-13 that the CRM-MenA conjugate was prepared in 0.01 M (or 10 mM)phosphate buffer and was "purified by hydrophobic chromatography or tangential flow ultrafiltration". It cannot therefore be concluded that the bulk solution comprising the CRM-MenA conjugate does not contribute to the ionic strength of the reconstituted composition.

The composition shown on page 23 is further used with an adjuvant when reconstituted having the following composition:

Component	Concentration	Concentration
Aluminium hydroxide	0.68 mg Al^{3+}/ml	-
Aluminium phosphate*	-	0.6mg Al^{3+}/ml
Sodium phosphate buffer	-	10 mM
Histidine buffer	10 mM	-
Sodium chloride	9 mg/ml	9 mg/ml
Tween 80	0.005%	0.005%
PH	7.2±0.05	7.2±0.05

* amorphous hydroxyphosphate, PO_4/Al molar ratio between 0.84 and 0.92

The subject-matter of claim 1 differs from the disclosure of D3 in the ionic strength which is less than 20 mM according to the claimed formula.

7.3 According to the appellant the problem is the provision of an alternative composition.

According to the respondent, the lower ionic strength results in a lower rate of hydrolysis of the polysaccharide carrier from the carrier protein.

7.4 The respondent relies *inter alia* on the experimental results of D17a to demonstrate said effect.

7.4.1 Document D17a shows in its example 5 an experiment conducted to investigate the effect of varying the ionic strength on the stability of a polysaccharide conjugated vaccine in an aqueous composition. The ionic strength was controlled by varying the concentration of sodium phosphate in the compositions, and was comprised between 25.39 mM and 4.23 mM. The results are shown in Table 6, reproduced below, wherein "Total I" is the ionic strength and "PS" means polysaccharide. An increase in the amount of polysaccharide is linked with the hydrolysis thereof from the protein carrier.

Formulation No.	Sodium phosphate (mM)	Total I* (mM)	Free PS (0 days)	Free PS (15 days)	Increase in % free PS in 15 days	Free PS (30 days)	Increase in % free PS in 30 days at 37°C
1	6	25.39	7.9%	24.8%	16.9%	34.6%	26.7%
2**	5	21.16	8.0%	22.9%	14.9%	31.2%	23.2%
3	4	16.93	7.8%	22.6%	14.8%	30.7%	22.9%
4	3	12.70	8.4%	21.8%	13.4%	30.7%	22.3%
5	2	8.46	7.4%	21.3%	13.9%	28.4%	21.0%
6	1	4.23	8.3%	19.3%	11.0%	26.0%	17.7%

Table 6 shows that an effect on stability is observed with formulations having a very low ionic strength, namely formulations 5 and 6. However the differences seen with the increase in free polysaccharide between formulation 2, which corresponds to the formulation disclosed in D3, and formulations 3 and 4 are very small. It is therefore questionable whether an improvement for these formulations has been credibly shown.

These doubts are confirmed by the results of the experiments of example 2 of D17a. This example compares several vaccine formulations having an ionic strength comprised between 313.6 mM and 5.6 mM (see Table 2 below, with "Total I" being the ionic strength):

Table 2

Formulation	Hib-TT (µg/ml)	Sodium chloride (mM)	1,2-propanediol (mM)	Sodium maleate (mM)	pH	Total I (mM)
1	25	154		1	6.7	313.6
2	25	75	150	1	6.7	155.6
3	25	16.7	266.6	1	6.7	39.0
4	25	16.7		1	6.7	39.0
5	25	6.7	286.6	1	6.7	19.0
6	25		300	1	6.7	5.6

The amounts of free polysaccharides which expresses the stability of the vaccine conjugate, i.e. the rate of hydrolysis of the polysaccharide carrier from the carrier protein, is given in Table 3 of example 2, as shown below:

Table 3

Formulation	Increase in free PS (%)
1	50.46
2	20.53
3	11.29
4	13.05
5	15.97
6	7.01

Table 3 shows clearly that some formulations having more than 20 mM of ionic strength, such as formulations

3 and 4, having an ionic strength of 39 mM, provide less polysaccharide formation than for instance formulation 5, which falls under the scope of the claims, since it has an ionic strength of 19 mM.

Therefore, it cannot be concluded from the data provided in D17a that the compositions of claim 1 are more effective than the compositions of D3 in reducing the rate of hydrolysis.

7.4.2 The technical effect of lowering the rate of hydrolysis of the polysaccharide carrier from the carrier protein is therefore not credibly achieved, in particular for an ionic strength between 10 and 20 mM.

Consequently, the technical problem must be rephrased as formulated by the appellant, namely the provision of an alternative composition. This problem is credibly solved by the claimed solution, namely the provision of a vaccine formulation with an ionic strength of less than 20 mM, as shown at least by the experiments of example 3 of the patent and of D17a.

7.4.3 The question remaining is whether the skilled person, starting from the formulation of page 23 of D3, would arrive at the subject-matter of claim 1 of the main request in an obvious manner in order to solve the problem posed.

In the present case, the appellant relied on documents D3, D5, D18 and common general knowledge to demonstrate that the diminution of the ionic strength was a routine modification.

7.4.4 With regard to D3, there is no teaching to make any modification relating to the ionic strength of the

vaccine formulation, in particular a reduction of the ionic strength. There is furthermore a great uncertainty as to the real value of the ionic strength of the formulation disclosed on page 23 of D3. In any case, D3 is not concerned with the ionic strength as a factor of stability but that it is simply a formulation parameter.

There is furthermore no teaching or suggestion in D3 to modify the amounts of phosphate buffer to provide a formulation having an ionic strength of less than 20 mM as argued by the appellant.

To the contrary, for administration purposes, D3 discloses using reconstituted solutions of high ionic strength containing a high amount of sodium chloride and aluminium salts (see the two reconstitution formulations on page 23 or the Table in point 10.2 above). D3 acknowledges indeed hydrolysis as a problem (see page 22 lines 32-33), but the solution proposed is preparing the conjugate in lyophilised form for reconstitution at high ionic strength, which is different from the claimed solution.

Accordingly, D3 clearly teaches away from the claimed solution and the claimed subject-matter is not obvious in the light of D3.

7.4.5 D5 relates to the study and chemistry of bacterial capsular polysaccharides and shows a repeating unit of Hib capsular polysaccharide (see Figure 1 page 2899), which shows that the Hib capsular polysaccharide is joined by phosphodiester linkages. Catalysis of the hydrolysis of this phosphodiester linkage reaction by metal ions is illustrated in scheme III on page 2902 of D5.

According to the appellant, it is clear from D5 that the presence of any metal ion in the solution catalyses the hydrolysis of the phosphodiester linkage in the Hib capsular polysaccharide. A skilled person looking to reduce the hydrolysis of the capsular polysaccharide would clearly reduce the number of metal ions in solution as a result of this disclosure. In reducing the concentration of phosphate buffer used in the example recited on page 23 of D3, the ionic strength of the solution would be reduced. Only a small reduction in ionic strength would be required to reduce the ionic strength from 21.16 mM to less than 20 mM.

As also mentioned by the respondent, D5 discloses however no recognition that ionic strength is a parameter involved in the stability or the preparation of vaccine polysaccharide-conjugates. For instance, the hydrolysis experiments reported in D5 were performed with the polysaccharide in a glycine-NaOH buffer (see page 2901, left hand column). Said buffer has alone, as shown in Table 6 of D16, an ionic strength of at least 255.1 mM. Accordingly, any conclusions drawn that this document points the skilled person towards reducing ionic strength cannot be drawn from D5. Moreover, in D5, different effects of different metal ions are demonstrated and these effects are not demonstrated for potassium, which would not incite the skilled person to reduce the level of the potassium phosphate buffer in D3.

Accordingly, the claimed subject-matter is not obvious in the light of D3 in combination with D5.

7.4.6 With regard to D18, the hydrolysis of organophosphorus esters is discussed on pages 122 to 124 of this

document. On page 147 of D18, the role of metal cations in the catalysis of a hydrolysis reaction is explained. As is clear from this disclosure, the presence of metal ions increases the rate of hydrolysis. Furthermore, D18 also discusses other nucleophilic substitution reactions where anions are involved.

There is however no teaching in D18 that ionic strength may be a parameter involved in the stability or the preparation of vaccine polysaccharide-conjugates and this document is furthermore not concerned with polysaccharide-based vaccines. The Board agrees with the respondent that the mere fact that cations and anions may be involved in hydrolysis reactions cannot be considered, in and of itself, as a pointer to arrive at the claimed solution, since otherwise polysaccharide based vaccines would never be formulated in saline solutions; the mere notion of involvement of cations and anions in the hydrolytic mechanisms cannot be considered as a pointer to modify the composition in the manner alleged by the appellant.

Accordingly,the claimed subject-matter is not obvious in view of D3 combined with D18.

7.4.7 The Board notes also that none of the cited documents shows a link between ionic strength and stability or more generally that ionic strength may be a parameter involved in the stability or the preparation of vaccine polysaccharide-conjugates. This does also not appear to be common general knowledge.

The Board could in particular not follow the appellant's argument that a skilled person simply looking at the chemical structure of the conjugates would be able to identify bonds susceptible to

hydrolysis, and then would also be aware that an increased ion concentration would make the bonds more susceptible to hydrolysis. Therefore, a skilled person would consider obvious to reduce the ionic strength of the composition.

This general conceptual argumentation made by the appellant has indeed no apparent basis in the disclosure of D3 or the common general knowledge, for which there is furthermore no evidence provided. For instance, as stated above, D3 indicates that lyophilisation is the approach taken to improve stability, and this document does not envisage any modification linked to the ionic strength of the vaccine formulation.

Accordingly, the claimed subject matter is not obvious in light of D3 when considered in combination with the common general knowledge.

7.5 Therefore, the skilled person is not provided with any teaching or suggestion towards the claimed subject-matter as solution to the problem of providing an alternative vaccine formulation. The claimed subject-matter is not obvious and the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated