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Datasheet for the decision of 5 July 2016

Case Number: T 1196/12 - 3.3.04

Application Number: 02767756.6

Publication Number: 1409013

IPC: A61K39/39, A61P31/00

Language of the proceedings: EN

Title of invention:
Vaccines comprising aluminium adjuvants and histidine

Patent Proprietor:
Novartis Vaccines and Diagnostics S.r.l.

Opponent:
Wyeth LLC

Headword:
Immunogenic composition/NOVARTIS

Relevant legal provisions:
EPC Art. 56, 114(2)
RPBA Art. 12(4)

Keyword:
Inventive step - main request, auxiliary requests 1 to 6 (no)

Decisions cited:
T 1329/04

Catchword:

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Case Number: T 1196/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 5 July 2016

Appellant: (Patent Proprietor)	Novartis Vaccines and Diagnostics S.r.l. Via Fiorentina 1 53100 Siena (SI) (IT)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	Wyeth LLC Five Giralda Farms Madison, NJ 07940 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 March 2012 revoking European patent No. 1409013 pursuant to Articles 101(2) and 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the proprietor ("appellant") lies against the decision of the opposition division revoking European patent No. 1 409 013 pursuant to Articles 101(2) and 101(3)(b) EPC.

II. The patent at issue has the title "Vaccines comprising aluminium adjuvants and histidine". It was granted in respect of European patent application No. 02767756.6, which originated from international patent application No. PCT/IB2002/003495, published as WO 2003/009869 ("application as filed").

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

D1 WO99/48525

D6 Sworn statement by Giovanna Campanella, dated 10 November 2011

D14 Declaration of Lakshmi Khandke, dated 21 December 2011

D17 Protein purification methods: A practical approach (1989), E. L. V. Harris and S. Angal, editors, pages 254 to 255

IV. The patent was opposed *inter alia* under Article 100(a) EPC on the ground of lack of inventive step (Article 56 EPC).

V. The opposition division held that the subject-matter of claim 1 of the seven requests before it failed to meet the requirements of Article 56 EPC and therefore

revoked the patent.

VI. In its statement of grounds of appeal the appellant maintained the main request (claims as granted) and auxiliary requests 1 to 6 dealt with in the decision under appeal, and provided arguments as to why they fulfilled the requirements of Article 56 EPC.

Claim 1 of the main request reads:

"1. A process for producing an immunogenic composition comprising a mixture of one or more antigens, an aluminium salt and histidine wherein the process comprises: a first step of admixing (i) the aluminium salt and (ii) histidine, to give a histidine/aluminium salt admixture; and a second step of admixing (i) said histidine/aluminium salt admixture and (ii) one or more antigens, wherein one or more antigen(s) is/are adsorbed to the aluminium salt and wherein the antigen is a bacterial antigen selected from the group consisting of:

— a protein antigen from *N.meningitidis;*
— an outer-membrane vesicle (OMV) preparation from *N.meningitidis;*
— a saccharide antigen from *N.meningitidis*."

Claim 1 of auxiliary requests 1 and 3 to 5 is identical to claim 1 of the main request.

Claim 1 of auxiliary requests 2 and 6 differs from claim 1 of the main request in that the aluminium salt is an aluminium phosphate.

VII. In response to the statement of grounds of appeal, the opponent (respondent) filed its counter-arguments and document D17.

VIII. The appellant filed with letter dated 28 August 2015 its reply to the respondent's letter and requested that document D17 be held inadmissible.

IX. Oral proceedings before the board took place on 5 July 2016. At the end of the oral proceedings the chairwoman announced the board's decision.

X. The arguments of the appellant made orally and in writing can be summarised as follows:

Admissibility of document D17

No new requests or arguments had been filed on appeal. Document D17 could have been filed in the first instance proceedings and hence should be held inadmissible in accordance with Article 12(4) RPBA.

It should also not be admitted because it was irrelevant. Its content was not part of the common general knowledge in the field to which the invention related.

Document D17 related to methods for purifying proteins by using an affinity adsorbent in the form of a solid column. The preparative adsorption of proteins in document D17 was unrelated to the adsorption of antigens to aluminium salts in compositions which were administered to animals to raise an immune response.

Main request (claims as granted)

Article 56 EPC

Document D1 was the closest prior art. It disclosed, like the patent, a process in which an aluminium salt adjuvant was pre-treated to modify its adsorptive properties before being used to prepare an immunogenic composition.

