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Datasheet for the decision of 18 September 2020

Case Number: T 0645/18 - 3.3.04

Application Number: 07865465.4

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IPC: A61K39/395, A61K39/02, A61K39/09

Language of the proceedings: EN

Title of invention:
Multivalent pneumococcal polysaccharide-protein conjugate composition

Patent Proprietor:
Wyeth LLC

Opponent:
Maiwald Patent- und Rechtsanwaltsgesellschaft mbH

Headword:
Polysaccharide-protein conjugate/WYETH

Relevant legal provisions:
EPC Art. 56, 83, 123(2), 100(a), 100(b), 100(c)

Keyword:

Amendments - added subject-matter (no)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 0645/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 September 2020

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)
Respondent: (Opponent)	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstrasse 3 80335 München (DE)
Representative:	Neuefeind, Regina Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 January 2018 revoking European patent No. 2094304 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the patent proprietor ("appellant") lies from the decision of the opposition division to revoke European patent No. 2 094 304. The patent is entitled "*Multivalent pneumococcal polysaccharide-protein conjugate composition*".

II. The patent was opposed on the grounds in Article 100(a) EPC, in relation to inventive step (Article 56 EPC), on the grounds of lack of sufficient disclosure (Article 100(b) EPC) and on the grounds of subject-matter extending beyond the content of the application as filed (Article 100(c) EPC).

III. In the decision under appeal, the opposition division considered sets of claims of a main request (claims as granted) and three auxiliary requests and decided that:

claims 14 to 18 of the main request related to subject-matter which extended beyond the content of the application as filed, whereas claims 7 to 10 did not;

the invention to which claims 1 to 13 of auxiliary request 1 related was sufficiently disclosed, but the subject-matter of these claims did not involve an inventive step in view of document D1 alone or in view of a combination of documents D1 and D3;

claims 4 to 8 of auxiliary requests 2 and 3 were identical to claims 14 to 18 of the main request and thus also related to added subject-matter.

IV. With their statement of grounds of appeal, the appellant re-filed the sets of claims of the main

request (claims as granted) and the three auxiliary requests as dealt with in the decision under appeal. The appellant argued that the opposition division erred in its adverse decision.

V. Claim 1 of the main request reads:

"1. A method for making an immunogenic conjugate comprising *Streptococcus pneumoniae* serotype 1 polysaccharide covalently linked to a carrier protein, the method comprising:

(a) reacting purified serotype 1 polysaccharide with an alkaline pH buffer resulting in a partially de-O-acetylated serotype 1 polysaccharide;

(b) reacting the partially de-O-acetylated serotype 1 polysaccharide with a mild acid or with a low ionic strength mineral acid resulting in a neutralized, partially de-O-acetylated serotype 1 polysaccharide;

(c) reacting the neutralized, partially de-O-acetylated serotype 1 polysaccharide with an oxidizing agent resulting in an activated serotype 1 polysaccharide;

(d) compounding the activated serotype 1 polysaccharide with a carrier protein;

(e) co-lyophilizing the compounded, activated serotype 1 polysaccharide and carrier protein;

(f) reacting the compounded, activated serotype 1 polysaccharide and carrier protein with a reducing

agent resulting in a serotype 1 polysaccharide:carrier protein conjugate; and

(g) capping unreacted aldehydes in the serotype 1 polysaccharide:carrier protein conjugate resulting in an immunogenic conjugate comprising *Streptococcus pneumoniae* serotype 1 polysaccharide covalently linked to a carrier protein."

Claim 14 of the main request reads:

"14. A process for preparing a multivalent immunogenic composition comprising 13 distinct polysaccharide-protein conjugates together with a physiologically acceptable vehicle, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein the capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*, wherein said serotype 1 polysaccharide-protein conjugate is made according to any one of the method [sic] of claims 1 to 13 and wherein after the individual glycoconjugates are purified, they are compounded to formulate the immunogenic composition."

VI. The opponent (respondent) did not reply to the appeal.

VII. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a separate communication pursuant to Article 15(1) RPBA.

VIII. In points 14 and 15 of this communication, the board informed the parties that it considered the incorporation of serotype 1 immunogenic conjugates into

the generic immunogenic composition to then comprise 13 distinct polysaccharide-protein conjugates (including serotype 1) as directly and unambiguously disclosed in the application as filed. Furthermore, the board was of the view that claims 7 to 10 and 14 to 18 did not relate to added subject-matter.

In point 16 of this communication, the board informed the parties that it was in agreement with the opposition division's reasoning in the decision under appeal that the invention, to which the claims of the main request related, was sufficiently disclosed, and that it also saw no reason for any examination of the issue of its own motion.

In reply to the appellant's submission that the 13 different serotypes in the vaccine could be divided into ionic categories and that serotype 1 was the only zwitterionic one, the board stated that it had not seen any evidence that the skilled person had actually been aware - at the priority date - of this distinct, special structure of *Streptococcus pneumoniae* serotype 1 polysaccharide (see point 30 of the communication).

The board finally foreshadowed "*the main topic at the oral proceedings will be whether or not the skilled person, looking for an alternative method to prepare serotype 1 polysaccharide conjugates, would have applied the teaching of co-lyophilisation disclosed in documents D1 and D3 to polysaccharides from serotype 1*".

IX. The appellant replied to the board's communication by submitting documents D6 and D7 and further arguments with regard to inventive step.

X. The respondent informed that they would not be attending the oral proceedings and, in a further letter, that they withdrew their request for oral proceedings.

XI. The board cancelled the oral proceedings scheduled for 29 April 2020 in view of the communication of the President of the Boards of Appeal of the EPO dated 1 April 2020 that no oral proceedings will be held by the Boards of Appeal until 30 April 2020 due to the "*pandemic spread of the new Coronavirus*".

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

D1 WO2006/110381

D3 EP0245045

D6 Kamerling, A., "Pneumococcal Polysaccharides: A Chemical View", *Streptococcus pneumoniae*, 2000, 81-114.

D7 Cobb, A. et al., "Zwitterionic capsular polysaccharides: the new MHCII-dependent antigens", Cellular Microbiology 7(10), 2005, 1398-1403.

XIII. The appellant's arguments submitted in writing may be summarised as follows.

Main request (claims as granted)
Amendments (Article 100(c) in combination with Article 123(2) EPC) - claim 14

The subject-matter of all the claims of the application as filed was a method for making a *Streptococcus pneumoniae* serotype 1 conjugate.

The methods in claims 1 to 13 referred to in claim 14, according to which the the serotype 1 polysaccharide-protein conjugate is made, were disclosed in the claims as filed (see claim 1 combined with claim 3, as well as dependent claims 2 and 4 to 15).

The application as filed provided a general disclosure of a 13-valent vaccine composition where the 13 serotypes were listed on page 2, lines 17 to 20.

The skilled person would not consider that the technical teaching of the application was limited to multivalent compositions where all conjugates were prepared according to "conventional methods", or to multivalent compositions where all conjugates were prepared according to the examples.

Although the exact wording of claim 14 could not be retrieved in the application as filed, its subject-matter could be derived directly and unambiguously by the skilled person from the application as filed.

Inventive step (Article 100(a) in combination with Article 56 EPC)

The purpose of the application was to provide a method for making *Streptococcus pneumoniae* serotype 1 conjugates to be used as a vaccine, in particular in a multivalent vaccine composition.

The effect of an improved reproducibility of the claimed method was related to the technical problem initially provided in the application as filed, see page 16, lines 13 to 15, and was in fact a desirable effect of any method for producing a complex vaccine component. The improved reproducibility could be derived from the data filed during the examination proceedings (reproduced as Tables 1 and 2 on page 8 of the statement of grounds of appeal).

Even if the submitted data were disregarded, the claimed method remained advantageous with regard to the method of document D1, as the presence of a co-lyophilisation step provided for "*more flexibility in terms of saccharide to protein input ratio and concentration reaction*" (statement of grounds, page 13, third paragraph). Therefore, it still had to be considered as inventive.

Document D1 provided detailed, specific protocols for preparing the individual polysaccharides of serotype 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C, 19F and 23F conjugates. A specific conjugation-process needed to be designed for each of the 13 serotypes because each had a different chemical structure.

In fact, the polysaccharides in the vaccine could be divided into four categories: (a) negatively charged,

e.g. types 3 and 5; (b) neutrally charged, e.g. types 7F and 14; (c) zwitterionic, e.g. type 1; and (d) phosphodiester containing, e.g. types 6A, 6B, 19A and 19F.

The structural diversity of *Streptococcus pneumoniae* polysaccharides was known to the skilled person, see for example the textbook D6 or the review article D7.

Thus, serotype 1 polysaccharide was the only zwitterionic polysaccharide in the 13-valent vaccine composition disclosed in document D1.

While the processes disclosed in document D1 for the conjugation to the carrier protein of serotype 3, 5, 19A, 4, 9V and 14 polysaccharides comprised a co-lyophilisation step, most of the processes disclosed in document D1 did not comprise such a step, and there was no suggestion in document D1 that this step could be used in the process for preparing the structurally unique serotype 1 conjugate.

No such suggestion could be found in document D3 either, because it did not disclose a process for the preparation of serotype 1 conjugates, but a process for the preparation of a serotype 6 conjugate and of polysaccharides of other pathogens such as *Haemophilus influenzae*.

XIV. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted or, alternatively, that the patent be maintained in amended form on the basis of the set of claims of one of auxiliary requests 1 to 3, and that oral proceedings be held if the patent could not be maintained as granted.

Reasons for the Decision

Main request (claims as granted)

Amendments (Article 100(c) in combination with Article 123(2) EPC)

Claims 7 to 10

1. The board agrees with the opposition division that the subject-matter of claims 7 to 10 does not extend beyond the content of the application as filed in view of, for example, page 16, line 1 to page 17, line 14 and Example 17.

Claims 14 to 18

2. Claim 14 relates to "[a] process for preparing a multivalent immunogenic composition comprising 13 distinct polysaccharide-protein conjugates". Only for *Streptococcus pneumoniae* serotype 1 conjugate is the method of preparation specified in the claim, namely that it is prepared according to the specific method recited in claims 1 to 13 (see section V. above).

3. In the decision under appeal, the opposition division found that claim 14 and the dependent claims 15 to 18 related to added subject-matter. In particular, the opposition division was of the opinion "*that the skilled person after reading the application would understand that the individual conjugates present in the multivalent immunogenic composition defined in claim 14 can either all be prepared by using standard/ conventional methods, as stated on pg. 11 (lines 7-8 and 21-23), or by using the methods described in*

examples 1-14. However, the skilled person would not understand that the serotype 1 conjugate should be prepared according to the method defined in claims 1-13 whereas all the remaining 12 conjugates can be prepared using any known process."(see page 6, paragraph 2 of the decision).

4. Indeed, the application as filed discloses "[a] *process for preparing a multivalent immunogenic composition comprising 13 distinct polysaccharide-protein conjugates*", in which all the 13 constituents, including the serotype 1 conjugate, are prepared by any known method, see the passages above referred to by the opposition division and also page 2, lines 17 to 20 and page 12, lines 16 to 21.

5. Furthermore, separately, the application discloses "[a] *method for making an immunogenic conjugate comprising Streptococcus pneumoniae serotype 1 polysaccharide covalently linked to a carrier protein*" (emphasis added), including the step of co-lyophilising the activated serotype 1 polysaccharide and the protein to be conjugated, in claims 1 and 3 of the application as filed.

6. In the light of the opposition division's reasoning, the pertinent question is therefore whether or not a method which combines these two methods, i.e. a method wherein the serotype 1 conjugate is prepared according to the method including co-lyophilisation whereas all the remaining 12 conjugates are prepared using any known process, is subject-matter extending beyond the content of the application as filed.

7. Firstly, it is noted that in the application as filed only methods for the preparation of serotype 1

conjugates are referred to in the claims: "[a] *method for making an immunogenic conjugate comprising Streptococcus pneumoniae serotype 1 polysaccharide covalently linked to a carrier protein*" (see independent claims 1 and 13; emphasis added) and "[a] *method for making an activated Streptococcus pneumoniae serotype 1 polysaccharide*" (see claim 16; emphasis added). No other serotypes or methods for preparing them are mentioned in the claims as filed.

Secondly, in the "*Summary of the invention*" (pages 2 to 4), *Streptococcus pneumoniae* serotype 1 is also the only serotype for which specific methods for making an immunogenic conjugate are listed (page 3, line 29 to page 4, line 27).

Thirdly, the application contains a section "*Activation of S. pneumoniae Serotype 1 Polysaccharides for Conjugation*", but no corresponding section(s) for other serotypes.

8. In the board's view, the skilled person when reading the application as a whole, especially when considering the claims, would have derived from its content the preference to prepare the immunogenic conjugate for serotype 1 by the specific method disclosed for it rather than by other known methods.

9. Thus, a process for preparing a 13-valent immunogenic composition of *Streptococcus pneumoniae* polysaccharide-protein conjugates according to claim 14, whereby the serotype 1 conjugate is prepared by the method in claims 1 to 13, is directly and unambiguously disclosed in the application as filed.

10. The claims of the main request fulfil the requirements of Article 123(2) EPC.

Inventive step (Article 100(a) in combination with Article 56 EPC)

11. The opposition division held in the decision under appeal that claims 1 to 13 of auxiliary request 1 did not involve an inventive step (see section III. above). These claims are identical to claims 1 to 13 of the present main request.

Closest prior art

12. Both parties and the opposition division in the decision under appeal considered document D1 as the closest prior art. The board sees no reason to deviate.

13. Document D1 discloses a method for the preparation of a 13-valent vaccine composition comprising *Streptococcus pneumoniae* polysaccharide-protein conjugates.

Technical problem and its solution

14. The difference between the method in present claim 1 and the relevant disclosure of document D1 is that the compounded, activated serotype 1 polysaccharide and the carrier protein are co-lyophilised according to step (e) of claim 1, whereas separate lyophylisation of the two is taught in document D1 (see Examples 1 and 2).

15. The board is not persuaded by the appellant's argument that the method in claim 1 provided for "*more flexibility in terms of saccharide to protein input ratio and concentration reaction*" (see statement of grounds of appeal, page 13). Indeed both methods,

separate lyophilisation or co-lyophilisation, allow to freely choose the input ratio and concentration of saccharide and protein.

16. From the evidence in the application (in particular Example 17) and/or evidence available before the priority date, the board cannot discern any special technical effect of this difference, so that the objective technical problem in view of document D1 is the provision of an alternative method for making an immunogenic conjugate comprising *Streptococcus pneumoniae* serotype 1 polysaccharide covalently linked to a carrier protein.

17. The appellant argues that, on the basis of evidence in the application and data generated after the priority/ filing date, the problem to be solved should be formulated as "*identifying a method for making an immunogenic conjugate comprising serotype 1 polysaccharide covalently linked to a carrier protein with improved reproducibility*" (see statement of grounds of appeal, page 11). In view of the board's conclusion as regards the obviousness of the claimed subject-matter, reasons as to why this formulation of the problem is not accepted need not be given.

Obviousness

18. In the decision under appeal, the opposition division, when assessing the obviousness of the claimed subject-matter in the light of documents D1 and D3, took the view that "*the skilled person when looking for an alternative method to that described in D1 for conjugating a carrier protein to S. pneumoniae serotype 1 polysaccharide would definitely consider the possibility of replacing the separate lyophilization of*

the carrier and polysaccharide by a co-lyophilization step. The fact that the chemical nature of this polysaccharide may be different from that of the polysaccharides described in D1 that are conjugated using a co-lyophilization step would not deter the skilled person from trying this approach".

The board takes a different view for the following reasons.

19. In document D1 some serotype conjugates (serotypes 3, 4, 5, 9V, 14 and 19A) were prepared using co-lyophilisation (see Examples 4, 6, 12 and 14). The remaining serotype conjugates (serotypes 1, 6A, 6B, 7F, 18C, 19F and 23F) were prepared using separate lyophilisation (see Examples 2, 10, 14). Document D1 does not provide any indication of an effect or advantage of one method over the other. However, document D1 associates different methods to different serotypes (see page 37, lines 21 to 29: "*For serotypes 4, 9V, and 14 the concentrated saccharide was mixed with CRM_{197} carrier protein* [...]. *The frozen concentrated saccharide-CRM_{197} was lyophilized* [...]. *For serotypes 6B, 19F, and 23F a specified amount of sucrose was added* [...]. *Serotype 18C did not require sucrose addition.* [...] *The frozen concentrated saccharide was lyophilized* [...]").

20. Document D1 also states in the introduction to Example 14: "*The different serotype saccharides follow different pathways for activation (hydrolysis or no hydrolysis prior to activation) and conjugation (aqueous or DMSO reactions) as described in this example*".

21. Thus, document D1 establishes defined and distinct processes for conjugating each of the 13 different serotypes to the carrier protein. Moreover, there is not a single serotype disclosed in document D1 for which lyophilisation and co-lyophilisation are considered as alternative methods.

22. Hence, from the whole teaching of document D1, the skilled person would conclude that the choice of lyophilisation and co-lyophilisation was essential to achieve optimal conjugation of the different serotypes.

23. In the board's view, the skilled person also arrives at this conclusion in the light of their knowledge of the different chemical structures and ionic charges of the different serotype polysaccharides and their influence on the preparation process. In this respect, as submitted by the appellant in their statement of grounds of appeal (see page 14) and backed up in their reply to the board's communication by documentary evidence from the textbook document D6 and the review article document D7, the skilled person would have been aware that the chemical structure and ionic charge of serotype 1 polysaccharide is different from that of the polysaccharides of all the other serotypes: "*Serotype 1 polysaccharide is the only zwitterionic polysaccharide in the 13-valent composition disclosed in D1*" (statement of grounds of appeal, page 14).

24. Document D3 discloses co-lyophilisation of *Streptococcus pneumoniae* serotype 6 polysaccharide and of polysaccharides of other pathogens such as *H. influenza*, but none for serotype 1 polysaccharides. Due to their knowledge about the different chemical structures and ionic charges of the different serotypes (see point 23. above), however, the skilled person

would not have considered that a method suitable for serotype 6 polysaccharide conjugation was also suitable for serotype 1 polysaccharide conjugation.

25. In summary, in the board's judgement, the disclosure in document D1 of specific conjugation methods for the different serotype polysaccharides and the skilled person's knowledge of the particular chemical nature of serotype 1 polysaccharide would have deterred the skilled person - who, according to established case law, has a conservative attitude (Case Law of the Boards of Appeal of the EPO, 9th edition 2019, I.D. 8.1.3) - from using co-lyophilisation in the process of preparing serotype 1 conjugates.

26. Consequently, the subject-matter of claim 1, and that of the dependent claims 2 to 18, involves an inventive step.

Sufficiency of disclosure (Article 100(b) in combination with Article 83 EPC)

27. The decision under appeal raised the issue of sufficiency of disclosure only with regard to auxiliary request 1. In the absence of arguments from the respondent, the board sees no reason to deviate from the assessment of the opposition division.

28. Hence, the invention claimed in claims 1 to 13 is disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated