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Datasheet for the decision of 13 January 2022

Case Number: T 1514/17 - 3.3.04

Application Number: 14166316.1

Publication Number: 2769734

IPC: A61K39/05, A61K39/39, A61K35/74, A61K39/00

Language of the proceedings: EN

Title of invention:
A vaccine directed against porcine pleuropneumonia and a method to obtain such a vaccine

Applicant:
Intervet International B.V.

Headword:
Apx subunit vaccine with polymyxin/INTERVET

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:
Inventive step - (no)
Late-filed line of argument - adjournment of oral proceedings would have been required (yes)

Decisions cited:
G 0001/92, T 0953/90, T 0969/90

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Beschwerdekammern

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Case Number: T 1514/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 January 2022

Appellant: (Applicant)	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer (NL)
Representative:	Intervet International B.V. Hertford Road Hoddesdon, Hertfordshire EN11 9BU (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 20 February 2017 refusing European patent application No. 14166316.1 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	P. de Heij
Members:	A. Chakravarty
	A. Schmitt

Summary of Facts and Submissions

I. The appellant (applicant) filed an appeal against the decision of the examining division to refuse European patent application No. 14 166 316.1 entitled "*A vaccine directed against porcine pleuropneumonia and a method to obtain such a vaccine*".

II. The decision was a "decision according to the state of the file", as requested by the appellant and was issued using EPO Form 2061 which reads:
"*Grounds for the decision - In the communication(s) dated 30.08.2016, 21.07.2015 the applicant was informed that the application does not meet the requirements of the European Patent Convention. The applicant was also informed of the reasons therein. The applicant filed no comments or amendments in reply to the latest communication but requested a decision according to the state of the file by a letter received in due time on 06.12.2016. The application must therefore be refused*".

III. In the communication dated 30 August 2016, the examining division held that the subject matter of *inter alia* claim 1 of the main request lacked an inventive step. The reasons for this were as follows: The commercially available Porcilis® App vaccine disclosed in document D16 represented the closest prior art. The claimed vaccine differed from the one disclosed in document D16 in that it further comprised polymyxin. The technical effect of this difference was a reduction in the symptoms of toxic shock associated with lipopolysaccharide (LPS). In view of this, the technical problem was the "*provision of an APP vaccine with reduced side effects*". The skilled person starting from the vaccine disclosed in document D16 would have

considered the addition of polymyxin B as obvious in view of the disclosure in any of documents D5, D7 and D18, that polymyxin was "*a 'simple means' to reduce the inflammatory activity of LPS in vaccine of gram-negative bacteria, and that polymyxin reduced the toxicity* ***but not the immunogenicity*** *of LPS*".

IV. In their statement of grounds of appeal the appellant requested that the decision under appeal be set aside and that a patent be granted based on the set of claims filed with the letter dated 7 October 2015 and considered by the examining division in the decision under appeal, as a main request. They also requested that "*if deemed necessary to comply with any objection of the Board of Appeal to amend claim 1 by introducing one or more of the restrictions of the dependent claims 2-6, or to delete on or more of the dependent claims, or to introduce features as present in the application as filed in claim 1, in particular features related to the type of polymyxin used, i.e. either polymyxin B or E*".

V. Claim 1 of the main request reads as follows:

"1. A vaccine directed against porcine pleuropneumonia, comprising lipopolysaccharide that originates from *Actinobacillus pleuropneumoniae* purified from a bacterial culture complexed with one or more repeats in toxins ApxI, ApxII and ApxIII, characterised in that the vaccine comprises a polymyxin to reduce symptoms of an endotoxic shock arising from the lipopolysaccharide".

VI. The board appointed oral proceedings as requested by the appellant and, subsequently, issued a communication pursuant to Article 15(1) RPBA. In this communication

the board informed the appellant that it could not consider claim requests that had not been presented and that corresponding sets of claims should be filed.

VII. The appellant replied to the board's communication. In this reply they stated "*with this response applicant files six auxiliary requests*". They also explained which amendments these auxiliary requests contained. However, sets of claims of these six auxiliary requests were not received by the board.

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

D3: Mahendrasingh R. *et al*. Molecular Microbiology, "*Mutation in the LPS outer core biosynthesis gene, galU, affects LPS interaction with the RTX toxins ApxI and ApxII and cytolytic activity of Actinobacillus pleuropneumoniae serotype 1*", 70(1), 29 August 2008 pages 221-235.

D5: Cooperstock M. and Riegle L. "*Polymyxin B Inactivation of Lipopolysaccharide in Vaccines of Gram Negative Bacteria*", Infection And Immunity, vol. 33(1), 1 July 1981, pages 315-318.

D7: Bannatyne R. M. and Cheung R. "*Reducing the endotoxic activity of pertussis vaccine*", Journal Of Hygiene, vol. 87, no. 3, 1981, pages 377-382.

D11: Bhor V. M. *et al*. "*Polymyxin B: An ode to an old antidote for endotoxic shock*", Molecular Biosystems, vol. 1, 29 July 2005, pages 213-222.

D13: EP-A-0 453 024

D16: Ridremont B. *et al.* "*Laboratory study of APP vaccination with a subunit vaccine on antibody serological response in SPF piglets*", Proceedings of the 19th IPVS Congress, Copenhagen, Denmark, vol. 2, Abstract No: P.16-01, 16 July 2006, 19 July 2006, page 235.

D18: Larter W.E. *et al.* "*In Vivo Effect of Polymyxin B on Pertussis Vaccine*", American Journal of Diseases of Children, vol. 1388(3), 1 March 1984, pages 281-283.

D25: Brown D.A. and Tsang J.C. "*Effect of polymyxin B on the antigenicity of outer membrane from Serratia Marcescens*", Microbios Letters, vol. 2, no. 7-8, January 1976, pages 189-196.

D26: Weber D.A. and Tsang J.C. "*Immunochemical behavior of lipopolysaccharides from Serratia-Marcescens after polymyxin B treatment*", Microbios Letters, vol. 1, no. 2, 1976, pages 125-130.

IX. Oral proceedings took place before the board on 13 January 2022. During these oral proceedings the appellant filed a set of claims as a first auxiliary request. Claim 1 of this request reads as follows:

"1. A vaccine directed against porcine pleuropneumonia, comprising lipopolysaccharide that originates from *Actinobacillus pleuropneumoniae* purified from a bacterial culture complexed with one or more repeats in toxins ApxI, ApxII and ApxIII, wherein the vaccine comprises a polymyxin to reduce symptoms of an endotoxic shock arising from the lipopolysaccharide, characterised in that the vaccine comprises less than 2000 IU of polymyxin per dosis [sic]".

X. At the end of the oral proceedings the Chair announced the decision of the board.

XI. The appellant's arguments, relevant to the decision, are summarised as follows.

Main request - claim 1
Inventive step (Article 56 EPC)

Starting from document D16 representing the closest prior art, the objective technical problem to be solved was to provide an improved vaccine having reduced side effects while maintaining the efficacy of Porcilis® App vaccine.

The examining division was wrong to hold that the claimed subject-matter was obvious. It had ignored that at the relevant date, the skilled person would have known that the commercially available vaccine used in the closest prior art document D16, Porcilis® App, contained LPS in an immunogenic complex with the repeats in toxins ApxI, ApxII and/or ApxIII. This was common general knowledge as shown in document D3 and the references therein. Indeed, LPS in complex with the other protein antigens was an explicit feature of the claim.

Furthermore, the disclosure in document D13 supported the line of argument that the skilled person knew that the Porcilis® App vaccine comprised Apx toxins in complex with LPS. The document disclosed *inter alia* the process used to produce the Porcilis® App vaccine. The skilled person would have recognised that, due to its production in bacterial culture, the Apx toxin was inherently produced in complex with LPS. Moreover, they could have verified the molecular weight of the toxins

produced using routine methods of analysis and would have immediately realised that the molecular weight measured could only correspond to Apx toxins in complex with LPS.

In addition, during the oral proceedings on the subject of whether or not the skilled person knew that Porcilis® App contained LPS in an immunogenic complex with the repeats in toxins ApxI, ApxII and/or ApxIII, the appellant put forward that the commercial availability of the Porcilis® App vaccine meant that all of its characteristics, including the fact that LPS and the Apx toxins were in complex, were available to the public. To find out the actual structure of the commercial vaccine, it could be analysed using routine techniques to determine the size of the proteins contained therein. Doing this the skilled person would have found out that the size of the proteins did not correspond to known sizes of the Apx toxins but to a considerably larger Apx/LPS complex.

The skilled person would also have known that the association between the LPS molecule and the Apx toxins was a critical factor for toxin activity. As they would have wanted to maintain efficacy, they would not have done anything that they knew would destroy or negatively influence the LPS-toxin complex, the major immunogen in this vaccine. They also knew from the disclosure in each of documents D5, D7, D11, D18, D25 and D26 how polymyxin acted on LPS and would have therefore known that it would interfere with the LPS-toxin complex which was essential for the efficacy of the claimed vaccine. They would therefore have expected that vaccine efficacy would be negatively influenced by the addition of polymyxin.

In summary, the skilled person had no reasonable expectation that by adding polymyxin, the vaccine efficacy of Porcilis® App would be maintained at an equal level to that without the polymyxin.

Auxiliary request - claim 1
Admission of a line of argument on inventive step (Article 13(1) and (3) RPBA 2007)

The claim specified that the vaccine comprised less than 2000 IU of polymyxin per dose. This low dose was not obvious to the skilled person from the prior art and the claimed subject-matter was therefore inventive. This line of argument was not a change of case and was therefore admissible because it was a development of the arguments in the statement of grounds of appeal (see paragraph 3 on page 7) and also had been a topic in the proceedings before the examining division.

XII. The appellant requested that the decision under appeal be set aside and a patent be granted based on the set of claims of the main request filed with the letter dated 7 October 2015 or, alternatively, based on the set of claims of auxiliary request 1 filed during the oral proceedings before the board.

Reasons for the Decision

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

The decision under appeal

2. The decision refusing the application referred to two communications of the examining division, the first

dated 21 July 2015 and the second dated dated 30 August 2016. The first communication dealt with the set of claims dated 12 February 2015. In this communication, the examining division raised objections under Articles 83 and 84 EPC. In the reply, dated 7 October 2015, the appellant submitted an amended set of claims and presented arguments concerning Articles 83 and 84 EPC.

3. The communication dated 30 August 2016 was issued together with the summons to oral proceedings. It raised objections under Articles 56, 83 and 84 EPC not mentioned in the previous communication. The objections raised in the communication 21 July 2015 were not mentioned again.

4. Since the communication dated 21 July 2015 raised objections to a set of claims superseded by the set of claims filed 7 October 2015, the board considers that the objections raised in the communication dated 21 July 2015 did not form part of the grounds for the decision to refuse the application, even though this communication was explicitly mentioned on EPO Form 2061.

Main request - claim 1
Inventive step (Article 56 EPC)

5. The claimed subject-matter is a product. The product is a vaccine composition comprising lipopolysaccharide (LPS) that originates from *Actinobacillus pleuropneumoniae* purified from a bacterial culture complexed with one or more ApxI, ApxII and ApxIII toxins (referred to in the claim as "repeats in toxins"). This vaccine further comprises a polymyxin. The claim specifies that the polymyxin is present "*to*

reduce symptoms of an endotoxic shock arising from the lipopolysaccharide". The board understands this to require that the amount of LPS is sufficient for this purpose.

6. In the decision under appeal, the commercial subunit *Actinobacillus pleuropneumoniae* vaccine comprising repeats in toxins ApxI, ApxII, ApxIII (Porcilis® App) disclosed in document D16 was said to represent the closest prior art for the claimed invention. The examining division held that the claimed subject-matter was obvious to the skilled person starting from the closest prior art, in the light of the disclosure in any of documents D5, D7 and D18 (see section III., above).

7. The appellant's arguments as to why the examining division was wrong to hold the subject matter of claim 1 as obvious rely entirely on the assumption that it was known to the skilled person at the relevant date, that the repeats in toxins ApxI, ApxII and ApxIII, present in the Porcilis® App vaccine, existed in complex with LPS. They had two main lines of argument which were purported to show that this was the case. The first was that the relevant information was available from the disclosure in document D3 as well as from documents referenced therein and also from the disclosure in document D13, which was a patent application disclosing the manufacture of the Porcilis® App vaccine. The second was based on the commercial availability of the Porcilis® App vaccine mentioned in document D16.

8. The board, having reviewed the available evidence, is not persuaded that the skilled person knew that the repeats in toxins ApxI, ApxII and ApxIII, present in

the Porcilis® App vaccine existed in complex with LPS, let alone that the complex formed the major immunogen in the vaccine.

9. Document D16 itself makes no mention of such a complex. It can be taken from the abstract that the authors considered that Porcilis® App was "*a subunit multivalent vaccine indicated for piglets and based on 3 Apx toxins (Apx I, Apx II, Apx III) and an OMP protein*". Residual LPS is mentioned in the discussion as an explanation for induced cross reactivity seen mainly with ELISA LPS tests: "*An explanation could be the presence of residual LPS in the subunit vaccine*" (see page 235, right column, "*Discussion*").

10. In the board's view, this disclosure imparts that the authors were surprised by the cross-reactivity with LPS and sought to explain it. The skilled person reading document D16 would therefore have considered that the Porcilis® App vaccine primarily consisted of three Apx toxins and an OMP protein. They would have considered any LPS present to be "*residual*", i.e. not as an essential constituent of the vaccine.

11. The appellant submitted that the knowledge that Apx toxins in the Porcilis® App vaccine existed in a complex with LPS was well established in the art, for instance from documents D3 and D13.

12. Document D3 was said to disclose details about the interaction between LPS and the Apx I and Apx II toxins via the core oligosaccharide (see abstract). The association between LPS and the toxin proteins had long been known in the art as was disclosed in the discussion section and the references mentioned therein (see page 228, right column).

13. However, document D3 does not concern or even mention the Porcilis® App vaccine. The board can accept that the skilled person knew from document D3 that LPS and Apx toxins could associate with each other. There is however nothing in this document to the effect that the Apx toxins in the commercially available Porcilis® App vaccine existed in a complex with LPS. Thus, the skilled person could draw no conclusions about the composition of this vaccine from document D3.

14. The board notes that at oral proceedings, the appellant also argued that skilled person would have known that Apx toxins in the Porcilis® App vaccine existed in a complex with LPS from the documents referenced in document D3. However, since none of these documents is on file, the board cannot take their disclosure into consideration, in as far as it goes beyond that reproduced in document D3 itself.

15. Turning to the disclosure in document D13, in the board's view this does the opposite of what was argued for by the appellant. Document D13 reports the molecular weight of the Apx toxin (referred to therein as hemolysin) as being 105 kD, i.e. the molecular weight of the toxin on its own (see page 8, section 2).

16. The only reference to products having a higher molecular weight is found in the passage bridging pages 8 and 9 which reads "*Hemolysin purified from serotype 1 and serotype 5b reference strain following the procedure described in the Methods, both showed a band in SDS-PAGE at 105 kD after CBB staining. A gel scan of purified serotype 5b hemolysin is shown in Fig. 4. Although the apparent MW in SDS-PAGE appeared to be approx. 105 kD, native hemolysin was retained during filtration using a filter with a MW cut-off of 300 kD.*

Furthermore, from the elution profile obtained in gel filtration it was concluded that the native hemolysin or aggregates thereof have a MW of at least 10x10^6 D (Fig. 5)".

17. From this it is apparent that the authors of document D13 were not of the view that high molecular weight forms were the result of the formation of a complex between Apx toxins and LPS, but rather considered that they were the result of hemolysin (Apx) aggregate formation.

18. Documents D5, D7, D11, D18 were cited to show that the skilled person knew that the LPS-protein complex would be disrupted by the binding of polymyxin to the LPS. The board accepts that the skilled person knew the mechanism by which polymyxin acts on protein/LPS complexes. However, this was not at issue here. Rather, the board is of the view that it has not been established that the skilled person at the relevant date knew that in the commercially available Porcilis® App vaccine, the Apx toxins were in complex with LPS.

19. Documents D25 and D26 were also cited by the appellant in support of the view the the skilled person at the relevant date knew that polymyxin would interfere with the LPS-Apx complex in the Porcilis® App vaccine.

20. However, both documents D25 and D26 concern the effect of polymyxin B on the antigenicity of LPS/outer membrane from *S. marcescens*. The skilled person reading them would not be able to draw any conclusions about the composition or structure of the Porcilis® App vaccine.

21. In a second line the appellant argued that the commercial availability of the Porcilis® App vaccine meant that all of its characteristics, including the alleged fact that LPS and the Apx toxins were in complex, were available to the skilled person. In their view, the skilled person would have merely needed to analyse the commercially available vaccine using standard techniques. Doing this, they would have found out that the size of the proteins did not correspond to known sizes of the Apx toxins but to the considerably larger Apx/LPS complex.

22. It is likely that the appellant had in mind the case law of the Boards of Appeal, according to which the internal structure of a product in prior use is made available to the public when a skilled person, relying on the normal means of investigation available, would have been able to analyse the product (see for example opinion G 1/92 of the Enlarged Board of Appeal (EBA) and decisions T 0953/90, T 0969/90).

23. In the present case, the board considers that the internal structure of the commercially available Porcilis® App vaccine as far as it concerns its composition, e.g. the fact that it contains Apx toxins and residual LPS was indeed state of the art. However, the board has seen no convincing evidence of the allegation that the Porcilis® App vaccine actually contains Apx toxins in complex with LPS, for instance in the form of an analysis of the relevant Porcilis® App vaccine. The findings of the EBA in Opinion G1/92 are therefore moot.

24. The fact that LPS in complex with Apx toxins is a feature of the claim does not advance the appellant's case on obviousness either, since the claim formulation

cannot alter the skilled person's knowledge of the state of the art at the relevant date and therefore cannot alter the board's assessment of obviousness according to the problem and solution approach.

25. In view of the above considerations, the board concludes that it has not been established that the skilled person at the relevant date knew that in the commercially available Porcilis® App vaccine, mentioned in document D16, the Apx toxins were in complex with LPS.

26. All of the appellant's submissions on the inventive step of the claimed subject matter rely on the skilled person at the relevant date knowing that in the commercially available Porcilis® App vaccine, mentioned in document D16, the Apx toxins were in complex with LPS. Since this had not been shown to the board's satisfaction, the appellant's submissions on inventive step must fail.

27. The board has therefore seen no persuasive reasons why the decision of the examining division that the subject matter of claim 1 lacks an inventive step should be overturned.

Auxiliary request - claim 1

Admission of a line of argument on inventive step (Article 13(1) and (3) RPBA 2007)

28. As the summons to oral proceedings was notified before the date of entry into force of the RPBA 2020, Article 13 RPBA 2007 is applicable to the admission of auxiliary request 1 and the associated line of argument

on inventive step into the appeal proceedings (Article 25 RPBA 2020).

29. This claim request was filed during the hearing before the board. The board admitted it into the appeal proceedings because the appellant could reasonably have been confident that their auxiliary requests (see section VII.) had been received and would therefore be considered by the board.

30. The appellant argued that the subject-matter of this claim request was inventive because of the particularly low dose of polymyxin used. They submitted that this was not a new line of argument presented for the first time at the hearing but rather had already been developed in the statement of grounds of appeal at page 7, third paragraph. This paragraph reads as follows:

"*So **D7** even makes a reservation regarding vaccine efficacy for a vaccine where in the LPS is not part of the essential immunogen. This makes even more clear that **D7** does not even remotely teach that for a vaccine wherein the LPS is actually part of the essential immunogen of the vaccine that "the powerful endotoxin disruptor polymyxin (as **D7** calls it) polymyxin will not negatively interfere with a LPS-protein immunogenic complex, let alone the LPS-Apx complex of the vaccine of **D16**. Interestingly (cf present claim 2), **D7** also discusses the level of polymyxin that would be needed to reduce the endotoxic effect of the LPS naturally present in the outer membrane of the bacteria in the vaccine: it is stated that a "more realistic concentration" would be "5000 µg of polymyxin/ml" (page 380, lines 1-3 of third paragraph), i.a. about 42.000*

(42 thousand) IU/ml, i.e. more than 20 times the amount according to the embodiment of claim 2".

31. In the board's view, the above referenced paragraph cannot be taken as containing an argument as to why the subject matter of claim 1 (then pending claim 2), which specifies that the vaccine comprises less than 2000 IU of polymyxin per dose, is inventive. In the paragraph it is merely noted that document D7 "*interestingly*" discusses the level of polymyxin that would be needed and that these were higher than the amount specified in the claim. The arguments presented at the oral proceedings before the board implying that this additional feature would overcome the inventive step objection against the subject-matter of the main request are therefore a change of the appellant's case.

32. Pursuant to Article 13(1) RPBA 2007, "(1) Any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the Board's discretion. The discretion shall be exercised in view of *inter alia* the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy". Article 13(3) RPBA 2007 provides that "Amendments sought to be made after oral proceedings have been arranged shall not be admitted if they raise issues which the Board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings".

33. In the present case admitting the appellant's argument on inventive step would have meant that the board was faced with a line of argument that had not been developed before and for which it was not prepared. Taking it into account would therefore have required

the adjournment of the oral proceedings. Such an action would naturally not be procedurally economic. For this reason alone the change of case could not be admitted into the appeal proceedings.

34. In view of the above, no claim request on file is allowable and the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

A. Chavinier-Tomsic P. de Heij

Decision electronically authenticated