The impact of the claimed pre-treatment step was clear from example 2 of the patent and confirmed by the data provided in documents D6 and D14. Example 2, when read in the light of paragraphs [0061] and [0062] of the patent, encompassed the pre-treatment of the aluminium salt with histidine. It confirmed that the addition of histidine modified the aluminium salt's adsorptive properties. It was not known how the addition of histidine changed the aluminium salt, but clearly something was changed. Paragraphs [0061] and [0062] of the patent linked the order of mixing the histidine, the aluminium salt and the antigen to achieving an effect.

Since the pre-treatment with histidine had a demonstrable effect on the adjuvant's adsorptive properties, this step had to be compared with document D1's step of pre-treatment washing rather than with its step of adding a post-adsorption histidine buffer.

Taking document D1 as closest prior art, the problem to be solved was therefore the provision of a process for producing an immunogenic composition comprising an alternative pre-treatment step of the aluminium salts.

Faced with this problem, a person skilled in the art would not have arrived at the claimed invention. The prior art had suggested that there was no interaction between histidine and aluminium salts. Therefore, admixing these two components would not have been expected to alter the adsorptive properties of the aluminium salt and thus to provide a useful "alternative pre-treatment step".

On page 10, line 22, document D1 did not say when histidine should be added and in the examples histidine was always added after adsorption of the antigen to the aluminium salt. There was no suggestion in document D1 to add histidine earlier.

The timing of the addition of histidine could be considered arbitrary only if no effect was achieved by it.

Auxiliary requests 1 and 3 to 5

Article 56 EPC

No additional arguments were submitted.

Auxiliary requests 2 and 6

Article 56 EPC

In these requests the aluminium salt was restricted to aluminium phosphate. In view of the board's opinion regarding the main request it was however not apparent how this restriction might change the board's view.

XI. The arguments of the respondent made orally and in writing can be summarised as follows:

Admissibility of document D17

Document D17 had only been looked for and found when filing the response to the grounds of appeal. Moreover, adsorption was at the core of the claimed invention and document D17 was concerned with affinity adsorption. The document belonged to the common general knowledge of the skilled person in the field and supported the concept that the skilled person would not carry out the adsorption in the absence of a buffer, see also the decision under appeal, page 6, last paragraph. Thus, document D17 had been filed as early as possible in the appeal proceedings, was highly relevant, and should therefore be admitted into the proceedings.

Main request (claims as granted)

Article 56 EPC

The application as filed described the problem to be solved at page 1, lines 27 to 29. The newly formulated problem of the appellant had no basis in the application as filed. According to the headnote of T 386/89 the alleged effect of a described feature could not be taken into account when determining the problem underlying the invention for the purpose of assessing inventive step, if it could not be deduced by the skilled person from the application as filed.

The passage referred to by the appellant - paragraph [0061] of the patent - was silent about any effect associated with adding histidine to the adjuvant before adding the resulting mixture to the antigen.

According to example 2, see paragraph [0080] of the patent, antigen adsorption was evaluated in the presence and absence of a histidine buffer. The process itself, and the order in which the antigen, the aluminium salt and histidine were mixed, were not mentioned in the description of the example. It was also not clear that example 2 was carried out in accordance with the disclosure in paragraphs [0061] and [0062]. There were no data in the patent, in particular in example 2, to show that the adsorptive properties of aluminium were changed by adding histidine to aluminium salt. Under these circumstances the appellant could not rely on data in documents D6 and D14 which had been generated only after the filing date of the application, see also the headnote of T 1329/04.

The problem could be formulated as the provision of an alternative process for producing an immunogenic composition comprising a mixture of one or more antigens, an aluminium salt and histidine. It was accepted that this problem was solved.

Changing the order of the process steps was arbitrary and not inventive. The options as to precisely when histidine could be added were limited. Moreover, document D1 disclosed that in un-washed aluminium phosphate the free phosphate ions had a disadvantageous effect. It therefore recommended using a histidine buffer, see page 10, lines 22 to 25.

Auxiliary requests 1 and 3 to 5

Article 56 EPC

The arguments relating to the main request applied *mutatis mutandis* to these auxiliary requests.

Auxiliary requests 2 and 6

Article 56 EPC

The limitation to aluminium phosphate did not change the fact that document D14 showed that no effect of histidine pre-treatment was observed.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained unamended or, alternatively, on the basis of one of auxiliary requests 1 to 6 filed with letter dated 17 November 2011.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Admissibility of document D17

1. The respondent filed document D17 with its response to the statement of grounds of appeal. However, it provided no valid explanation, let alone justification, for filing it at this stage in the proceedings. As the appellant had not filed any new claim requests on appeal and as the common general knowledge of the skilled person was not in dispute, the board was not persuaded that document D17 could not have been filed earlier, i.e. during the opposition proceedings.

2. Therefore, it was in the board's discretion whether or not to admit document D17 in the appeal proceedings (Article 114(2) EPC and Article 12(4) RPBA).

3. When exercising its discretion under Article 114(2) EPC and Article 12(4) RPBA, the board had regard, *inter*

alia, to the relevance of document D17. Document D17 relates to methods for purifying proteins by using an affinity adsorbent in the form of a solid column (see page 254, point 3.1). The respondent submitted that document D17 illustrated the common general knowledge of the skilled person and was thus relevant. The board considered that the preparative adsorption of proteins was unrelated to the adsorption of antigens to aluminium salts for the preparation of immunogenic compositions. Therefore, document D17 was not considered to be even part of the common general knowledge in the field of vaccine formulation, to which the invention relates (see paragraph [0001] of the patent).

4. For these reasons the board decided in the exercise of its discretion under Article 114(2) EPC and Article 12(4) RPBA to not admit document D17 in the appeal proceedings.

Main request (claims as granted)

Article 56 EPC

Closest prior art

5. The parties agreed that document D1 is the closest prior art and the board sees no reason to differ.

6. Document D1 relates to a method for making combination vaccines that are able to maintain stable adsorption of each antigen onto an aluminium-based adjuvant (see page 3, lines 16 to 20). The method disclosed in document D1 involves washing the aluminium phosphate prior to adsorption of antigen, so that the free phosphate ion concentration is reduced. The antigen is then adsorbed

to the extra-washed aluminium phosphate (see page 10, lines 12 to 21). Document D1 further discloses that any buffer used in the combination vaccine to stabilise the pH should preferably be cationic and most preferably L-histidine monohydrate/monochloride (see page 10, lines 23 to 25). In addition to DTPa antigens and Hib, the combination vaccine of document D1 may also comprise other antigens such as *N.meningitidis* A capsular polysaccharide and *N.meningitidis* C capsular polysaccharide (see page 6, lines 25 to 29).

The technical problem to be solved

7. The process according to claim 1 differs from the process disclosed in document D1 in that the aluminium salt and histidine are admixed to give a histidine/ aluminium salt mixture which is then admixed with the antigens, while in the process of document D1 the histidine is added to the antigen/aluminium salt mixture (see e.g. example 1, step 4). In other words, the order of mixing the aluminium salt, the antigen and the histidine differs.

8. Concerning the technical effect related to this difference, the appellant submitted that the purpose of admixing the aluminium salt and histidine was generally to change the aluminium salt's adsorptive properties during antigen adsorption, whereby the change could also involve a reduction in overall adsorptive capacity. The appellant therefore formulated the problem to be solved as the provision of a process for producing an immunogenic composition comprising an alternative pre-treatment step of the aluminium salts.

9. The board notes that this problem differs from the objective set out in the application as filed.

According to page 1, lines 27 to 29 of the application as filed, it was "an object of the invention to provide improvements in the stability of vaccines which include aluminium salts and, in particular, improvements in pH stability (buffering) and adjuvant adsorption at various temperatures and/or improvements in antigen stability (e.g. reduction in hydrolysis)."

10. In principle, any effect provided by the invention may be used as a basis for reformulating the technical problem, as long as that effect is derivable from the application as filed (see Case Law of the Boards of Appeal, 7th edition 2013, section I.D.4.4.1).

11. The appellant relied primarily on example 2 of the patent as providing evidence that a pre-treatment effect of histidine on aluminium salts occurred, while documents D6 and D14 were relied on as providing further supporting data.

12. The board notes that example 2 of the application as filed (which is identical to example 2 of the patent) relates to the adsorption of a conjugate of meningococcus serogroup C oligosaccharide (MenC) and a CRM_{197} carrier protein to an aluminium adjuvant. It is explained that "CRM_{197} is acidic and thus does not completely adsorb to negatively charged aluminium phosphates. Histidine, however, is positively charged and it was thought that this might be able to mask the negative charge. Histidine buffer was thus tested with the aim of improving adsorption of MenC-CRM_{197} to aluminium hydroxyphosphate. Antigen adsorption was evaluated in the presence and absence of histidine buffer by measuring protein concentration in the vaccine supernatant using the BCA protein assay, after centrifugation to separate the adjuvant pellet." It

concludes that "antigen adsorption thus improves when histidine is present in the formulation". The board accepts that example 2 shows that under the particular circumstances tested, i.e. an acidic carrier protein in combination with aluminium hydroxyphosphate as aluminium salt, adsorption improves when histidine is present in the formulation.

13. However, example 2 is silent as regards the order in which the aluminium salt, the antigen and histidine were mixed. The board considers that from the mere statement that antigen adsorption improved "when histidine is present in the formulation" it is impossible to directly and unambiguously conclude that the aluminium salt and histidine were admixed to give a histidine/aluminium salt mixture which was then admixed with the antigen.

14. The appellant further submitted that example 2 had to be understood in the light of paragraphs [0061] and [0062] of the patent, which are both also present in the application as filed. The paragraphs read as follows: "[0061] Histidine is thus present during adsorption to the aluminium salt. This compares with adding histidine to an antigen/aluminium salt combination which already exists *i.e.* the histidine in the process is not simply added as a buffer after antigen and aluminium salt have interacted, but instead it is present during their interaction.
[0062] In the process of the invention, therefore, antigen is preferably admixed with a histidine/ aluminium salt mixture (...)."

15. There is nothing in example 2 to indicate to the skilled person that this example has been carried out according to the teaching of paragraphs [0061] and

[0062]. The board is thus not convinced that example 2 has been carried out according to the process of claim 1. Consequently, the technical effect of the feature distinguishing the claimed process from the prior art process is not derivable from example 2.

16. There is no other disclosure in the application as filed that indicates that the adsorptive properties of aluminium are changed - i.e. decreased or increased - by adding histidine to aluminium salts.

17. The board concludes that the effects relied on by the appellant in its formulation of the problem are not derivable from the application as filed. Under these circumstances, the appellant cannot rely on the data in documents D6 and D14, which were generated only after the filing date of the application, because inventive step - like all other patentability requirements - must be ascertained at the effective date (see e.g. T 1329/04, reasons, point 12).

18. No effect of adding histidine, beyond working as a buffer, is derivable from the application as filed. The purpose of adding histidine in the present claims is thus considered to be the same as in document D1.

19. In the board's judgement, starting from document D1, the technical problem to be solved can thus be formulated as the provision of an alternative process for producing an immunogenic composition comprising a mixture of one or more antigens, an aluminium salt and histidine. The board is satisfied that the subject-matter of claim 1 solves this technical problem.

Obviousness

20. The question is whether the skilled person faced with the technical problem defined in point 19 above would have modified the teaching in the closest prior art document D1 so as to arrive at the claimed invention in an obvious manner.

21. The skilled person faced with the problem of providing an alternative process for producing an immunogenic composition is free to choose the order in which the histidine buffer, the aluminium salt and the antigen are mixed. Adding the histidine to the aluminium salt before admixing the antigen is thus one of the possible solutions available. In the absence of any surprising technical effect, linked to the selected order of steps, distinguishing the claimed solution from all other possible solutions, it has to be considered an arbitrary selection of one of several equally available alternatives. The claimed process is therefore to be regarded as obvious (see also Case Law of the Boards of Appeal, *ibid.*, section I.D.9.18.7).

22. The board considers moreover that document D1 in any case provides an incentive to use the histidine early in the process to reduce the disadvantageous effect of free phosphate ions if un-washed aluminium phosphate is used to adsorb the antigen (see point 6 above). Thus, by following this teaching in document D1 the skilled person would also have arrived in an obvious manner at the claimed process.

23. For the reasons set out above the main request fails to meet the requirements of Article 56 EPC.

Auxiliary requests 1 and 3 to 5

Article 56 EPC

24. Claim 1 of auxiliary requests 1 and 3 to 5 is identical to claim 1 of the main request. The reasoning set out above for the main request (see points 5 to 23) therefore applies *mutatis mutandis* to the subject-matter of claim 1 of auxiliary requests 1 and 3 to 5.

25. Therefore, auxiliary requests 1 and 3 to 5 likewise fail to meet the requirements of Article 56 EPC.

Auxiliary requests 2 and 6

Article 56 EPC

26. Claim 1 of these requests differs from claim 1 of the main request in that the aluminium salt has been defined as being aluminium phosphate. This is the same aluminium salt as used in document D1. The reasoning set out above for claim 1 of the main request (see points 5 to 23) thus applies *mutatis mutandis* also to the subject-matter of claim 1 of auxiliary requests 2 and 6.

27. Therefore, auxiliary requests 2 and 6 also fail to meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated