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Datasheet for the decision of 8 October 2019

Case Number: T 0917/16 - 3.3.04

Application Number: 06762248.0

Publication Number: 1896066

IPC: A61K39/095, A61K39/102, A61K39/116, A61P31/04

Language of the proceedings: EN

Title of invention:
Immunogenic composition

Applicant:
Pfizer Ireland Pharmaceuticals

Headword:
Conjugate vaccine/PFIZER

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0917/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 8 October 2019

Appellant: (Applicant)	Pfizer Ireland Pharmaceuticals Operations Support Group Ringaskiddy Cork (IE)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 October 2015 refusing European patent application No. 06762248.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	P. de Heij

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the decision of the examining division refusing European patent application No. 06 762 248.0, entitled "*Immunogenic composition*". The application was filed as an international application which was published as WO 2007/000342.

II. In the decision under appeal the examining division dealt with a main request and six auxiliary requests and held that the subject-matter of claim 1 of each of those requests did not involve an inventive step (Article 56 EPC).

The closest prior art was considered to be represented by document D1 or, alternatively, by document D7, which had equivalent disclosure.

The applicant had submitted that the effect attained by the claimed composition over the closest prior art was an optimised immune response. In relation to the main request, the examining division reasoned that this technical effect could not be taken into account in the formulation of the objective technical problem. On the basis of the data in the application, it was not possible to determine that the modification of the conjugates resulted in an optimised or improved vaccine composition with respect to the composition disclosed in document D1 or D7.

The post-published documents submitted did not allow for any comparison with the prior art that could lead to an effect being attributed to the distinguishing

features. Thus, the post-published documents did not constitute evidence of the effect either.

The examining division came to the conclusion that the distinguishing features were merely an arbitrary selection within the skilled person's ambit of routine experimentation. It was prior-art knowledge that the conjugation method, choice of carrier and presence of a linker had an effect on the efficacy of a vaccine, so it was in the skilled person's common general knowledge to modify and combine any of these in order to provide an improved vaccine.

III. With the statement of grounds of appeal, the appellant filed sets of claims according to a main request and seven auxiliary requests, while also referring to further auxiliary requests 8 to 13.

IV. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA, indicating the board's preliminary opinion with respect to the requirements of Articles 84 and 56 EPC.

V. With a reply dated 11 September 2019 the appellant filed new sets of claims according to a main request and auxiliary requests 1 to 6 and renumbered all previous requests to become auxiliary requests 7 to 20.

VI. At the oral proceedings, the board indicated that the claim requests filed with the letter dated 11 September 2019 had been admitted into the appeal proceedings. The appellant subsequently withdrew all other claim requests.

At the end of the oral proceedings the chair announced the board's decision.

VII. The main request before the board consists of 11 claims. Claim 1 is directed to an immunogenic composition, claims 8 and 9 are directed to a vaccine and to a kit, respectively, comprising the composition of claim 1, and claims 10 and 11 are directed to a process of preparing the vaccine and to a medical use of the composition, respectively.

Claim 1 reads as follows:

"1. An immunogenic composition comprising at least 2 different *N. meningitidis* capsular saccharides, wherein one or more is/are selected from a first group consisting of MenA and MenC, which is/are conjugated through a linker to a carrier protein(s), and one or more different saccharides is/are selected from a second group consisting of MenC, MenY and MenW which is/are directly conjugated to a carrier protein(s) wherein the composition comprises MenA and MenC capsular saccharides conjugated through a linker to a carrier protein(s), and MenY and MenW capsular saccharides directly conjugated to a carrier protein(s) or MenA capsular saccharide conjugated through a linker to a carrier protein, and MenC, MenY and MenW capsular saccharides directly conjugated to a carrier protein(s) and wherein each *N. meningitidis* capsular saccharide is conjugated to the same carrier protein selected from the group consisting of TT, DT, CRM197, fragment C of TT and protein D."

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

D1: WO 2004/103400

D3: Carmenate, T. et al., FEMS Immunology and Medical Microbiology, 2004, 40, 193-199

D4: WO 03/007985

IX. The appellant's arguments, in so far as relevant to this decision, may be summarised as follows:

Tetravalent meningococcal conjugate vaccines were disclosed, for example, in documents D1 and D4. Document D1 could be considered to represent the closest prior art.

As stated at the oral proceedings, the appellant identified the objective technical problem as being the provision of an alternative optimised quadrivalent vaccine which was simpler to produce. This problem was solved by the subject-matter of claim 1.

The preparation of the vaccine was made simpler by having some of the saccharides directly conjugated to the carrier protein instead of via a linker. This could be seen from the application in example 1a, which described the preparation of conjugates using a linker, in comparison with example 1, which described the preparation of conjugates by direct coupling to the carrier. The application provided evidence of a working vaccine in examples 8 and 9.

The skilled person faced with the stated problem had no suggestion in the prior art to change the conjugation chemistry for some of the conjugates but not for others. Moreover, the use of a linker for the MenA conjugate was decisive, as could be seen from example 8, which showed improved immunogenicity in a

composition in which the saccharides of MenC, MenY and MenW were directly linked and the MenA was conjugated via a linker. This improvement was achieved in terms of immunogenicity not only to the MenA serogroup but to the other serogroups too (page 48, first paragraph). This was surprising as effects on immunogenicity were unpredictable.

Thus, the skilled person was not prompted to provide a vaccine with a mixture of conjugate chemistry, nor one in which the conjugate of MenA had a linker.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request or, alternatively, on the basis of one of the sets of claims of auxiliary requests 1 to 6, all filed with the letter dated 11 September 2019.

Reasons for the Decision

Admissibility of the appeal

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Main request

Amendments - Article 123(2) EPC

2. The board is satisfied that the requirements of Article 123(2) EPC are met.

Inventive step - Article 56 EPC

Closest prior art

3. Claim 1 is directed to a composition comprising four conjugates of *N. meningitidis* capsular saccharides with a carrier protein, the saccharide of *N. meningitidis* serogroup A (MenA) being conjugated to the carrier protein via a linker and those of serogroups Y (MenY) and W (MenW) being directly conjugated to the carrier protein. The claim encompasses two embodiments, which differ on account of the conjugation of the serogroup C saccharide (MenC): one composition in which the MenA saccharide is conjugated via a linker whereas the MenC, MenY and MenW saccharides are directly conjugated, and one composition in which both the MenA and MenC saccharides are conjugated via a linker whereas the MenY and MenW saccharides are directly conjugated.

4. The board concurs with the appellant and the examining division that document D1 represents the closest prior art.

Document D1 addresses the provision of improved meningococcal vaccines, in particular multivalent vaccines for *N. meningitidis* serogroups A, C, Y and W135 (MenACYW). To that end, the polysaccharide of each serogroup is provided in a conjugate with a carrier protein. The conjugated saccharides provide improved immune responses in comparison with the unconjugated saccharides (see paragraph bridging pages 3 and 4). Specifically disclosed in the examples are MenACYW vaccines in which each saccharide is conjugated via a linker to diphtheria toxoid (DT) as the carrier protein

(see examples 3, 5 and 6). As detailed in example 5, each conjugate is prepared by a separate reaction involving the conjugation of polysaccharide derivatised with adipic acid hydrazide (ADH, the linker) to the carrier protein in the presence of a carbodiimide (EDAC).

Objective technical problem and its solution

5. The composition of claim 1 is distinguished from the compositions disclosed in document D1 in that the MenY and MenW saccharides or, alternatively, the MenY, MenW and MenC saccharides are directly conjugated.

6. In defining the objective technical problem solved by the claimed subject-matter, the effect associated with the distinguishing feature needs to be established; in this case, the effect is associated with the different conjugation chemistry.

7. The appellant submitted that the claimed composition was a simplification over that disclosed in the prior art, in that the conjugates without any linker were easier to prepare. In this respect, the appellant pointed to the preparation of the directly linked conjugates, exemplified in the description in example 1, in comparison with the preparation of the conjugates having a linker, as described in example 1a.

Upon comparison of those passages, the board comes to the conclusion that it can indeed be accepted that easier preparation is associated with the conjugates used in the claimed composition, not least because a further step – the addition of the linker – is necessary to prepare linker-conjugates.

In the light of this technical effect, the objective technical problem may be formulated as the provision of a working, tetravalent, conjugated MenACYW vaccine which is easier to prepare.

Examples 8 and 9 in the application concern clinical trials with various tetravalent compositions. The observed titers in the serum bactericidal assay (SBA) and the percentage of individuals responsive to the vaccination are indicated. On the basis of the results in these experiments the board is satisfied that the problem of providing a working vaccine is indeed solved.

Thus, on the basis of the application as a whole, it can be accepted that the objective technical problem formulated above is solved by the composition defined in claim 1.

Obviousness

8. It remains to be assessed whether the skilled person starting from document D1 and faced with the problem formulated above would, in an obvious way, have arrived at a composition comprising saccharides provided in a mixed conjugate chemistry as defined in the claim.

9. The most pertinent documents to answer this question are those addressing the preparation of multivalent vaccines and the impact of conjugation methods on the conjugate immunogenicity. In this regard documents D1, D3 and D4 are the most relevant on file; the content of each is considered below in turn.

Document D1, the content of which is summarised above (see point 4.), focuses on the provision of the saccharides in conjugate form - as opposed to non-conjugated forms - without elaborating on preferences for the conjugation method. At best, the skilled person could have inferred from this document a preference for the use of a linker since a linker is used throughout the specific disclosure detailing the conjugate chemistry. In fact, the disclosure in document D1 does not seem to attribute any relevance to the conjugate chemistry.

Document D4, to which the appellant referred in its statement of grounds of appeal, concerns the purification of meningococcal polysaccharides and the preparation of saccharide conjugates and their use in vaccines, including MenACYW vaccines. This document discloses a number of possibilities for the conjugation, stating: "*Any suitable conjugation reaction can be used, with any suitable linker where necessary*" and "*A process involving the introduction of amino groups into the saccharide [...] followed by derivatisation with an adipic ester (e.g. adipic acid N-hydroxysuccinimido diester) and reaction with carrier protein is preferred*" (see page 4, line 26 and page 5, lines 8 to 10). Thus, without providing any discussion on what conjugation chemistry would be preferable, this document states in one instance that the use of a linker would be preferred.

Document D3, referred to by the examining division during the examination proceedings, discloses a study on the impact conjugation has on the immunogenicity and efficacy of a MenC saccharide composition. For this purpose both directly conjugated and linker-conjugated saccharides were prepared. Protein P64K was used as the

carrier in both conjugates. The results of experiments in mice indicated a difference in immunogenicity. Upon evaluating all the data, the authors suggest that the directly linked saccharide resulted in increased immunogenicity (see abstract). The authors note, however, that the conjugates also differed on account of the ratio of carrier to saccharide, observing that, in their experience, that ratio has the greatest influence on the immunogenicity results (see paragraph bridging pages 195 and 196 as well as page 197, right-hand column, first paragraph).

10. Having summarised the content of documents D1, D3 and D4, the board observes that none of those documents addresses the simplification of vaccine preparation.

11. Moreover, documents D1 and D4 both address multivalent vaccines but neither suggests any relevance of conjugate chemistry. At most, these documents disclose a preference for conjugation via a linker.

12. Thus, neither document D1 nor document D4 would motivate the skilled person to modify the conjugate chemistry with the aim of providing a vaccine which is easier to prepare.

13. Additionally, none of the documents before the board discloses multivalent conjugate vaccines in which all the saccharides are directly linked to the carrier protein. Nor do any of the documents suggest providing a mixture of conjugate chemistry.

14. Of the citations above, only document D3 addresses the impact the conjugation chemistry has on the conjugate's immunogenicity. However, the document teaches that modifying the conjugate chemistry is accompanied by

changes to other parameters, all of which also have an impact on the immunogenicity of the resulting conjugate. Moreover, the skilled person would not infer from this document that changing the conjugate chemistry would generally improve immunogenicity. Document D3 would therefore offer them the changing of the conjugate chemistry as a possible modification, one that they could, but not necessarily would, implement when aiming at a vaccine that is easier to prepare.

15. Thus, none of documents D1, D3 or D4 would have led the skilled person to modify only some of the conjugates with a view to providing a vaccine that is easier to prepare.

16. In light of all the above, the board is convinced that the skilled person seeking to provide a tetravalent conjugate MenACYW vaccine that is easier to prepare would not have provided a composition with a mixture of directly conjugated and linker-conjugated saccharides.

17. Thus, the subject-matter of claim 1 is considered to comply with the requirements of Article 56 EPC. The same conclusion applies to the subject-matter of claims 2 to 11 since they all share the features discussed above.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution on the basis of the claims of the main request, filed with the letter dated 11 September 2019.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated