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# Datasheet for the decision of 24 October 2017

**Case Number:** T 1765/14 - 3.3.04

**Application Number:** 11184022.9

**Publication Number:** 2478916

**IPC:** A61K39/145

**Language of the proceedings:** EN

**Title of invention:**
Influenza vaccines containing hemagglutinin and matrix proteins

**Applicant:**
Seqirus UK Limited

**Headword:**
Method for preparing influenza vaccine/SEQIRUS

**Relevant legal provisions:**
EPC Art. 54, 56, 76(1), 83, 84, 123(2)

**Keyword:**
Main request - requirements of the EPC met - (yes)

**Decisions cited:**

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 1765/14 - 3.3.04**

# D E C I S I O N
# of Technical Board of Appeal 3.3.04
# of 24 October 2017

| | |
|---|---|
| **Appellant:** (Applicant) | Seqirus UK Limited<br>Point<br>Level 3, 29 Market Street<br>Maidenhead, Berkshire SL6 8AA (GB) |
| **Representative:** | Wise, Daniel Joseph<br>Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 13 March 2014 refusing European patent application No. 11184022.9 pursuant to Article 97(2) EPC** |

**Composition of the Board:**

| | |
|---|---|
| **Chairwoman** | G. Alt |
| **Members:** | M. Montrone |
| | P. de Heij |

## Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application No. 11 184 022.9, which was published as EP 2 478 916 (hereinafter the "application"). The application is a divisional application of the earlier European patent application No. 07 734 467.9, which was filed as an international application and published as WO 2007/085969 (hereinafter "the earlier application as filed") with the title "*Influenza vaccines containing hemagglutinin and matrix proteins*".

II. In the decision under appeal the examining division dealt with a main and two auxiliary requests. With regard to the main request it took the view that the subject-matter of claim 1 lacked clarity. The claim referred to the addition of proteases in general, while in order to obtain the immunogenic composition it was deemed essential to add the specific protease trypsin.

The subject-matter of claims 1 of auxiliary requests 1 and 2 lacked an inventive step in view of the teaching of document D2 as the closest prior art combined with that of document D16 (see section VII below). With regard to the obviousness of the subject-matter of claim 1 of auxiliary request 1, the examining division found that the skilled person "*would know from D16 that MDCK cells are the best choice for the industrial production of an influenza vaccine (pg. 146, §2) and that they yield high influenza virus titers in the presence of trypsin (see abstract and also pg. 142, materials and methods, §3; pg. 143, reactor cultures §6). It is therefore very reasonable to assume that the*

*skilled person would add trypsin to the cell culture described in D2*".

In this context, the examining division further held that in "*view of this and assuming that claim 1 contains all the essential technical features of the claimed method i.e. that the addition of trypsin to influenza virus grown in cell culture is the only requirement necessary to obtain a composition comprising HA and M proteins which form a stable complex, the skilled person would arrive at a method which would result in such a composition in straightforward manner without the need of inventive skill*".

III. With its statement of grounds of appeal the appellant submitted a main and three auxiliary requests. The main request and auxiliary requests 1 and 3 were identical to the main request and auxiliary requests 1 and 2 dealt with in the decision under appeal, while auxiliary request 2 was first filed in the appeal proceedings.

IV. In a communication pursuant to Article 15(1) RPBA the board expressed its preliminary view that it agreed with the examining division's view that the subject-matter of claim 1 of the main request lacked clarity. Moreover, it took the view (pursuant to Article 111(1) EPC) that auxiliary request 1 did not meet the requirements of Article 83 EPC. The application did not disclose how complexes between hemagglutinin and fragments of matrix proteins other than fragments of the M1 matrix protein could be obtained.

V. In reply the appellant submitted auxiliary request 4. Having been informed by the board that this request was considered to meet the requirements of the EPC, the appellant made auxiliary request 4 its new main request. Moreover, it withdrew its request for oral proceedings.

Claims 1 to 16 of the new main request read:

"1. A method for preparing an immunogenic composition comprising the steps of:

(i) growing influenza virus in cell culture wherein trypsin is added to allow viral release;

(ii) preparing an antigen composition from the viruses grown in step (i), wherein the antigen composition comprises haemagglutinin and matrix proteins not as a whole virion which form a stable complex; and

(iii) combining the antigen composition with a pharmaceutical carrier, to give the immunogenic composition

wherein the matrix protein has an amino acid sequence which is a fragment of a full-length M1 matrix protein amino acid sequence.

2. The method of claim 1, wherein the influenza viruses are grown in MDCK cells, for example MDCK 33016 (DSM ACC 2219).

3. The method of claim 1 or claim 2, wherein the influenza viruses are grown in a cell line which is adapted for growth in suspension.

4. The method of any preceding claim, wherein the antigen composition in step (ii) is prepared by splitting the influenza viruses with cetyl trimethyl ammonium bromide.

5. The method of any preceding claim, wherein the matrix protein comprises a sequence of 20 amino acids that has at least 80% identity to SEQ ID NO: 2 and/or wherein the matrix protein comprises a T cell epitope from influenza virus Ml protein.

6. The method of any preceding claim, wherein the matrix protein comprises one or the following amino acid sequences: SEQ ID NO: 1; SEQ ID NO: 21; SEQ ID NO: 22; SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27.

7. The method of any preceding claim, wherein the matrix protein lacks the N-terminal methionine of the natural Ml sequence.

8. The method of claim 7, wherein the matrix protein has a N-terminal sequence SLLTEVETYVLS (SEQ ID NO: 30), for example wherein the N-terminal serine of SEQ ID NO: 30 is covalently modified, e.g. acetylated.

9. The method of any one of claims 1 to 7, wherein the matrix protein has a N-terminal sequence EISLSYSAGALA (SEQ ID NO: 18).

10. The method of any preceding claim, wherein the composition comprises: (i) a first matrix protein having a N-terminal sequence SLLTEVETYVLS (SEQ ID NO: 30); and (ii) a second matrix protein having a N-terminal sequence EISLSYSAGALA (SEQ ID NO: 18).

11. The method of any preceding claim, wherein matrix protein is present at a concentration between lµg/ml and 15µg/ml.

12. The method of any preceding claim, wherein the immunogenic composition comprises split influenza virus or purified influenza surface antigens.

13. The method of any preceding claim, wherein the haemagglutinin is from a H1, H2, H3, H5, H7 or H9 influenza A virus subtype.

14. The method of any preceding claim, wherein the influenza virus proteins is prepared from an influenza virus grown on a culture of a host cell and the composition contains less than l0ng of cellular DNA from the host cell.

15. The method of any preceding claim, wherein the composition contains between 0.1 and 20µg of haemagglutinin per viral strain.

16. The method of any preceding claim, wherein the composition includes an adjuvant, for example an oil-in-water emulsion, or one or more aluminium salts".

VI. The board cancelled the oral proceedings and continued the appeal proceedings in writing.

VII. The following documents are cited in this decision:

D2: EP 0 870 508

D5: US 5 741 493

D9: Brands R. *et al.*, Dev. Biol. Stand., 98: 93-100, 1999

D16: Merten O.W. *et al.*, Adv. Exp. Med. and Biol., 397: 141-151, 1996

VIII. The appellant's written arguments, where relevant for the present decision, may be summarised as follows:

*Articles 76(1) and 123(2) EPC*

The amendment in claim 1 had a basis in claim 9 of the earlier application as filed and in "*embodiment 9*" on page 38 of the application.

*Inventive step (Article 56 EPC)*

The application related to the problem of providing influenza vaccine compositions which comprised both hemagglutinin (HA) and matrix (M) proteins. This was also the problem to which document D5 related. Document D2, considered by the examining division to represent the closest prior art, related to a different problem, namely the removal of residual host cell DNA in an influenza vaccine, while it was silent on M proteins. Hence, document D5 was the closest prior art document.

Document D5 differed from the method according to claim 1 in that the vaccine was prepared in a laborious process from influenza virus grown in eggs which involved the separate production of a fraction containing the M proteins before it was mixed with an inactivated split influenza vaccine comprising HA (see examples 1 and 2). Thus, the M proteins were added extemporaneously, and as a result of this production process the two proteins did not form a stable complex.

The complex formation between HA and the M1 fragment according to the claimed method resulted in an improved immune response based on T-cells due to an effect known as "*cognate help*", and the technical problem was thus how to provide a method for preparing an influenza vaccine which induced cognate help against HA and M proteins in the recipient.

If one were to follow the examining division's view that the application did not make it plausible that the composition obtained by the claimed method induced cognate help, then, alternatively, the technical problem could be formulated as how to provide a simplified method for producing influenza vaccines which comprised HA and M1 proteins.

With regard to the latter problem, the method according to claim 1 was not an obvious solution, since none of the cited prior art documents suggested the technical steps needed to arrive at an immunogenic composition comprising HA and M1 proteins in a stable complex.

IX. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a patent on the basis of the main request filed as auxiliary request 4 with the letter dated 13 September 2017, or on the basis of one of the auxiliary requests.

## Reasons for the Decision

1. The appeal is admissible.

2. The main request is admitted into the proceedings.

*Main request*

*Articles 76(1) and 123(2) EPC*

3. In the following the references are to passages and claims in the earlier application as filed.

4. The examining division did not raise objections pursuant to Articles 76(1) and/or 123(2) EPC against the subject-matter of claims 1 to 16 of any of the requests dealt with in the decision under appeal, in particular against the claims of auxiliary request 1, to which the claims of the present main request are identical, except for claim 1, to which the feature "wherein the matrix protein has an amino acid sequence which is a fragment of a full-length M1 matrix protein amino acid sequence" has been added. This feature is derived from dependent claim 7.

5. The board has no objections either, since the subject-matter of claim 1 is based on claims 5 and 9 in conjunction with the disclosure on page 7, lines 35 and 36, where it is disclosed that "*proteases (typically trypsin) are added during cell culture to allow viral release*", and the disclosure on page 11, lines 3 and 4, where it is disclosed that "*matrix protein may bind to HA in a vaccine to form a stable complex*".

5.1 The subject-matter of claims 2 and 3 is based on the disclosure on page 7, lines 9 and 10 or lines 8 and 9, respectively.

5.2 The subject-matter of claim 4 is based on the disclosure on page 3, lines 11 to 15.

5.3 Moreover, the subject-matter of claims 5 to 16 corresponds to claims 6 to 8 and 10 to 22, respectively.

6. Furthermore, the board notes that the description, the numbered embodiments 1 to 26 (see paragraph [0173]) and figures 1 and 2 in the application are identical to the respective parts of the earlier application as filed, including claims 1 to 26. Therefore the board concludes that the subject-matter of claims 1 to 16 of the main request meets the requirements of Articles 76(1) and 123(2) EPC.

*Clarity, support (Article 84 EPC)*

7. In the decision under appeal the examining division did not raise any objections pursuant to Article 84 EPC against the subject-matter of any of claims 1 to 16 of either auxiliary request.

8. In the board's view, the subject-matter of present claim 1 is clear and supported by the description, in particular because the process steps and the antigens referred to are generally known in the art (see e.g. paragraphs [0012], [0016], [0036], [0040] and [0041] of the application), while the formation of a stable complex between haemagglutinin (HA) and matrix 1 (M1) protein fragments can be readily tested by the person skilled in the art. With regard to the subject-matter of dependent claims 2 to 16, the board has no objections either.

9. Thus, the subject-matter of claims 1 to 16 meets the requirements of Article 84 EPC.

*Novelty and sufficiency of disclosure (Articles 54 and 83 EPC)*

10. Furthermore, the examining division did not raise any objections pursuant to Articles 54 and 83 EPC against any of the requests dealt with in the decision under appeal.

10.1 With regard to novelty, the board notes that the subject-matter of claim 1 of the main request is not disclosed in any of the available prior art documents, and that claims 2 to 16 are all dependent on claim 1.

10.2 Regarding sufficiency of disclosure, the application mentions, for example in paragraphs [0031] to [0036], suitable cell lines and conditions for growing influenza virus in cell culture and reports in paragraph [0166] on a mode for performing the method according to claim 1. In particular, the formation of a stable complex between an M1 fragment and HA is derivable from the disclosure in paragraph [0166] that "*[t]his low MW polypeptide was also present during further antigen purification, and was present in the final preparation of surface antigens*" (see lines 5 and 6), which indicates to the skilled person that a protein of low molecular weight is co-purified with the viral surface antigens in combination with figure 1 showing the presence of HA and M1 in the prepared vaccine (see paragraph [0165]). The low molecular weight protein is further characterised by its weight of about "*5 kDa*" and the N-terminal sequence identifying it as an M1 fragment (see paragraph [0166], line 8, and paragraph [0168], lines 16 to 18).

11. Thus in view of the above considerations, the board concludes that the subject-matter of claims 1 to 16

meets the requirements of Articles 54 and 83 EPC. The board's observation in its preliminary view that complex formation between HA and M proteins other than M1 fragments could not be put into practice is no longer relevant, as claim 1 of the current main request is now limited to a fragment of a full-length M1 protein.

*Inventive step (Article 56 EPC)*

*Closest prior art*

12. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as its first step the identification of the closest prior art. In accordance with the established case law, the closest prior art is generally a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention (see Case Law of the Boards of Appeal, 8th edition 2016 ("CLBA"), I.D.3.1).

13. The examining division considered document D2, while the appellant considered that document D5 represented the closest prior art for the method according to claim 1.

14. Document D2 discloses a Madin Darby Canine Kidney (MDCK) cell culture-based method for the preparation of an influenza vaccine comprising the purified surface antigens HA and neuraminidase (NA) and having a low residual host cell DNA content (see abstract, page 2,

lines 10 and 11, and page 3, line 6, example 1). Document D2 is silent on matrix (M) proteins and on the use of proteases for releasing the virus from the infected cells during the production step.

15. Document D5 discloses several methods for the preparation of influenza vaccines, including "*split vaccines*", i.e. "*virions subjected to treatment with agents which dissolve lipids*" (see column 1, lines 27 and 28), or in other words viral compositions lacking the whole virus. It further discloses that the vaccines may be produced from virus cultivated either in chicken embryos or in cell cultures (see e.g. column 2, lines 7 to 8). The vaccines comprise first and second constituents, wherein the first, if used in humans, is defined by the content of HA (see column 3, lines 1 and 2, and column 4, lines 61 to 67), and in that it may be prepared by the addition of a protease, for example, bromelain (see column 2, lines 19 to 26). The second constituent is the M1 protein, a major component of the viral core (see column 3, lines 49 to 59).

Document D5 further reports that split vaccines originating from virus multiplied on chicken embryos (see column 7, lines 4 to 6) comprising either HA and core proteins (see column 7, lines 56 to 67) or HA and purified M1 proteins (see column 11, lines 45 to 50) are more effective in the protection of mice from an influenza virus infection compared to split vaccines lacking core proteins (see Tables 1 to 4, column 8, lines 30 to 36, and column 11, lines 58 to 62).

The skilled person would derive from document D5 that the split vaccine comprising HA and purified M1 protein contains full-length M1 protein, since the document suggests in example 4 that "*a protease inhibitor such*

*as TLCK [...] may be added, to avoid later degradation of the M protein*" during the purification process (see column 10, lines 14 to 17).

16. Therefore, document D2 is directed to the preparation of influenza vaccine compositions derived from cell culture comprising purified HA and NA proteins that are free of host cell DNA, while document D5 is directed to the preparation of influenza vaccine compositions comprising HA and full-length M1 proteins.

17. Thus, since the method according to claim 1 is directed to the preparation of immunogenic compositions comprising HA and fragments of the M1 protein, document D5, and not D2 as held by the examining division, represents the closest prior art for the subject-matter of claim 1.

18. Thus, with regard to the closest prior art, the board arrives at a different conclusion than the examining division in the decision under appeal.

*Technical problem and solution*

19. The claimed method differs from the method disclosed in example 4 of document D5 in that (i) the virus is grown in cell culture, as opposed to chicken embryos, (ii) trypsin is added to release the virus, and (iii) the prepared immunogenic composition contains a fragment of the M1 protein forming a stable complex with the HA protein.

20. The addition of trypsin during the cell culture step to release the virus has the effect that viral full-length M1 protein is degraded to fragments (see paragraph [0047] of the application). These fragments of the M1

protein form a stable complex with the HA protein, allowing the co-purification of both proteins in a single procedure (see paragraph [0055] and Figure 1 of the application). This obviates the need to purify the M1 and the HA antigens in two separate processes including their subsequent mixing, which simplifies the overall process due to a significant reduction of required working steps compared to the method disclosed in document D5.

21. The objective technical problem is thus how to provide a method for preparing an immunogenic composition of influenza virus comprising HA and M1 proteins in a simplified manner.

22. In view of the disclosure in paragraphs [0165] and [0166] and in Figure 1 of the application, the board is satisfied that the method according to claim 1 solves this technical problem.

*Obviousness*

23. It has to be assessed whether or not the skilled person, starting from the method disclosed in document D5, involving the separate production and subsequent mixing of HA and M1 proteins, and faced with the technical problem defined above, would modify the teaching of document D5 - in view of that document either alone or in combination with a further prior art document, document D16 - so as to arrive at the claimed subject-matter in an obvious manner.

24. As observed in point 19 above, the claimed method differs from the method disclosed in document D5 in the three features (i) to (iii). Since at least two of them, i.e. features (ii) and (iii), are associated with

the advantageous effect that the claimed preparation of the immunogenic composition can be performed in a simplified manner (see point 20 above), it has to be considered whether or not the skilled person would have arrived at them in an obvious manner.

25. As set out in point 15 above, document D5 suggests adding protease inhibitors during purification of the M1 protein from the viral core protein fraction for the avoidance of protein degradation, so that the composition prepared rather contains full-length M1 in addition to HA. The document therefore does not hint at the preparation of compositions comprising M1 fragments, let alone at the preparation of tryptic M1 fragments forming stable complexes with HA allowing simplification of the method for preparing immunogenic compositions comprising both HA and M1 proteins.

26. Therefore, the subject-matter of claim 1 is not obvious in the light of the teaching of document D5 alone.

27. In the decision under appeal the examining division argued with regard to inventive step in auxiliary request 1 (see section II above) that it was very reasonable to assume that the skilled person would have added trypsin to a cell culture-based production of influenza virus in view of the high viral titers reported in document D16. Furthermore it found that, since the addition of trypsin to an influenza virus grown in cell culture resulted in the preparation of a composition comprising HA and an M1 protein fragment in a stable complex, the skilled person was led to the method according to claim 1 in a straightforward manner without the need for inventive skill.

28. Document D16 discloses a study comparing the production of influenza virus grown in different animal cell lines in serum-free medium in the presence of trypsin for the production of inactivated influenza vaccines. The document reports that MDCK cells in particular produce high titers of the virus under these conditions (see abstract, Table 1).

28.1 However, reasons for adding trypsin to the cell culture other than for increasing the viral titer are not mentioned in document D16, which moreover is silent on the preparation of immunogenic viral compositions comprising HA and the M1 protein, a fragment of the M1 protein, let alone a complex formed between HA and an M1 protein fragment.

28.2 In the absence of such a disclosure, the skilled person would not have derived hints from document D16 that trypsin might degrade full-length M1 protein into fragments, let alone into fragments which would form complexes with HA that might allow the preparation of immunogenic compositions comprising both proteins to be simplified.

28.3 In these circumstances, the board is not persuaded by the examining division's argument that the skilled person "*would have added trypsin to a cell culture-based production of influenza virus*". In the board's view, without having the expectation of achieving a simplification of a method for preparing compositions comprising HA and an M1 fragment, the skilled person certainly could have added trypsin to a cell culture-based production of influenza virus, but he would not have done so (see CLBA, I.D.5).

29. In the board's view, the assessment of the situation in the present case might be different if for the skilled person the addition of trypsin was inherent, i.e. a necessary step, in the cell-based production of the virus. However, the available prior art documents do not support this conclusion. On the contrary, various prior art documents teach an MDCK cell-based production of influenza virus not relying on the addition of trypsin (see e.g. document D2, point 14 above and document D9, page 94, last paragraph, to page 97, first paragraph, and page 111, where use of trypsin is mentioned but not actually used in the method described). Therefore, the skilled person would not have arrived at the claimed method in a straightforward manner.

30. Thus, the board concludes that the subject-matter of claim 1 is not obvious in the light of the combined teachings of documents D5 and D16 either.

31. Therefore the subject-matter of claim 1 is based on an inventive step and meets the requirements of Article 56 EPC. The same applies to the subject-matter of dependent claims 2 to 16.

**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 with the order to grant a patent on the basis of the following claims and a description and figures to be adapted thereto:

   the set of claims of the main request referred to in the letter of 4 October 2017 (filed as auxiliary request 4 with the letter of 13 September 2017).

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated