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**Datasheet for the decision
of 23 August 2018**

Case Number: T 0816/14 - 3.3.04

Application Number: 04744126.6

Publication Number: 1644035

IPC: A61K39/095, B01D61/14,
C12R1/36, C07K16/12

Language of the proceedings: EN

Title of invention:

Ultrafiltration and ultracentrifugation for preparing outer
membrane vesicles

Patent Proprietor:

Novartis Vaccines and Diagnostics S.r.l.

Opponent:

The Kingdom of the Netherlands, represented by
the Minister of Public Health, Welfare and Sports

Headword:

Ultrafiltration of OMVs/NOVARTIS

Relevant legal provisions:

EPC Art. 123(2), 111(1)

Keyword:

Amendments - added subject-matter (no)

Decisions cited:

Catchword:



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Case Number: T 0816/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 23 August 2018

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 20 January 2014
revoking European patent No. 1644035 pursuant to
Article 101(3) (b) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
P. de Heij

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. 1 644 035, entitled "*Ultrafiltration and ultracentrifugation for preparing outer membrane vesicles*". The patent was granted in respect of European patent application No. 04 744 126.6, published as international application No. WO 2005/004908.
- II. The patent was opposed on the grounds of Article 100(a), lack of novelty and inventive step, Article 100(b), lack of sufficient disclosure and Article 100(c), added subject-matter.
- III. The opposition division held that claim 1 and paragraph [0009] of the patent did not comply with the requirements of Article 123(2) EPC because "*the insertion of the term "crude" [...] lacks basis in the application as filed*". In an *obiter dictum*, the opposition division stated that, in its opinion, the claimed invention complied with the requirements of Article 83 EPC.
- IV. Claim 1 as granted read:
- "1. A process for preparing bacterial outer membrane vesicles (OMVs) for use in vaccines, comprising steps of: (i) ultrafiltration performed on an aqueous suspension of crude OMVs that have been prepared from Gram negative bacteria, wherein the OMVs remain in suspension after the ultrafiltration step; (ii) ultracentrifugation of the suspension; and (iii) re-suspension of ultracentrifuged OMVs from the ultracentrifugation pellets".

V. The board issued a summons to oral proceedings together with a communication pursuant to Article 15(1) RPBA in which it informed the parties that review of the opposition division's decision on Article 123(2) EPC would be the main consideration in the appeal and at the oral proceedings before the board. It further informed the parties that, should it come to the conclusion that the appeal was allowable, it was minded to remit the case to the opposition division for further prosecution.

VI. The following documents are mentioned in this decision.

D1: US 2003/059444

D8: WO 01/91788

VII. The appellant's arguments, made in writing, are summarised as follows:

The main issue in the appeal was whether a process according to claim 1 as granted, which was *inter alia* characterised in that ultrafiltration is performed on 'crude' outer membrane vesicles (OMVs), was subject-matter that extended beyond the content of the application as filed (the application).

As correctly recognised in section 2.5 of the decision under appeal, the term 'crude' was commonly used in the art to describe OMVs which had been separated from bacteria (usually by centrifugation) but which had not been further treated, except for trivial steps such as concentration or dilution. The application also taught the skilled person to perform ultrafiltration directly on an aqueous suspension of OMVs after they were prepared from bacteria (see page 3, lines 8 to 9).

Performing 'pre-ultrafiltration steps', as disclosed at page 3, lines 1 to 30 of the application, was also consistent with the common meaning of obtaining 'crude' OMVs.

The cited page mentioned various steps which might be performed between OMV formation and ultrafiltration and the resulting material would still be seen as 'crude' by the skilled reader even though it has been treated in one of these ways. For instance, the product obtained after the centrifugation step for separation from bacterial cells and cell debris, disclosed at lines 19 to 22, was nevertheless 'crude'.

The use of 'crude' to describe OMVs obtained after a centrifugation step was also supported in the prior art, e.g. in document D1, paragraph [0089] and document D8, page 18, lines 12-13, and page 30, lines 14-17.

The remaining methods mentioned on page 3, at lines 23 to 27 of the application were explicitly referred to as alternatives to this centrifugation step and the product obtained from them would also have been seen as 'crude'. Thus, methods including 'pre-ultrafiltration steps', such as disclosed at page 3, lines 1 to 30 of the application, resulted in OMVs consistent with the common meaning of 'crude' OMVs.

In summary, although claim 1 as granted contained the extra word 'crude', the method it related to did not contain any technical information not present in the application.

VIII. The respondent's arguments, made in writing, are summarised as follows:

Claim 1 of the patent as granted had been amended to require that the ultrafiltration in step (i) of the claimed process was carried out on 'crude' OMVs, not on OMVs in general.

The appellant took the position that the term 'crude' OMVs had a specific technical meaning which excluded that the OMVs were treated or processed in any other way, e.g. by steps including ion exchange chromatography as disclosed in document D1. According to the appellant, the term 'crude' OMVs was well known in the art to have such a meaning.

However, none of the documents cited by the appellant supported the view that the term 'crude' OMVs was known in the art to refer to "*OMVs which have been separated from bacteria (usually by centrifugation) but which had not been further treated, except for trivial steps such as concentration or dilution*". Thus, the skilled person could not have relied on common general knowledge for a consistent interpretation of the term as required for the appellant's reasoning to succeed.

Even if the appellant were correct in the assessment that the art contained a consistent interpretation of the term 'crude' OMVs, disclosures in the application directly contradicted this. In particular, the "*Other methods*" disclosed at lines 22 to 26 at page 3, explicitly taught further treatments of the OMVs prior to ultrafiltration.

The appellant's argument that these "*Other methods*" were no more than alternatives for the separation of

OMVs from bacterial and cell debris (see statement of grounds of appeal page 2, point 10) was not correct. In fact, a skilled person would generally perform the separation of OMVs from cytoplasmic molecules only after separation of OMVs from bacterial and cell debris by centrifugation. Thus, the centrifugation step mentioned at lines 19 to 22 of page 3 was used to separate the OMVs from bacterial cells and cell debris while the "*Other methods*" mentioned at lines 22 to 26 were used for separating outer membrane fractions from cytoplasmic molecules. The skilled person would have understood that the step of separation of OMVs from cytoplasmic molecules was different from the step of separation of OMVs from bacterial cells and cell debris. Thus, they would have considered the "*Other methods*" to be further treatments of the OMVs prior to ultrafiltration.

Turning to the alleged disclosures in the application, on page 3, lines 8 to 9 and 19 to 22. These did not provide a basis for the term 'crude' OMVs having the meaning imparted to it by the appellant. While they did not exclude the appellant's interpretation of 'crude' OMVs being those separated from bacteria without further treatments, they also did not exclude that further treatments were performed prior to ultrafiltration.

The application therefore lacked a direct and unambiguous disclosure that excluded any further treatments of OMVs prior to ultrafiltration and hence claim 1 contravened the requirements of Article 123(2) EPC.

Finally, the amendment of the description to include the term "crude" in paragraph [0009] also lacked a

basis in the application as filed, for the same reasons as given for claim 1. Therefore, the description did not fulfill the requirements of Article 123(2) EPC.

IX. Both parties informed the board in writing that they would not attend the oral proceedings.

X. Oral proceedings were held on 23 August 2018 in the absence of the parties. At the end of the proceedings the chair announced the decision of the board.

XI. The requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and the opposition be rejected; that, if the board were to conclude that the patent application met the requirements of Article 123(2) EPC, the requirements of Article 83 EPC be considered; that the case be remitted to the opposition division for consideration of Article 100(a) EPC.

The respondent requested that the appeal be dismissed; that, in the event the board were to set aside the decision of the opposition division on Article 100(c) EPC, the patent be revoked for not complying with Article 100(b) EPC; that, in the event the board were to set aside the decision of the opposition division on Article 100(c) EPC and were to hold that the patent met the requirements of Article 100(b) EPC, the case be remitted to the opposition division for consideration of the grounds of opposition under Article 100(a) EPC.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.
2. Neither the appellant nor the respondent attended the oral proceedings. Both parties are treated as relying on their written case (Article 15(3) RPBA).

Article 123(2) EPC - Amendments

3. The appeal is directed against the finding in the decision under appeal of lack of compliance with Article 123(2) EPC because "*the insertion of the term "crude" [...] lacks basis in the application as filed*" (see section III above).
4. In the decision under appeal, no objection was raised against any part of the claim 1 other than that set out above and no decision about the compliance or otherwise of the remaining subject-matter of the claim with the requirements of Article 123(2) EPC was given. The board has no objections of its own against this remaining subject-matter of claim 1.
5. In their appeal, the appellant argued that the opposition division erred in finding that claim 1 related to subject-matter that extended beyond the content of the application as filed (see section VII, above), while the respondent agreed with opposition division that the amendment to introduce the term 'crude' resulted in the claim relating to subject-matter that extended beyond the content of the application as filed (see section VIII, above).

6. The question to be answered in deciding on compliance with Article 123(2) EPC is whether or not the whole of the application as filed, directly and unambiguously discloses the subject-matter of claim 1 as granted, when read in the light of common general knowledge and when seen objectively and relative to the date of filing (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.E.1.2.1).
7. The subject-matter of claim 1 as granted is a process for preparing bacterial outer membrane vesicles (OMVs) for use in vaccines, comprising steps of:
 - (i) ultrafiltration performed on an aqueous suspension of **crude** OMVs that have been prepared from Gram negative bacteria, wherein the OMVs remain in suspension after the ultrafiltration step; (emphasis added by the board)
 - (ii) ultracentrifugation of the suspension; and
 - (iii) re-suspension of ultracentrifuged OMVs from the ultracentrifugation pellets"
8. There was disagreement between the parties as to whether or not the expression 'crude' OMVs had a particular meaning in the art (see sections VII and VIII above) and consequently about whether or not the application as filed (application) disclosed the claimed method comprising the step of ultrafiltration performed on an aqueous suspension of 'crude' OMVs that have been prepared from Gram negative bacteria.
9. The appellant considered that the expression 'crude' OMVs was commonly used in the art to describe OMVs which had been separated from bacteria (usually by

centrifugation) but which had not been further treated, except for trivial steps such as concentration or dilution. They cited documents D1 and D8 to support this interpretation. The respondent on the other hand considered that there was no support in the cited art for the interpretation of the expression 'crude' OMVs having the meaning given to it by the appellant. Instead, the term was not consistently used in that art and thus the common general knowledge of skilled person did not support the appellant's interpretation of the expression.

10. Document D1 makes reference to a 'crude' (cell) extract (see Examples 4 and 5 and Table 3) which includes the bacterial material after the first ultracentrifugation step (see paragraph [0089]) and to OMV containing-material before isolation of OMVs by ultracentrifugation (see paragraph [0094]).
11. In document D8 preparation of 'crude' OMV is disclosed on page 30 as follows: "*Preparation of crude OMV was done by distributing the inactivated suspension to centrifuge tubes of 500 ml, and centrifuging in a Sorvall RC-26 PLUS centrifuge at 15,000 g for 90 min at 4°C in, collecting 8.0 l of supernatant*" (see lines 14 to 17).
12. This disclosure supports the view that crude OMVs may be those obtained after disrupting the bacterial cells and centrifuging the resultant suspension. The document also mentions crude OMVs at page 18, line 13, but only to set out the subject of the invention: "*The integrated way of processing bacteria, from bacterial growth to non-infectious crude OMV, is a new and advantageous part of an overall procedure for*

preparation OMV for use in vaccines according to the invention...".

13. In the board's view, neither document D1 nor D8 can be taken as providing evidence of a definitive meaning attached to the expression 'crude' OMVs in the art, *inter alia* because citations of specific passages from (only) two patent documents cannot automatically be taken as representing common general knowledge in the art.
14. In the absence of a definitive definition of 'crude' OMVs in the art, the skilled person has to interpret the term based on its use in the application alone. It must therefore be determined whether or not the application discloses the subject-matter claimed after its meaning has been established on the basis of the application.
15. On page 2, paragraphs 2 to 5 of the application it is disclosed that "*[t]he invention is based on the finding that, compared to the centrifugation used in step (e) of the process of reference 11, ultrafiltration allows much larger amounts of OMV-containing supernatant to be processed in a much shorter time. [...]. As well allowing step (e) to be performed more quickly, the use of ultrafiltration allows step (f) to be avoided because the OMVs remains in suspension.*

Thus the invention provides a process for preparing bacterial OMVs, comprising a step of ultrafiltration. The ultrafiltration step is performed on an aqueous suspension of OMVs after they have been prepared from bacteria and the OMVs remain in suspension after the ultrafiltration step.

The invention also provides, in a process for preparing OMVs from a bacterium, the improvement consisting of the use of ultrafiltration of an OMV suspension in place of a step of centrifugation. The invention also provides a process for purifying bacterial OMVs, wherein the process does not include a centrifugation step in which the OMVs are pelleted, particularly a centrifugation step performed on crude OMVs."

16. Under the heading "*Pre-ultrafiltration steps*" the application discloses that prior to ultrafiltration the OMVs may be separated from "*bacterial cells and cell debris*" by "*centrifugation*" or by "*Other methods for separating outer membrane fractions from cytoplasmic molecules*", namely methods that "*may involve filtration (e.g. cross flow filtration), differential precipitation or aggregation of outer membranes and/or OMVs, affinity separation methods using ligands that specifically recognize outer membrane molecules, etc*" (see page 3, lines 19 to 26).
17. The above cited passages can be summarised as disclosing that, in a process for preparing purified OMVs from an aqueous solution of OMVs after they have been prepared from bacteria, the invention lies in the replacement of a centrifugation step with an ultrafiltration step. Additional steps may be performed on the OMV suspension directly obtained from bacteria, for instance, bacterial cells and cell debris may be removed, as may cytoplasmic molecules.
18. In the light of this disclosure, the board considers that the claimed method, which refers to the material applied to the ultrafiltration step as '*crude*' OMVs, is to be construed as encompassing all of the above mentioned options. '*Crude*' OMVs thus refers to the

starting material for the ultrafiltration step, irrespective of whether the material has been prepared in a previous step or not. The expression 'crude' OMVs is also used in the examples of the application and in the associated Figures.

19. Two experiments are mentioned in Example 1. In the first (a comparative experiment), 'crude' OMVs were prepared by centrifuging an inactivated bacterial (*N. meningitidis*) suspension, prior to ultracentrifugation.
20. In the second experiment 'crude' OMVs were prepared by cross-flow filtration, prior to an ultrafiltration step, which here was diafiltration (see also page 2, lines 23 to 25, the passage on page 3, referred to in point 16. and Figures 1 and 2).
21. The board agrees with the conclusion reached in the decision under appeal that this latter reference to 'crude' OMVs is an error, since the cross-flow filtration is in fact part of the ultrafiltration step (see point 2.3 of the decision under appeal). Furthermore, it is apparent that the second experiment was done with the aim of comparing the cross flow/ diafiltration step to the ultracentrifugation step (see page 13, lines 18 to 20). Thus the ultrafiltration step could not sensibly regarded as leading to 'crude' OMVs.
22. Example 2 concerns the preparation of purified OMVs from a different strain of *N. meningitidis*. The example discloses the: "*Preparation of **crude** OMVs was as before, except: (a) centrifuge tubes were 1000ml volume; (b) centrifugation was at 8000 rpm (16650 x g), to give 17.5L of supernatant*", and "*Cross-flow filtration for purifying OMVs (in place of centrifugation) was as in experiment B above, except:*

*(a) using 17.5L **crude** OMVs; (b) using two P2B300V05 polyethersulphone filters (300kD cutoff); (c) using an initial transfer of 4L **crude** OMVs; [...]" (emphasis added by the board).*

23. From all of the above mentioned passages and reading the application as a whole, the board concludes that the application discloses a method for the purification of OMVs, starting from a preparation of OMVs in suspension prepared from bacteria and referred to as 'crude' OMVs, where this 'crude' OMV preparation is that which is applied to the ultrafiltration step and where the expression 'crude' OMVs is construed as set out in point 18., above.
24. The application as filed therefore discloses a process for preparing OMVs as set out in claim 1. The subject-matter of claim 1 as granted meets the requirements of Article 123(2) EPC.
25. The opposition division gave no opinion of whether or not the subject-matter of the dependent claims met the requirements of Article 123(2) EPC. The board is of the opinion that the subject-matter of claims 3 to 15 of the application provides a basis for the subject-matter of claims 2 to 4 and 7 to 14 as granted. The subject-matter of claims 5 and 6 is to be found on page 4, lines 13 to 15 of the application.
26. The amendment to paragraph [009] of the description of the patent, i.e. the insertion of the word "crude" before the word "OMVs" was done to bring that paragraph into line with the claims. The reasons given above for the subject-matter of claim 1 apply equally.

27. The claims and description as granted therefore meet the requirements of Article 123(2) EPC and the appeal is allowable.

Article 111(1) EPC - Remittal

28. Article 111(1) EPC provides that the decision whether or not to remit a case to the department of first instance is at the board's discretion and is to be taken on the basis of the facts and circumstances of the particular case (see generally "Case Law of the Boards of Appeal of the European Patent Office", 8th edition, IV.E.7.1).
29. The decision of the opposition division was based only on one ground of opposition in Article 100(c) EPC, namely that the subject-matter of the European patent extends beyond the content of the application as filed. The opposition division did not decide on the other grounds of opposition relied on by the respondents - lack of novelty, lack of inventive step and insufficiency of disclosure - although it did include in its written decision a short passage headed "*Obiter dictum*" in which it commented on compliance with Article 83 EPC.
30. Both parties have requested that the case be remitted to the opposition division for consideration of the ground of opposition under Article 100(a) EPC. In view of the considerations in point 29. above, the board agrees.
31. Moreover, both parties have requested that the board decide the issues relating to Article 100(b) EPC. However, in view of the fact that the case will be remitted to the opposition division for consideration

of issues under Article 100(a) EPC (see point 30. above), the board sees no procedural advantage in deciding Article 100(b) EPC itself.

32. Thus the circumstances of this case lead the board to exercise its discretion in favour of remitting the case to the first instance for further prosecution of the grounds of opposition pursuant to Article 100(a) and 100(b) EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division for further prosecution.

The Registrar:

The Chair:



S. Lichtenvort

G. Alt

Decision electronically authenticated