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Datasheet for the decision of 12 January 2012

Case Number: T 0415/11 - 3.3.04

Application Number: 00992589.2

Publication Number: 1233784

IPC: A61K 39/385, A61K 39/095, A61K 47/22, A61K 47/26

Language of the proceedings: EN

Title of invention:
Compositions and methods for stabilizing biological molecules upon lyophilization

Applicant:
Novartis Vaccines and Diagnostics, Inc.

Opponent:
GlaxoSmithKline Biologicals s.a.

Headword:
Lyophilized Neisseria meningococcus vaccine/NOVARTIS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and auxiliary requests 1 to 8 - inventive step (no)"

Decisions cited:
T 0939/92, T 0097/00, T 1329/04, T 1336/04

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0415/11 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 12 January 2012

Respondent: (Patent Proprietor)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 1 February 2011 concerning maintenance of the European patent No. 1233784 in amended form.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
R. Gramaglia

Summary of facts and submissions

I. The subject of this appeal is the decision of the opposition division announcing its intention to maintain the European patent EP 1 233 784 in amended form on the basis of the claims of the auxiliary request. The patent has the title "Composition and methods for stabilizing biological molecules upon lyophilisation".

II. The patent had been opposed pursuant to Article 100(a) EPC for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), pursuant to Article 100(b) EPC for insufficiency of disclosure (Article 83 EPC) and pursuant to Article 100(c) EPC for the presence of added matter (Article 123(2) EPC).

III. The decision of the opposition division dealt with a main request and an auxiliary request (identified as "Auxiliary request 2" in the decision under appeal). The main request was refused for the reason of non-compliance of the subject-mater of claims 3 to 5 with the requirements of Article 123(2) EPC.

IV. Originally both the patent proprietor and the opponent appealed against the decision of the opposition division. The patent proprietor withdrew its appeal during the oral proceedings (see section VIII below).

V. With its letters of 10 June 2011, 26 October 2011 and 22 December 2011 the patent proprietor filed a main request and auxiliary request 1, auxiliary requests 2 to 11 and documents D35 to D38, and auxiliary requests 12 to 14 and document D40, respectively.

With its letters of 10 June 2012 and 9 December 2011 the opponent filed documents D27 to D34 and D39, respectively.

VI. With a letter dated 11 July 2011 the opponent requested "accelerated processing of the appeal in view of its legitimate interest". It was stated that the legitimate interest in this case was "that GlaxosmithKline Biologicals s.a. wishes to establish legal certainty in respect of commercial activity undertaken by GSK. In this context GlaxosmithKline has also launched national revocation actions within the last week in Belgium and the UK", and that "it was anticipated that the expense to both parties would be reduced". Reference was also made to decision T 18/90.

VII. The board sent two communications dated 22 July 2011 and 7 November 2011. By the first one the board informed the parties of its intention to accelerate the processing of the appeal to which the patent proprietor agreed after receipt of the communication. The second communication set out the board's preliminary view on some of the substantive issues in the case.

VIII. Oral proceedings were held on 12 January 2012. Both parties were represented.

During the oral proceedings the patent proprietor withdrew its main request and auxiliary requests 1 to 3, 8 and 9 and made auxiliary requests 4 to 7 and 10 to 14 its new main and auxiliary requests 1 to 8.

Claims 4 and 6 of the new **main request** read (relevant features in this and the auxiliary requests have been emphasized by the board):

"4. A method for stabilizing one or more meningococcus C (MenC) immunogens upon lyophilization comprising:
(a) dissolving the meningococcus C (MenC) immunogen in a dissolution buffer comprising at least one amorphous excipient and an amorphous organic buffer to form a mixture, wherein the amorphous excipient is sucrose, and
(b) lyophilizing the mixture.

6. A lyophilized composition stabilized according to the method of claim 4 comprising at least one amorphous excipient, at least one amorphous organic buffer, and at least one meningococcus C (MenC) immunogen, wherein the amorphous excipient is sucrose."

Auxiliary request 1 contained the same claims, numbered 3 and 5, so that claim 5 referred to claim 3.

Claims 4 and 6 of **auxiliary request 2** read:

"4. A method for stabilizing one or more saccharides that are meningococcus C (MenC) immunogens upon lyophilization comprising:

(a) dissolving the meningococcus C (MenC) immunogen in a dissolution buffer comprising at least one amorphous excipient and an amorphous organic buffer to form a

mixture, wherein the amorphous excipient is sucrose, and
(b) lyophilizing the mixture.

6. A lyophilized composition stabilized according to the method of claim 4 comprising at least one amorphous excipient, at least one amorphous organic buffer, and at least one meningococcus C (MenC) immunogen, wherein the amorphous excipient is sucrose."

In **auxiliary request 3** claims 3 and 5 were the same as claims 4 and 6 of auxiliary request 2 with the exception that claim 5 referred to claim 3.

Claims 1 and 3 of **auxiliary request 4** read:

"1. A method for stabilizing one or more meningococcus C (MenC) immunogens upon lyophilization comprising:

(a) dissolving the meningococcus C (MenC) immunogen in a dissolution buffer comprising at least one amorphous excipient and an amorphous organic buffer to form a mixture, wherein the excipient is sucrose, and

(b) lyophilizing the mixture, wherein the buffer and the excipient remain amorphous upon lyophilization."

3. A lyophilized composition stabilized according to the method of claim 1, comprising at least one amorphous excipient, at least one amorphous organic buffer, and at least one meningococcus C (MenC) immunogen, wherein the amorphous excipient is sucrose."

Auxiliary request 5 contained the same claims 1 and 3 as auxiliary request 4 with the exception that the preamble of claim 1 was the same as that of claim 3 of auxiliary request 3.

Claims 1 and 3 of **auxiliary request 6** read:

"1. A method for stabilizing one or more meningococcus C (MenC) immunogens upon lyophilization comprising:

(a) dissolving the meningococcus C (MenC) immunogen in a dissolution buffer comprising sucrose and an organic buffer to form a mixture, and

(b) lyophilizing the mixture, wherein the buffer and sucrose remain amorphous upon lyophilization."

3. A lyophilized composition stabilized according to the method of claim 1, comprising sucrose, at least one organic buffer, and at least one meningococcus C (MenC) immunogen."

Auxiliary request 7 contained the same claims with the exception that in the preamble of claim 1 - as in that of claims 3 and 1 of auxiliary requests 3 and 5 - the expression "saccharides that are" was present.

The three claims of **auxiliary request 8** read:

"1. A method for stabilizing a saccharide that is a meningococcus C (MenC) vaccine upon lyophilization comprising:

(a) dissolving the meningococcus C (MenC) vaccine in a dissolution buffer comprising sucrose and an organic buffer to from a mixture, and

(b) lyophilizing the mixture, wherein the buffer and sucrose remain amorphous upon lyophilization.

2. The method of claim 1 wherein the meningococcus C (MenC) vaccine is MenC-CRM 197.

3. A meningococcus C (MenC) vaccine stabilized according to the method of claim 1 comprising at least one amorphous excipient and at least one amorphous organic buffer, wherein the amorphous excipient is sucrose."

IX. In view of the scope of its claim requests the patent proprietor withdrew its appeal at the oral proceedings.

X. The parties' requests were as follows:

The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked.

The respondent-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main or one of its

auxiliary requests 1 to 8 filed at the oral proceedings.

XI. The following documents are referred to in the present decision:

D4 Pharmaceutical Research, vol. 14, no. 8, 1997, pages 969-975, Carpenter, J.F. et al.

D15 Infection and Immunity, vol. 40, no. 1, 1983, pages 39-45, Beuvery, E.C. et al.

D26 Mencevax ACWY; International data sheet, 15 May 2000

D30 Product summary of Meningococcal group C conjugate vaccine (diphteria CRM197 protein conjugate); Meningitec™

D31 Product summary of Haemophilus type b conjugate vaccine("ACT-HIB")

D37 electronic Medicines Compendium (eMC): ACWY Vax Vaccine (Mencevax™); Summary of product characteristics in the UK; last updated on the eMC: 10 February 2011

D37a electronic Medicines Compendium (eMC): ACWY Vax Vaccine (Mencevax™); Formulation history in the UK;

D38 Opinion of the "French Transparency Committee" on "Mencevax powder and solvent for solution for injection"; 4 March 2009,

D40 Assessment Report on "Mencevax ACWY Powder and solvent for solution for injection" of the Belgian "Federal Agency for Medicines and Health Products"

XII. The submissions by the appellant-opponent (hereinafter "appellant"), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of requests and documents

There were no objections against the admission of any of the requests and documents filed by the respondent-patent-proprietor (hereinafter "respondent") during the appeal proceedings.

Main request

Added matter - Article 123(2) EPC

The combination in claim 6 of a MenC immunogen, which, on the respondent's interpretation was a MenC polysaccharide, and an organic amorphous buffer in general terms was the result of an intermediate generalisation which was not derivable from the application as filed.

Inventive step - Article 56 EPC

Adopting the respondent's interpretation, the term "MenC immunogen" in claim 6 referred to polysaccharides of Neisseria meningococcus group C which were either conjugated to a protein or unconjugated. Each of these

embodiments of claim 6 lacked an inventive step, yet for different reasons.

Claim 6 - unconjugated MenC immunogen

In view of decision T 939/92 it was a necessary prerequisite for the acknowledgement of an inventive step that what was claimed should not be arbitrary, but should achieve the technical effect required by the problem to be solved, an effect which should moreover be seen with substantially everything of the claimed subject matter, i.e. substantially all of the claimed subject-matter should be a solution to the underlying problem.

It was clearly derivable from the patent as a whole, and also from the prior art, for example document D4, that the effect exerted by the buffer and the excipient during and after lyophilisation was protein-related, i.e. it would not occur with unconjugated MenC.

The respondent who, according to established case law (see for example decision T 97/00), had the burden of proof, did not establish, either by data in the patent or otherwise that the combination of an amorphous organic buffer and sucrose had an influence on the stability during lyophilisation of unconjugated MenC immunogen.

In particular, the passage on page 51 of the post-published document D40 referred to by the respondent did not provide such proof. The statement was the result of a misinterpretation of the responsible authority.

Thus, insofar as claim 6 related to lyophilized compositions comprising unconjugated MenC immunogen its subject-matter lacked an inventive step because this embodiment could not be considered as solving the problem.

Claim 6 - conjugated MenC immunogen

Insofar as claim 6 related to lyophilized compositions comprising MenC polysaccharide conjugated to a protein its subject-matter lacked an inventive step because it was obvious in view of the prior art.

Either of documents D4, D15, D30 or D31 could be regarded as the closest prior art document. Yet document D15 appeared to be the least realistic starting point because it was old - it had been published in the year 1983 - and it disclosed only laboratory scale experiments.

However, taking document D15 as the closest prior art document, the subject-matter of claim 6 was obvious in view of a combination of this document with document D4:

Document D15 disclosed lyophilisation of a composition containing MenC polysaccharide conjugated to the protein carrier tetanus toxoid, lactose and phosphate buffered saline (PBS).

The problem to be solved in view of this teaching was the provision of an alternative lyophilized conjugated MenC-containing composition.

It was acknowledged that the claimed compositions solved this problem.

Document D4 was a review article about lyophilisation of proteins published 2 years before the priority date of the patent and 14 years after the publication of document D15. The document taught that the buffer was one of three important parameters to be considered during the freezing step of lyophilisation, that sodium phosphate and potassium phosphate-containing buffers should be avoided because they could underwent drastic pH changes during freezing, but that buffers containing citrate, histidine or Tris, i.e. amorphous organic buffers, should be used instead.

Moreover, document D4 taught that disaccharides were the most effective stabilizing excipients during drying and storage, that reducing sugars such as lactose should be avoided and that the best first choices of excipients were sucrose or trehalose.

Thus document D4 disclosed several obvious alternative excipient/buffer combinations for improving the stability during and after lyophilisation of a conjugated MenC immunogen containing composition, one being to use a combination of sucrose und Tris.

XIII. The submissions by the respondent-patent proprietor (hereinafter "respondent", insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of documents

There were no objections against the admission of any of the documents filed by the appellant during the appeal proceedings.

Added matter - Article 123(2) EPC

None of the claims of the main request contained added matter. The requirements of Article 123(2) were fulfilled.

Inventive step - Article 56 EPC

The appellant's approach to split the claimed subject-matter in two, i.e. compositions containing protein-conjugated and unconjugated MenC polysaccharides and to run an individual inventive step argument against each part was unconventional and without precedent in the case law. It was moreover not tenable because the invention was not defined in claim 6 in a "split" manner, but in relation to Neisseria meningococcus serotype C immunogen (MenC) in general.

The invention consisted in the finding that pH control during and after lyophilisation was necessary for the stability of the MenC immunogen. Since none of documents D4, D15, D3 or D31 appreciated the necessity of pH control in the case of MenC, it did not matter which of them was used as closest prior art document.

However, according to the criteria developed by the case law of the Boards of Appeal document D15 was the correct choice.

Document D15 disclosed a lyophilized composition containing MenC immunogen, lactose and a phosphate containing anorganic buffer, phosphate buffered saline ("PBS"). In contrast, the claimed subject matter was a lyophilized composition containing MenC immunogen, sucrose and an amorphous organic buffer.

The technical effect achieved by the differing features was improved stabilization of the MenC immunogen by reducing aggregation and breakdown during and after lyophilisation.

Thus, the problem to be solved was the provision of a MenC immunogen with improved stability during and after lyophilization.

The reasoning of decision T 939/92 only applied to circumstances where on the one hand the claims covered compounds of a broad structural variety, but where on the other hand there were only data proving an effect for one or very few of the many compounds. This was not the situation here.

The examples of the patent demonstrated that by the inclusion of sucrose and histidine or imidazole in the formulation, aggregation was reduced and thus that the desired effect was achieved. Consequently, in view of this evidence in the patent, it had to be acknowledged that the claimed compounds solved the problem.

The appellant alleged that the examples did not show that the technical effect existed for unconjugated MenC polysaccharides, but did not provide any evidence in support.

Moreover, the appellant's argument that the evidence in the patent only supported an effect for the conjugated MenC immunogen was not tenable in view of documents D26, D37, D37a, D38 and D40 relating to the appellant's own pure polysaccharide-containing meningococcus vaccine Mencevax™ and demonstrating a direct link between the inclusion of sucrose and Tris, an amorphous organic buffer, and the stability of the formulation through the extension of its shelf-life from two to three years.

The skilled person would not have arrived at the claimed subject-matter in an obvious way in the light of the disclosure in document D4 because he would not have considered that this document would provide useful hints for solving the underlying problem. The document concerned only the lyophilization of proteins and not the lyophilisation of saccharides, let alone the MenC capsular saccharide. Proteins and saccharides had different stability considerations and there was no reason why the skilled person would have thought that the teachings in document D4 could also be applied to saccharides, still less to MenC in particular.

At the priority date of the patent the prior art had not realized that pH control was necessary in MenC containing compositions.

In fact, of the three commercially available lyophilized MenC vaccines available at the priority date - Mencevax™, Menommune™, and Menjugate™ - two did not comprise a buffer. One (Menjugate™) comprised PBS which was a buffer but was known to loose its buffering capacity during lyophilisation.

The lyophilized composition disclosed in document D15 comprised PBS, yet it was not mentioned that it was there for buffering. The skilled person would rather consider it as an "historical accident" of dialysis.

Moreover, two of the vaccines included - as the composition disclosed in document D15 - lactose as the excipient and the third one (Menjugate™) comprised mannitol.

Thus, in particular in the light of the commercially available vaccines, the skilled person neither had an incentive to add a buffer to a MenC containing composition, because he would not have considered it necessary, nor had he an incentive to add sucrose instead of lactose, because he would have considered lactose as the best choice for stabilising MenC immunogens.

Even if the skilled person wanted to exchange lactose, he would not know against what because he would not know why lactose was considered as good.

If the skilled person had realized that the reason was that lactose was a reducing sugar and that it was this capacity that was needed, he could have used another reducing sugar, or he could have replaced it with a

crystalline sugar - there was even a commercialized product which contained the crystalline sugar mannitol.

The skilled person could have used sucrose, but there was no reason why he would have with a view to achieving a benefit.

Reasons for the decision

Admissibility of requests and documents

1. None of the parties objected to the admissibility of any of the documents filed during the appeal proceedings and the appellant did not object to the admission of the claim requests during these proceedings. The board has no objections to their admission either. Hence, documents D27-D40 and the main request and auxiliary requests 1 to 8 are admitted into the proceedings.

Main request

Article 123(2) EPC

2. The board does not consider it necessary to address in this decision the issue of whether or not the requirements of Article 123(2) EPC are fulfilled since the subject-matter of all requests lacks an inventive step (see below).

Article 56 EPC

3. The board can accept the view of both parties that in the context of the present patent the term "MenC immunogen" is to be interpreted as referring to both "pure", unconjugated polysaccarides" from the capsule of Neisseria meningitidis serotype C, and conjugates of such polysaccarides with a protein carrier.

4. It is established case law that the subject-matter of a claim is considered to involve an inventive step only if substantially all of its embodiments are not obvious in the light of the prior art.

Therefore it is not prohibited to analyse individual groups of embodiments of a claim, or even single embodiments, for their compliance with the requirements of Article 56 EPC.

5. The main request comprises several independent claims of which claim 6 relates to a "lyophilized composition [...] comprising at least one meningococcus C (MenC) immunogen". The board's analysis starts with the embodiment of claim 6 relating to MenC immunogen-protein conjugates (see point 3 above).

The closest prior art document

6. The parties submit that each of documents D4, D15, D30 and D31 could be considered as the closest prior art document, but the respondent submits moreover that, in view of the criteria established by the case law, document D15 is the correct choice.

Thus, there is agreement between the parties that document D15 is the closest prior art document and this is also the view of the board.

7. Document D15 discloses the lyophilization of a composition containing (i) MenC-polysaccharides coupled to the protein tetanus toxoid, (ii) lactose and (iii) phosphate buffered saline (PBS).

The thermostability of this composition was determined by incubating a fluid and the lyophilized composition at 4°C, 37°C, and 56°C for **one month**. Thereafter the antigenic activities of both components of the conjugate, i.e. their ability to bind their corresponding antibodies, were tested in an ELISA system. It was found that, in contrast to the compounds in fluid condition, the ones in the lyophilized composition had not altered their antigenic properties at 4°C and 37°C, whereas the compounds in both compositions had lost these properties at 56°C. In view of these results, the thermostability of the MenC-tetanus toxoid conjugate in lyophilized condition in the presence of lactose is qualified in document D15 as "excellent" (see the last sentence of abstract and the last paragraph).

8. The parties submit that the difference between the composition disclosed in document D15 and that of claim 6 is that the claimed composition contains sucrose instead of lactose and an amorphous organic buffer instead of PBS and that, according to the patent, the effect of these modifications is an increase in the stability of the composition during lyophilisation and upon storage.

Problem to be solved

9. Both parties agree that the problem to be solved by the claimed invention with regard to the composition disclosed in document D15 could be considered as the provision of a MenC-containing composition with improved stability and that this problem has to be considered as having been solved by the claimed subject-matter.

10. However, the board notes that the comparative experiments in the patent were not carried out with the composition disclosed in the document D15, but with a composition containing a MenC polysaccharide-diphteria toxin- conjugate, mannitol and phosphate buffer (obtained from Siena; see paragraphs [0040], [0059], [0061], Table 3 and Figure 5). Therefore, it is prima facie questionable, if the data in the patent are suitable at all to demonstrate that the claimed composition solves the problem. It can be left open whether or not the objective technical problem has to be considered as the provision of an alternative composition or a composition improved with regard to its stability, since the solution to the more ambitious problem, i.e. the provision of a more stable composition, is to be regarded as obvious (see below).

11. Hence, in the following the board will explain why in its view the teachings in the prior art would have motivated the skilled person, faced with the problem of improving the stability of the composition disclosed in the closest prior art document D15, i.e. a composition comprising MenC-polysaccharides conjugated to the protein carrier tetanus toxoid, lactose and PBS, to

modify this composition such as to arrive at the embodiment of claim 6 considered here, i.e. a composition comprising MenC-polysaccharides conjugated to a protein carrier, sucrose and an amorphous organic buffer.

12. The appellant submits that the skilled person would have been motivated to provide the claimed MenC-conjugate-containing subject-matter in the light of document D4.

13. The respondent submits that the skilled person would not even have considered to find a solution to this specific problem in document D4 because it is not concerned with lyophilisation of saccharides, let alone the MenC capsular saccharide, but instead is a review of the lyophilization of proteins (e.g. see the title). "Proteins and saccharides have different stability considerations, and no document on file suggests that knowledge from protein lyophilisation could readily be applied to saccharides" (see respondent's submission dated 26 October 2011, point 3.9).

14. In the board's understanding this argument aims at establishing that the stabilization requirements of **"pure"** polysaccharides are different from those of proteins during lyophilisation. Claim 6 relates, inter alia, to a composition comprising a MenC-polysaccharide-protein conjugate, i.e. it does not relate exclusively to "pure" polysaccharides (see point 3 above). The respondent does not argue that the disclosure in document D4 would not be applicable to protein-polysaccharide conjugates. Thus, the board

cannot come to the conclusion that the skilled person would not have considered the teachings in document D4.

15. Document D4 is a seven page long scientific publication with the title: "Review Article - Rational design of stable lyophilized protein formulations: some practical advice." The document deals with problems that may arise during the lyophilisation and the subsequent storage of protein compositions. The "problems" dealt with are put down as headings formulated as questions.

Why use lyophilization to prepare stable protein drug products?

What constraints govern the design of the formulation?

At what steps is stabilization of the protein required?

Which excipients are the best first choices?

What are some unexpected dangers?

16. Under the first heading "Why use lyophilization to prepare stable protein drug products?" it is inter alia explained why proteins require stabilization:

"Also - of greatest concern for the current review - without appropriate stabilizing excipient(s) most protein preparations are at least partially denatured by the freezing and dehydration stresses encountered during lyophilization (2,3-6, 11-16). The result is often irreversible aggregation of a fraction of the protein population, either immediately after processing or after storage (e.g. 15,16)."

17. Under the second heading "At what steps is stabilization of the protein required?" the factors to be considered when designing a proper lyophilized formulation are discussed in six individual paragraphs: "Protein Stability"; "Final Product Configuration"; "Formulation Tonicity"; "Cake Structure"; "Product Glass Transition Temperature" and "Product Collapse Temperature".

18. Subsequently, one of these factors, namely protein stability, is considered in detail. The chapter "At what steps is stabilization of the protein required?" has two parts.

19. The first part has the title "Stabilization during freezing". It is noted on page 971 at the top of the second column that "the three most important parameters to consider are protein concentration, buffer choice and freezing protocol".

19.1 As far as the buffer choice is concerned, the following is said:

"Buffer choice can also be critical. The main culprits here are sodium phosphate and potassium phosphate, which can undergo drastic changes in pH during freezing and annealing (6, 23, 24). [...]. The risk of alteration in pH and its damage to proteins can be minimized by increasing the initial cooling rate, limiting the duration of annealing steps and minimizing the buffer concentration, [....]. [...] Although other excipients can aid in inhibiting the pH change (24), the best approach is to avoid using sodium phosphate

or potassium phosphate buffers. Buffers that have minimal pH change upon freezing include citrate, histidine and Tris (22, 24; T.J. Anchordoquy and J.F. Carpenter, unpublished observations)."

20. The second part of the chapter "At what steps is stabilization of the protein required?" has the title "Stabilization during drying and storage in the dried solid". It is inter alia stated:

"Even if the entire population of protein survives the freezing step, there will be denaturation during subsequent dehydration unless the appropriate stabilizers are added. [...] To date, infrared spectroscopic studies with dozens of proteins have shown that, in the absence of the appropriate stabilizer(s) (e.g. sucrose) proteins will be unfolded in the dried solid. [...] Fortunately, appropriate excipients can prevent or at least minimize unfolding [...]. More importantly, in the few studies published to date, it has been shown that stability during long-term storage in the dried solid is dependent of retention of the native protein during freeze-drying. [...]"

21. The next chapter "Which excipients are the best first choices?" deals with these excipients. At the beginning of the first subchapter with the heading "Specific conditions for the stability of a given protein" the authors emphasize the relation between protein stability and pH:

"Before choosing the appropriate "general" stabilizers, which are effective at protecting most proteins, it is

absolutely essential that the formulation be optimized for the specific factors that increase the physical and chemical stability of a given protein. For example, simply avoiding extremes in pH can drastically reduce the rate of deamidation (1). Moreover, it has been found that the resistance of a protein to unfolding during freeze-drying can be dramatically increased by optimizing the pH of solution."

22. In the next subchapter under the subheading "Excipients that can fail to stabilize proteins" the following is inter alia disclosed:

"Among the numerous compounds tested it appears that the most effective stabilizers during the lyophilization cycle are disaccharides (2, 5, 6, 11, 15, 16, 25-28). However, one group of compounds that should be avoided are the reducing sugars. These compounds may effectively inhibit protein unfolding during the lyophilization cycle, but during storage in the dried solid they have the propensity to degrade proteins via the Maillard reaction [...]. Compounds in this undesireable category include glucose, lactose maltose and maltodextrins."

23. The next subchapter has the title "Rational choice of stabilizing excipients". It is stated:

"At this point, the major component missing is a non-reducing disaccaride, which forms an amorphous phase with the protein in the dried solid and serves as the primary stabilizer. The main choices are sucrose and trehalose. These compounds are relatively effective at protecting proteins during freezing and usually

excellent at inhibiting unfolding during dehydration. [...] Both sucrose and trehalose have advantages and disadvantages. [...] Sucrose is commonly used in parenteral products that are approved by the Food and Drug Administration (33). In contrast, trehalose has not yet been used in an approved product. [...] Safety of trehalose will most likely not be a concern. Thus, if there is a clear advantage of trehalose over sucrose in a given product, use of trehalose should not hinder regulatory approval."

24. In summary, the skilled person inter alia learns from the disclosure in document D4 that, for the successful lyophilization and subsequent storage of a protein-containing composition, it is necessary (i) to include a buffer in the composition in order to control the pH and that it is important (ii) to avoid sodium phosphate or potassium phosphate containing buffers and (iii) to use buffers containing citrate, histidine or Tris instead. The skilled person also learns that (iv) the inclusion of excipients in the composition is indispensable in order to avoid protein unfolding during the lyophilization and storage, (v) that some compounds, such as lactose, are not suited as excipients because they may interfere with the product during storage, and (vi) that either sucrose or trehalose are the best first choices with a preference as the first choice for sucrose because it is an excipient already approved by the FDA.

25. The board has no indications to the effect either that the skilled person would have considered the disclosure in document D4 - for whatever reason - as not trustworthy and/or that the skilled person would have

considered that the advice given in the document would not be applicable to the problem to be solved, i.e. the improvement of the stability of the composition disclosed in document D15, because, although document D4 discloses that every protein has unique stabilization requirements, it is also stated that "for many proteins the advice given above will probably lead to successful lyophilized formulation" (page 974, second column, first paragraph).

26. Thus, the board concludes that the skilled person would follow the advice from document D4 and would have been motivated by the disclosure in document D4 to omit lactose and PBS from the composition of document D15.

27. Having learnt from document D4 that at least a buffer and an excipient are necessary for stabilizing a protein-containing composition upon lyophilisation, the skilled person would also derive from this document that citrate, histidine or Tris, i.e. amorphous organic buffers and sucrose are the best first choices as replacements for lactose and PBS.

28. Since document D4 teaches that PBS and lactose are not ideal for the stability of proteins upon lyophilization, but that sucrose and organic amorphous buffers are the best choices, the skilled person would have good reasons to expect to obtain an improved MenC polysacharide-protein-conjugate composition when including these two ingredients.

29. The respondent argues that the skilled person would neither have included sucrose, nor an amorphous organic buffer in a MenC-polysaccharide-protein conjugate

containing composition to be lyophilized because he would have thought neither that pH control is necessary in MencC-containing compositions nor that anything is wrong with lactose. This would have been so because, at the priority date, none of the three commercially available MenC-containing vaccines, Mencevax™, Menommune™ and Menjugate™ included a buffer and moreover two of them (Mencevax™, Menommune™) included lactose as an excipient and one (Menjugate™) included mannitol. Also the composition disclosed in document D15 included lactose, and although a buffer was also included - PBS - it was not used for pH control, but for dialysis before lyophilisation. Document D15 explicitely states that no pH control was applied (see document D15, page 40, first column, first paragraph).

30. The relevant date for assessing which course of action the skilled person would have pursued is the priority date of the patent, strictly speaking the day before the priority date, i.e. in the present case the 1 December 1999. Document D4 was published in the year 1997 i.e. about two years before that day and 14 years after the publication of document D15.

31. It is conceivable that after the publication of document D15 the skilled person's perception was that, in order to comply with the stability requirements of a MenC-polysaccharide-protein conjugate containing composition, lactose is the best excipient and that no buffer is needed. However, once document D4 became available, it is not imaginable that the skilled person - even if he is considered to be conservative and cautious - would not have changed this view.

32. The fact alone that the commercially available compositions had not been modified at the priority date of the disputed patent, i.e. in the two years after the publication of document D4, does not convince the board that, for example, a prejudice or a prevailing opinion had deterred the skilled person from applying the teachings of document D4. Time-consuming regulatory procedures may for example be a possible reason why modified compositions had not been made commercially available at the priority date.

33. Thus, the board concludes that the embodiment of claim 6 relating to a lyophilized composition containing MenC polysaccharide-protein conjugates is obvious in the light of a combination of the teachings in documents D15 and D4.

34. In view of established case law that a claim is only considered to involve an inventive step if substantially all of its embodiments involve an inventive step (for example decision T 929/92, point 2.4.2 of the reasons), the board's conclusion in point 33 has the consequence that the subject-matter of claim 6 has to be considered to lack an inventive step.

35. Hence, the main request is rejected.

Auxiliary Requests 1, 4 and 6

36. For the reasons given in relation to claim 6 of the main request, the subject-matter of claim 5 of auxiliary request 1 and of claim 3 of auxiliary requests 4 and 6 does not fulfil the requirements of Article 56 EPC.

Auxiliary requests 2, 3, 5 and 7

37. The wording of claim 6 of auxiliary request 2 and claim 5 of auxiliary request 3 correspond to the wording of claim 5 of auxiliary request 1; the wording of claim 3 of auxiliary request 5 corresponds to that of claim 3 of auxiliary request 4 and the wording of claim 3 of auxiliary request 7 corresponds to that of claim 3 of auxiliary request 6. However, the above cited claims of auxiliary requests 2, 3, 5 and 7 all refer to a method claim which is worded differently from the one to which the corresponding claims of auxiliary requests 1, 4 and 6 refer, i.e. in contrast to the respective method claims of auxiliary requests 1, 4 and 6 which relate to "[a] method for stabilizing one or more meningococcus C (MenC) immunogen upon lyophilization", the respective claims in auxiliary requests 2, 3, 5 and 7 relate to "[a] method for stabilizing **one or more saccharides** that are meningococcus C (MenC) immunogens upon lyophilization". The board considers that by virtue of the feature "one or more saccharides" in the claims to the method, the term "meningococcus C (MenC) immunogen" in the claims to the lyophilised composition - which refer to the claims to the method - has to be interpreted in a limited way, i.e. as meaning "MenC saccharides". In other words, the board considers that these claims relate to lyophilized compositions containing unconjugated MenC immunogen and are thus restricted to the second one of the two groups of embodiments of claim 6 of the main request(see points 3 and 5 above).

38. The appellant submits that this subject-matter does not involve an inventive step because it cannot be considered to solve the underlying problem. The appellant's approach is based on case law such as decision T 939/92 of 12 September 1995, in which the board held that it followed from the principle that everything falling within a valid claim has to be inventive (see paragraph 2.4.2 of the decision) that it should be credible that the desired technical effect according to the problem to be solved is seen with substantially every embodiment of a claim (see paragraph 2.5.4 of that decision).

39. The respondent submits that decision T 939/92 relates to circumstances where on the one hand the claims cover compounds of a broad structural variety, but where on the other hand there are only data proving an effect for one or very few of the many compounds. These are however not the circumstances here and therefore the reasoning of decision T 939/92 is not applicable to the present case.

40. The independent claim under consideration in decision T 939/92 related to chemical compounds which were summarized in the form of a Markush formula, i.e. the claims covered in fact a wide variety of compounds. However, in the present board's understanding, the issue as to whether all compounds covered by the independent claim have the technical effect according to the problem to be solved did not arise because the number of claimed compounds was large, but because the claim was drafted such that it referred to the compounds per se without stating the effect to be achieved according to the problem to be solved. That

this was also the board's view in decision T 939/92 may be inferred from paragraph 2.2.1 of the decision:

"However, the present independent claim covers certain chemical compounds per se, and not just those compounds having a particular biological activity. Hence the biological activity of these compounds is not an essential technical feature of the claimed subject-matter, and thus not part of the definition of the claimed subject- matter."

41. Also the product claims considered here do not recite any effect, let alone the one to be achieved according to the problem to be solved. Hence, therefore, in the board's view, the reasoning of decision T 939/92 is applicable.

42. The respondent further submits that the examples in the patent show that the use of sucrose and an amorphous organic buffer such as histidine or imidazole reduce the aggregation of MenC immunogen and thus make it credible that the inclusion of sucrose and an amorphous organic buffer improves the stability upon lyophilization of a composition comprising MenC immunogen.

43. The board notes that the claims under consideration here are directed to compositions containing "pure", unconjugated, i.e. "protein-free" MenC polysaccharides (see point 37 above). All the experiments in the patent were carried out with MenC polysaccharides conjugated to a protein carrier - a mutant diphteria toxin denoted as "CRM 197". In other words, there is not a single

result in the patent from an experiment with "pure" MenC polysaccharides.

44. Moreover, the patent specification consistently discloses that the instability of MenC-protein conjugates upon lyophilization is due to the protein part of the conjugate.

44.1 It is disclosed in paragraph [0004]:

"Some problems are associated, however, with the use of the conjugate meningococcal polysaccharide vaccine MenC-CRM 197, and, indeed, with protein-containing vaccines in general. To extend the shelf-life of vaccines, formulations are frequently lyophilized. Lyophilization of MenC-CRM 197, however, can lead to protein aggregation during freezing and storage. In the case of MenC-CRM 197, the aggregates represent noncovalently bound, multimers of MenC-CRM 197 which apparently associate through hydrophobic interactions. The use of present dissolution buffer formulations, i.e. containing 10mM sodium phosphate (pH 7.2) as a buffer and 1.5% mannitol as an excipient, can yield aggregation as high as 9.5 to 10%. As aggregation increases, the concentration of available immunogen decreases. Therefore, a need exists for compositions and methods which overcome the problem of aggregation by stabilizing biological molecules against aggregation during lyophilization.

197 vaccine [sic] is composed of two fragments, A and B, covalently bound to one another. Fragment A has been found to be stable and highly resistant to denaturation. Fragment B, however, is highly sensitive

to denaturation and is subject to proteolytic breakdown during lyophilization. As proteolytic breakdown increases, the concentration of available functional immunogen decreases. Therefore, a further need exists for compositions and methods of preparation of biological molecules that will minimize breakdown during lyophilization and storage."

44.2 Moreover, it is stated in paragraph [0061]:

"Use of histidine or imidazole buffers in the MenC-CRM 197 formulation increased the vaccine stability. Although the inventors do not wish to be bound to this mechanism, it is thought that stabilization maybe due to the interaction of the tryptophan of CRM 197 with the structurally similar imidazole ring."

45. It is stated very generally in the patent, for example in paragraph [0022]:

"The present invention provides buffer compositions, biological molecule compositions, and methods for the preparation and stabilization of biological molecules by reducing aggregation and breakdown of biological molecules upon lyophilization."

45.1 However, in the board's opinion, in the absence of supportive evidence, this general statement is not sufficient to establish in the context of the patent that stability of "pure", i.e. unconjugated MenC polysaccharides is improved by inclusion of sucrose and an amorphous organic buffer. Both the patent and the prior art, such as for example document D4, explicitly teach only that aggregation during lyophilisation

occurs with proteins. In other words, neither the patent nor any of the prior art documents in these proceedings report that polysaccharides, which are composed of hydrophilic sugar residues, aggregate during lyophilization and thus could be stabilized by reducing aggregation. Even if the heat and drying stress during lyophilization had a detrimental effect on polysaccharides, and be it even by aggregation, then, due to their different chemical nature - sugar residues versus amino acids - it is questionable whether polysaccharides could be stabilized by the same means as proteins. Also the respondent alleges that proteins and polysaccharides have different stabilisation requirements during lyophilization (see section XIII above, *inventive step*, 10th paragraph).

46. In view of the circumstances depicted above, the board concludes that neither the patent nor the prior art provides convincing evidence that the claimed lyophilized compositions achieve the desired technical effect to be achieved in accordance with the underlying problem, i.e. the improvement of the stability of an unconjugated MenC polysaccharide-containing composition.

46.1 When the credibility that a technical effect is achieved by substantially all claimed compounds is at issue and in a situation where, as in the present case, it is prima facie unlikely that this is credible, it is - contrary to the respondent's view - not the opponent (here: the appellant), but the patentee (here: the respondent) who has the burden of proving that the effect is achieved (for example decision T 939/92 of 12 September 1995, point 2.6.1 of the reasons; decision

T 97/00 of 25 September 2003, point 3.1.6 of the reasons).

47. The respondent submits that the modifications applied by the appellant to its own meningococcus vaccine, Mencevax™, confirm that the inclusion of sucrose and an amorphous organic buffer in the formulation enhances not only the stability of conjugated, but also of unconjugated MenC immunogen during lyophilisation. It refers (i) to document D26 published in the year 2000 disclosing that the product Mencevax™, which contains unconjugated MenC polysaccharides and lactose but no buffer, has a shelf life of **2** years; (ii) to documents D37 and D37a published in the year 2008 disclosing that a modified Mencevax™, which includes sucrose and Tris, has a shelf life of **3** years; (iii) to document D38 disclosing that the new Mencevax™ vaccine contains Tris as a "stabilizing agent" and finally,
(iv) to document D40, a report published by the Belgian Federal Agency for Medicines and Health Products and published in the year 2008, comparing the old and new Mencevax™ products, and coming on page 51 to the conclusion that the addition of Tris "assures pH stability over the new Mencevax ACWY shelf-life".

48. The appellant submits that the change in the composition had not been made with the aim of increasing the stability of the composition, but was triggered by completely different considerations.

49. All documents D26, D37, D37a, D38 and D40 referred to by the respondent are published **after** the priority date of the patent at issue.

50. Post-published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved. In other words, supplementary post-published evidence may not serve as the sole basis to establish that the problem is solved (see for example decision T 1329/04, point 12).

50.1 Therefore, the board decided in decision T 1329/04 that the post-published evidence could not be regarded as supportive of evidence in the application as filed since there was not any. Therefore, the post-published evidence was considered to be the first disclosure going beyond speculation and was therefore not taken into consideration.

50.2 In contrast, for example, the board in decision T 1336/04, who was confronted with a different technical situation, namely one where the quality of evidence provided in the respective patent was such that the claimed invention was considered to be a bona fide solution to the problem to be solved, decided to take the disclosure in a post-published document into consideration as a further support (T 1336/04).

51. The present circumstances are that (i) there are no indications either in the patent or in the prior art that the stability of a MenC polysaccharide-containing formulation is improved by sucrose and an amorphous organic buffer and that (ii) the patent indicates that stability problems are caused by proteins. The board therefore sees the present situation as being closer to that in decision T 1329/04 than to that in decision

T 1336/04 because the post-published documents relied on by the respondent would, if the disclosures therein were suitable to support the respondent's view, be the first disclosures establishing that the problem was solved by the claimed compositions. The board decides therefore that these documents cannot be taken into consideration.

52. It follows that no decision is necessary therefore as to whether or not the disclosures in documents D26, D37, D37a, D38 and D40 demonstrate at all that the inclusion of sucrose and Tris in the formulation enhances the stability of a composition comprising unconjugated MenC immunogen during and after lyophilisation.

53. Hence, the board comes to the conclusion that not substantially all (in fact: none) of the claimed compositions can be considered as being improved unconjugated MenC-polysaccharide-containing lyophilized compositions and therefore cannot acknowledge that the problem is solved by the claimed subject-matter.

54. Besides the argument that the technical problem is not solved, no further arguments were submitted by the parties, for example as to the reformulation of the technical problem or as to whether or not a reformulated, solved problem could be considered as obvious in view of the prior art.

55. Consequently, auxiliary requests 2, 3, 5 and 7 are refused for failure to comply with the requirements of Article 56 EPC.

Auxiliary Request 8

56. The three claims of auxiliary request 8 differ from claims 1 to 3 of auxiliary request 7 only in that the term "vaccine" is used instead of the term "immunogen", i.e. claim 3 relates to a "Meningococcus C (MenC) vaccine" (see section X above).

57. An "immunogen" is a compound that elicits a cellular or humoral immune response. A "vaccine" comprises immunogens that elicit a cellular or humoral immune response. However, the term "vaccine" carries the additional meaning that the intended use of the composition is to prevent or cure a disease (see also paragraph [0002] of the patent: "Vaccines are widely used for the prevention and /or therapy of many different diseases."). Thus, as far as the purpose or use is concerned, the meaning of the term "vaccine" is more limited than the term "immunogen". In line with this interpretation it is stated in the patent in paragraph [0026]: "As used herein, the term "immunogen" refers to any compound capable of eliciting a cellular and/or humoral immune response when in contact wit a cell, and includes, without limitation, vaccines and compositions comprising immunogens."

58. Nevertheless, the reasons for finding in points 37 to 54 above that the lyophilized MenC-polysaccharide-**immunogen** containing compositions cannot be considered to solve the problem to be solved also apply to a MenC-polysaccharide containing **vaccine** according to claim 3 of auxiliary request 8. This is so because the reason for finding that the lyophilized MenC-polysaccharide-**immunogen** containing compositions do not solve the

problem is the lack of evidence for the improved stability of lyophilized compositions containing MenC-polysaccharide, sucrose and an amorphous organic buffer - a reason which is unrelated to the above-described difference in the meanings between the terms "immunogen" and "vaccine". Consequently, also auxiliary request 8 is refused for failure to comply 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 patent is revoked.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith