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Datasheet for the decision of 11 September 2018

Case Number: T 0117/13 - 3.3.01

Application Number: 06808434.2

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IPC: A61K39/39, A61K39/145

Language of the proceedings: EN

Title of invention:
EMULSIONS WITH FREE AQUEOUS-PHASE SURFACTANT FOR ADJUVANTING SPLIT INFLUENZA VACCINES

Applicant:
Seqirus UK Limited

Headword:
Adjuvanted split influenza vaccines/SEQIRUS

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

Keyword:
Inventive step - (no) for main request and auxiliary requests 1 to 4 and 6
Late-filed request - auxiliary request 5 not examined by the examining division

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Case Number: T 0117/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 September 2018

Appellant: (Applicant)	Seqirus UK Limited Point Level 3, 29 Market Street Maidenhead, Berkshire SL6 8AA (GB)
Representative:	Wise, Daniel Joseph Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 2 August 2012 refusing European patent application No. 06808434.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	M. Pregetter
	L. Bühler

Summary of Facts and Submissions

I. The present appeal lies from the decision of the examining division refusing European patent application No. 06 808 434.2, published as WO2007/052061.

II. The following documents are referred to below:

(3) WO 2005/107797

(7) Stephenson et al., Vaccine, 2003, 21, 1687-1693

(8) Wood et al., Med Microbiol Immunol, 2002, 191, 197-201

(9) Scheifele et al., CID, 2003, 36, 850-857

(10) Canada Communicable Disease Report, 1 August 2001, volume 27, ACS-4, 1-24

(12) Nicholson et al., Lancet, 2001, 357, 1937-1943

(19) Wong et al., Hong Kong Med J, 2005, 11(5), 381-390

(21) EMEA, Assessment Report for Celvapan, 1 October 2009, 1-65

III. The decision under appeal was based on the set of claims filed during oral proceedings before the examining division on 16 February 2012.

The examining division found, *inter alia*, that the subject-matter of the product claims, especially of claim 1, did not involve an inventive step.

IV. With its statement of grounds of appeal, the appellant (applicant) re-submitted the set of claims underlying the impugned decision as main request and submitted auxiliary requests 1 to 3.

V. In a communication pursuant to Article 15(1) RPBA the board informed the appellant that during the oral proceedings issues relating to Articles 123(2), 54 and 56 would be discussed.

VI. By letter dated 11 July 2018 the appellant submitted an amended main request and auxiliary requests 1 to 6.

Claim 1 of the main request, which is identical to claim 1 of auxiliary requests 1 to 4, reads as follows:

"1. An immunogenic composition comprising a split influenza virus antigen and an oil-in-water emulsion which includes a squalene and has droplets with a sub-micron diameter, wherein the emulsion includes free surfactant in its aqueous phase, wherein the composition is a monovalent vaccine against a pandemic influenza virus strain and the surfactant is a polyoxyethylene sorbitan ester."

Claim 1 of auxiliary request 5 reads as follows:

"1. A method for preparing an immunogenic composition by mixing two liquids at a volume ratio of 1:1, wherein the liquids are:
(i) a split influenza virus antigen; and
(ii) an oil-in-water emulsion that includes free surfactant in its aqueous phase and has droplets with a sub-micron diameter, selected from;
• an emulsion having by weight 4.3% squalene, 0.5% polysorbate 80 and 0.48% sorbitan trioleate; or

• an emulsion having 2 to 10% squalene, 2 to 10% tocopherol and 0.3 to 3% polysorbate 80, with a squalene:tocopherol weight ratio of ≤1 and a squalene:polysorbate 80 volume ratio of 5:2, wherein the immunogenic composition is (a) a monovalent vaccine against a pandemic influenza virus strain or (b) thiomersal-free."

Claim 1 of auxiliary request 6 reads as follows:

"1. A method for preparing an immunogenic composition by mixing two liquids at a volume ratio of 1:1, wherein the liquids are:
(i) a split influenza virus antigen; and
(ii) an oil-in-water emulsion that includes free surfactant in its aqueous phase and has droplets with a sub-micron diameter, and having by weight 4,3% squalene, 0.5% polysorbate 80 and 0.48% sorbitan trioleate."

VII. Oral proceedings were held on 11 September 2018.

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

Admission of auxiliary request 5

The appellant presented no arguments in favor of the admission of auxiliary request 5.

Main request - inventive step

In Canada in 2000-2001 influenza vaccines were associated with occurrence of adverse effects named oculorespiratory syndrome (ORS). From document (9) it could be seen that ORS had been in particular linked to

one vaccine, Fluviral. However, there had also been occurrences of ORS with two other vaccines, Vaxigrip and Fluzone (page 850, right column). The occurrence of ORS was linked to the presence of aggregates of unsplit virions (page 851, left column, second paragraph). A change of splitting procedure reduced the incident rate of ORS, but there remained a certain risk (page 856, right column, middle paragraph). Document (10) reported the experts' conclusion that a high proportion of unsplit virus and aggregates was the cause of ORS (page 12, left column, point 2). Document (19) indicated that about 4% of the ORS cases came from vaccines that were deemed to be safe (page 384, right column).

The technical problem underlying the invention could be seen as providing a composition further reducing the likelihood that a recipient of a split influenza vaccine would develop ORS, and thus as a further improvement to that obtained by the change of splitting procedure as taught by the closest prior art in the form of document (9).

The present invention surprisingly found a solution to reduce the risk of ORS even further by adding free surfactant to the vaccine. The free surfactant stopped micro-aggregation of whole virions, and interacted with the surface membrane of virions thereby breaking up already formed aggregates. This mechanism was backed up by document (21), which described the function of polysorbate 80 as the prevention of micro-aggregation (page 8, table 1). The effect of the free surfactant was thus plausible. Document (21), although formally post-published, had been published within the period relevant for the invention and thus represented the knowledge of the skilled person.

Although no prediction for an improvement on the level of individual patients was possible, a benefit for at least some patients was provided. Such an improvement was comparable to an additional safety measure.

Even though claim 1 of the main request did not define the amount of unsplit virions present, it was clear from the prior art, e.g. document (9), page 856, middle paragraph of right column, that in a split influenza vaccine there would always be some unsplit virions.

The technical problem was solved over the whole scope in a non-obvious way. An inventive step was thus present.

The same line of argument applied to the respective claims 1 of auxiliary requests 1 to 4, which were identical to claim 1 of the main request.

Auxiliary request 6 - inventive step

A corresponding line of argument applied to claim 1 of auxiliary request 6, which defined subject-matter which was directly exemplified in the description. The closest prior art could be seen in the disclosure of document (9), as discussed above for the main request. The technical problem was the provision of a method for preparing an improved vaccine in which the likelihood of ORS was further reduced. The subject-matter of claim 1 of auxiliary request 6 was not obvious for the same reasons as the main request.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request, or, alternatively,

of one of auxiliary requests 1 to 6, all filed by letter dated 11 July 2018.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of auxiliary request 5*

Auxiliary request 5 corresponds to auxiliary request 2 submitted together with the statement setting out the grounds of appeal. It appears from the minutes of the oral proceedings before the examining division that said set of claims had been submitted as auxiliary request 1, but had been replaced, during the same oral proceedings, by another set of claims. Consequently, the examining division had not issued a decision based on said withdrawn set of claims.

It is established jurisprudence of the boards of appeal that the primary purpose of an appeal is to provide the adversely affected party with the opportunity to challenge the decision on its merits and to obtain a judicial ruling as to whether the first-instance decision was correct.

The fact that the request was withdrawn in the first-instance proceedings precluded the issue of a reasoned decision on its merits by the examining division. Reinstating this request upon appeal would compel the board either to give a ruling on the critical issues, which runs contrary to the purpose of the second-instance ruling, or to remit the case to the department of first instance, which is clearly contrary to procedural economy.

It is precisely with the purpose of forestalling these unsatisfactory options that Article 12(4) RPBA provides the board with the discretionary power to hold inadmissible requests which could have been presented in the first-instance proceedings. Consequently, the board did not admit auxiliary request 5 into the proceedings.

3. *Main request - inventive step*

3.1 The object of the application is to minimise the risk that a split influenza vaccine might suffer from the same problems as those seen in Canada in the 2000-01 season (page 1, lines 32/33). In Canada in the season 2000/2001 the so-called oculorespiratory syndrome (ORS) was observed in patients who received split vaccines. ORS has been associated with incomplete splitting of virions during manufacture, resulting in compositions with a high proportion of micro-aggregates of unsplit virions (page 1, lines 17-20).

This object is met, according to the description, by adjuvanting a split virus vaccine with an oil-in-water emulsion that contains free surfactant in its aqueous phase. The free surfactant is said to continuously exert a splitting effect, thereby disrupting any unsplit virions and/or virion aggregates that might be present (page 2, lines 1 to 5).

3.2 Document (9), which has been identified as the closest prior art document both by the examining division and by the appellant, clearly indicates that ORS does not arise with the same incidence rate with all split virus antigen-based vaccines. As can be seen from the

paragraph bridging pages 850/851, only very few problems arise with Vaxigrip and Fluzone, which have few microaggregates or unsplit virions (≤2%: page 851, left column, second paragraph). A high incidence rate of ORS has been found for Fluviral S/F having up to one-third unsplit virions. ORS is thus linked to the presence of unsplit virions and the formation of aggregates of said unsplit virions. Document (9) finds that revision of the manufacturing process by using improved splitting methods is successful in removing the ORS trigger and consequently teaches to minimise the amount of unsplit virions in influenza vaccines (page 856, right column, middle paragraph).

3.3 The difference between the subject-matter of claim 1 and the disclosure of document (9) lies in the addition of an adjuvant in the form of an oil-in-water emulsion which comprises squalene, has droplets with a sub-micron diameter and includes free surfactant in its aqueous phase in the form of a polyoxyethylene sorbitan ester.

3.4 The appellant has referred to the teaching of the description that the presence of free surfactant leads to a (continuous) splitting effect, resulting in the disruption of any unsplit virions and/or virion aggregates that might be present (page 2, lines 1 to 5, and page 30, lines 3 to 5).

As a consequence of said reduced number of unsplit virions and virion aggregates a reduction in the incidence rate of patients suffering from the oculorespiratory syndrome is to be expected.

3.5 The appellant has formulated the technical problem as the provision of a composition which will reduce the

likelihood that a recipient of a split influenza vaccine will develop oculorespiratory syndrome.

3.6 The appellant has formulated the technical problem in the form of an improvement, i.e. the reduction of the likelihood of side effects. In order for such a problem to be solved the improvement must arise over the whole scope of the claim. The technical effect which underlies the improvement is the prevention of aggregation of unsplit virions or the breaking up of already formed aggregates of unsplit virions. It must thus be determined whether such a reduction of aggregates will plausibly occur over the entire scope of the claim.

The subject-matter of claim 1 of the main request defines a composition comprising a split influenza virus antigen. Having in mind the disclosure of document (9), it is understood that vaccines based on split virions as antigen source may include unsplit virions in various amounts. In document (9) possible amounts of "up to one-third" and "≤2%" are explicitly disclosed (page 851, left column, second paragraph).

However, it is not known whether unsplit virions in compositions comprising only very few unsplit virions (e.g. ≤2%) will aggregate to the same extent (same degree of aggregation, same size of aggregates, etc.) as unsplit virions in compositions that comprise unsplit virions in a more than ten-fold concentration (e.g. up to one-third). Starting from this state of a certain, albeit low, number of aggregates of unsplit virions in the composition, the question to be answered is whether it is plausible that any amount of free polyoxyethylene sorbitan ester, i.e. polyoxyethylene sorbitan ester that is present in the aqueous phase of

the emulsion, may stop the aggregation of the unsplit virions either by preventing the formation of aggregates or by disrupting already formed aggregates. It is common general knowledge that such dynamic processes are concentration-dependent.

The application as filed does not contain any data relating to the occurrence of unsplit virion aggregates or to the influence of polyoxyethylene sorbitan esters on such aggregates. Although the decision under appeal explicitly mentions this deficiency (see page 3, last paragraph: "No effect on continued splitting or microaggregation of unsplit virus under the claimed conditions is shown in a practical example", and page 4, middle paragraph: "The *minimal* concentration of Tween sufficient to prevent aggregation of unsplit virions in neither known from the prior art, nor derivable from the application, and appears to be dependent on the amount of virus in the composition"), the appellant has decided not to file any experimental data in the appeal proceedings.

The appellant has merely referred to table 1 of document (21), which discusses the composition of Celvapan, a whole virion based vaccine, and labels Tween 80 (polysorbate 80) at a concentration of 0.10 to 0.15%, in the absence of an emulsion, i.e. entirely in the aqueous phase, as having the function of "preventing of micro-aggregation". The board notes that document (21) was published on 1 October 2009, several years after the effective date of the present application (priority dates of 4 November 2005 and 8 June 2006 and a filing date of 6 November 2006). Also, document (21) relates neither to vaccines based on split virus antigens nor to low concentrations of polysorbate 80. Consequently, the disclosure of

document (21) cannot make up for the missing experimental evidence. There is no further disclosure linking free polyoxyethylene sorbitan ester to the prevention or breaking up of aggregates on file.

In sum, there is no evidence, either from cited documents or from experimental data, that the effect (minimisation of the amount of aggregated unsplit virions) underlying the solution of the problem, which is the further reduction of the likelihood of developing ORS, will occur in compositions having low concentrations of unsplit virions and low concentrations of free polyoxyethylene sorbitan ester. Thus the effect does not plausibly arise over the whole scope of the claim and therefore the problem is not plausibly solved over the whole scope of the claim.

3.7 Consequently, the technical problem has to be re-formulated as a less ambitious one. The technical problem can be seen as the provision of a further split virus influenza vaccine.

3.8 It has to be determined whether it was obvious to add an adjuvant in the form of a sub-micron emulsion as defined in claim 1 of the main request to split virus influenza vaccines.

Sub-micron oil-in-water emulsions that include free surfactant in their aqueous phase and have (by weight) 4.3% squalene, 0.5% polysorbate 80 (i.e. a polyoxyethylene sorbitan ester) and 0.48% sorbitan trioleate are well-established adjuvants known under the name MF59 (see application as filed: page 10, lines 20 to 25).

Various documents suggest adding MF59 to influenza

vaccines:

Document (3) defines an influenza vaccine (claim 1). Said vaccine may comprise split viruses (claim 8, page 5, line 3). One of the two preferred adjuvants is MF59 (page 10, line 31, or page 17, line 14).

Document (7) describes a surface antigen influenza vaccine adjuvanted with MF59 (abstract).

Document (8) discloses a H5N3 subunit vaccine adjuvanted with MF59 to have improved immunogenicity (page 200, right column, "Conclusions").

Document (12) also relates to a surface antigen influenza vaccine adjuvanted with MF59 (page 1938, left column, last full paragraph).

Document (19) mentions Fluad, a MF59 adjuvanted subunit influenza vaccine (page 383, left column, first paragraph).

MF59 is thus an adjuvant commonly used for influenza vaccines. A person skilled in the art aiming to provide an alternative influenza vaccine would consider MF59 as an adjuvant suitable for all types of influenza vaccines and add it to a split virus influenza vaccine without exercising inventive skill.

The subject-matter of claim 1 of the main request does not involve an inventive step.

4. *Auxiliary requests 1 to 4 - inventive step*

Claim 1 of auxiliary requests 1 to 4 is identical to claim 1 of the main request.

The subject-matter of claim 1 of auxiliary requests 1 to 4 does not involve an inventive step for the same reasons as claim 1 of the main request.

5. *Auxiliary request 6 - inventive step*

Claim 1 of auxiliary request 6 differs from claim 1 of the main request in that it is a method claim defining method-related technical features and in that it defines the oil-in-water emulsion in more details. It contains no limitation to a monovalent vaccine against a pandemic influenza virus strain.

6. The appellant has referred to its line of argument for claim 1 of the main request and pointed to the fact that the emulsion now claimed was the one used in the experimental section of the description. No arguments have been raised that the technical features relating to the method as such, i.e. the mixing of two liquids at a volume ratio of 1:1, were linked to any surprising technical effect.

The board considers that the technical features defining method steps are to be considered as routine method steps taken in the preparation of an immunogenic composition.

Concerning the definition of the oil-in-water emulsion the appellant has argued that the emulsion now claimed corresponds to the adjuvant used in the experimental section of the description which is MF59 (page 29, line 5 to page 30, line 5). The board notes that the experimental data relates only to the immune response elicited. There is no data concerning the presence of unsplit virions and/or the formation or prevention of

aggregates.

6.1 The appellant has formulated the technical problem as the provision of a method for preparing an improved vaccine in which the likelihood of ORS is reduced further.

The situation corresponds to the situation discussed for claim 1 of the main request. The only technical feature that has been presented as being linked to the solution of the above-defined problem is the presence of low concentrations of surfactant in the form of free polysorbate 80. Whether the low concentration of polysorbate 80 present in the claimed emulsion has an effect on possibly present aggregates of unsplit virions is not known. Mere speculation that a certain effect is present cannot render said effect plausible. Reference is made to the point 3.6 above.

6.2 Consequently, no effect can be acknowledged and the technical problem has to be reformulated as the provision of a method for preparing a further split influenza vaccine.

6.3 The same line of argument as for claim 1 of the main request (see point 3.8 above) applies mutatis mutandis to the subject-matter of claim 1 of auxiliary request 6.

6.4 The subject-matter of claim 1 of auxiliary request 6 does not involve an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated