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Datasheet for the decision of 10 October 2019

Case Number: T 1342/16 - 3.3.07

Application Number: 10252044.2

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Language of the proceedings: EN

Title of invention:
Hydrophilic filtration during manufacture of vaccine adjuvants

Patent Proprietor:
Novartis AG

Opponent:
GlaxoSmithKline Biologicals SA

Headword:
HYDROPHILIC FILTRATION DURING MANUFACTURE OF VACCINE ADJUVANTS / NOVARTIS

Relevant legal provisions:
EPC Art. 56
EPC R. 103(1)(a)

Keyword:
Inventive step - all requests (no)
Reimbursement of appeal fee (no) - appeal not allowable

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Case Number: T 1342/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 October 2019

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
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Respondent: (Opponent)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Dalton, Marcus Jonathan William GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 March 2016 revoking European patent No. 2343052 pursuant to Articles 101(2) and 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	S. Albrecht
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 2 343 052 was granted on the basis of a set of 13 claims.

Independent claim 1 as granted read as follows:

"1. A method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:

(i) formation of a squalene-containing emulsion having an average oil droplet size of 500nm or less comprising the steps of

a. formation of a first emulsion having a first average oil droplet size;
b. microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size of 500nm or less, which is less than the first average oil droplet size; and

(ii) filtration of the second emulsion using a hydrophilic double-layer polyethersulfone membrane with a first layer having a pore size of ≥0.3μm and a second layer having a pore size of <0.3μm, thereby providing a vaccine adjuvant."

II. An opposition was filed under Article 100(a) and Article 100(b) EPC against the patent as granted on the grounds that its subject-matter lacked novelty and inventive step and was not sufficiently disclosed.

The documents filed during the opposition proceedings included the following:

D2: Ott G. et al (2000), "The Adjuvant MF-59: a 10-year perspective", Methods in Molecular Medicine, Vol. 42, Vaccine Adjuvants, Preparation Methods and Research Protocols, Ed. D.T. O'Hagan, Chapter 12, pages 211 to 228
D6: Lidgate D.M. et al (1992), "Sterile Filtration of a parenteral Emulsion", Pharm. Res. 9(7), 860-863
D7: Lidgate D.M. and Byars N.E. (1995), "Development of an Emulsion-Based Muramyl Dipeptide Adjuvant Formulation for Vaccines", Vaccine Design: The Subunit and Adjuvant Approach, Ed. M.F. Powell and M.J. Newman, Plenum Press, Chapter 12, pages 313 to 324
D8: Allison A.C. (1999), "Squalene and Squalane Emulsions as Adjuvants", Methods 19, 87-93
D9: Jornitz M.W. et al (2003), "Modern Sterile Filtration: The Economics", Pharm. Technol. Europe, June, 29-32
D15: Dixit M. (2008), "Membrane filtration in the biopharm industry", Filtration+Separation, October, 18-21

III. The appeal by the patent proprietor (hereinafter the appellant) lies against the decision of the opposition division to revoke the patent. The decision was based on a main request and on six auxiliary requests, referred to in this decision as auxiliary requests 1, 2, 3, 5, 6, and "new 6th auxiliary request" respectively. The main request was the patent as granted. Auxiliary request 1 was filed with letter dated 30 October 2015, auxiliary requests 2, 3, 5 and 6 were filed with letter dated 3 November 2014 and the new 6th auxiliary request was submitted in the oral

proceedings before the opposition division on 18 December 2015.

IV. In its decision, the opposition division agreed with the patent proprietor's selection of D8 as the closest prior art, from which the subject-matter of claim 1 of the main request differed in terms of the material of the membrane and its configuration. Since the alleged improvement of the percentage filtration recovery vis-à-vis D8 had not been credibly shown, the objective technical problem was seen as the provision of alternative filters for performing the terminal sterile filtration step in the manufacture of microfluidized squalene-containing oil-in-water emulsion vaccine adjuvants with high filtration recovery suitable for use on a commercial scale. The solution proposed, i.e. the method of claim 1, was obvious in the light of the teaching of D9 or D15.

Auxiliary requests 1 to 3, 5 and 6 were considered to lack an inventive step for the same reasons as the main request, whereas the new 6th auxiliary request was not admitted into the opposition proceedings.

V. With its statement setting out the grounds of appeal, the appellant submitted auxiliary requests 1 to 5 that corresponded to auxiliary requests 1 to 3, 6 and 5 underlying the decision under appeal.

Claim 1 of auxiliary request 1 pertained to a method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant in accordance with claim 1 of the main request, wherein this adjuvant comprised 2-20 vol% oil.

Claim 1 of auxiliary request 2 related to a method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant in accordance with claim 1 of the main request, wherein the squalene-containing emulsion formed in step (i) comprised (i) squalene, polysorbate 80 and sorbitan trioleate or (ii) squalene, an α-tocopherol and polysorbate 80.

Claim 1 of auxiliary request 3 corresponded to claim 1 of auxiliary request 2, wherein step (i) was limited to the formation of a squalene-containing emulsion comprising squalene, polysorbate 80 and sorbitan trioleate.

Claim 1 of auxiliary request 4 was directed to a method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant in accordance with claim 1 of the main request, wherein this adjuvant had a pH between 6.0 and 8.0.

Claim 1 of auxiliary request 5 pertained to a method for manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant in accordance with claim 1 of the main request, wherein in step (ii) a volume of ≥ 50 litres of the second emulsion was filtered.

VI. With a letter dated 2 May 2017, the appellant submitted experimental data.

VII. In a communication pursuant to Article 15(1) RPBA issued on 15 April 2019, the Board informed the parties of its preliminary opinion on *inter alia* inventive step of all requests on file, expressing the view that these requests did not appear to be inventive. The Board noted in particular that document D2 appeared to be a

more suitable starting point for the assessment of inventive step than D8.

VIII. With letter dated 10 May 2019 the appellant withdrew its request for oral proceedings and requested a reasoned decision according to the state of the file.

IX. The appellant's written arguments, as far as they are relevant for the present decision, may be summarised as follows:

(a) Article 56 EPC:

Claim 1 of the main request differed from the closest prior art D8 in the type of filter used in the filtration step. Example 4 of the patent as well as the experimental data provided in the letter of 2 May 2017 demonstrated that the claimed filters provided for larger volumes of a squalene-containing emulsion to be filtered before blocking than filters falling outside the claim such as the filter used in D8. Hence, the objective technical problem consisted in the selection of a filter for filtering a squalene-containing emulsion which achieved a high recovery for a prolonged period. The solution defined in claim 1 was inventive in view of the absence of any suggestion in the prior art to select the claimed filters in order to solve the technical problem as posed.

Auxiliary requests 1 to 4 were inventive for the same reasons as the main request.

Claim 1 of auxiliary request 5 specified in step (ii) a filtering volume of the second emulsion of ≥ 50 litres. As the closest prior art D8 did not disclose this

feature, the objective technical problem was the provision of means to manufacture a much larger volume of a squalene-containing oil-in-water emulsion to improve emulsion recovery while removing larger oil droplets, thereby enhancing the end-product stability. The solution defined in claim 1 was not rendered obvious by any of the cited prior art documents, as none of these disclosed or suggested to filter at least 50 litres of a squalene-containing emulsion by means of a filter as defined in claim 1.

(b) Reimbursement of the appeal fee:

The decision of the opposition division was based i.a. on the following three factors:

(i) the term "squalene" encompassed squalane,

(ii) the characteristics of filters 3 to 7 as used in example 4 of the patent were unknown,

(iii) the lack of conditions or limitations on the microfluidization step defined in claim 1 as granted had an impact on inventive step.

Nevertheless, these factors had not been discussed either in writing or during oral proceedings. The appellant was thus deprived of the opportunity to address these. This amounted to a substantial procedural violation justifying the reimbursement of the appeal fee.

X. The written arguments of the opponent (hereinafter the respondent), as far as they are relevant for the present decision, may be summarised as follows:

(a) Article 56 EPC:

The subject-matter of claim 1 of the main request differed from D6/D8 as the closest prior art in terms of the filter used, i.e. the membrane material and the membrane structure. As far as the membrane material was concerned, the data on file did not support any technical effect attributable to it. Hence, this feature was merely a trivial choice among a number of equally valid/suitable options. As for the feature of the membrane structure, D9 and D15 already taught that recovery through the final filter could be improved by performing a pre-filtration to remove large particles. Accordingly, this feature could not account for an inventive step either.

As for claim 1 of auxiliary requests 1 to 5, the additional features comprised therein were arbitrary, obvious choices in the absence of any special technical effect linked thereto. Accordingly, these requests lacked inventive step for the same reasons as the main request.

(b) Reimbursement of the appeal fee:

The appellant was incorrect in stating that the first two factors (see point IX (b) above) had not been raised and considered during the opposition proceedings. Accordingly, the opposition division did not commit a substantial procedural violation in this regard. As for the third factor, this did not have any bearing on the assessment of inventive step starting

from D8 and could thus not amount to a substantial procedural violation either.

XI. Requests:

The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of auxiliary requests 1 to 5 filed with the statement setting out the grounds of appeal. Additionally, the appellant requested reimbursement of the appeal fee in light of a substantial procedural violation committed by the opposition division.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

2. Main request - Inventive step of claim 1

2.1 The closest prior art

2.1.1 Claim 1 relates to a method for manufacture of a squalene-containing oil-in-water emulsion as vaccine adjuvant, comprising *inter alia* a microfluidization step and a filtration step.

2.1.2 In its decision, the opposition division identified D8 as a suitable starting point for the assessment of inventive step. The appellant was of the same opinion (see point 3.4. of its statement setting out the grounds of appeal).

2.1.3 D8, by reference to D6 via D7, discloses the manufacture of an oil-in-water emulsion vaccine adjuvant comprising squalane (i.e. SAF adjuvant; see

page 88). D8 also mentions the preparation of the squalene-containing oil-in-water emulsion vaccine adjuvant MF-59 (see the first paragraph of the second column of page 91; hereinafter referred to as "MF-59 emulsion"). Hence, D8 discloses 2 different oil-in-water emulsion vaccine adjuvants as follows:

(a) the SAF adjuvant which comprises squalane,
(b) the MF-59 emulsion which comprises squalene.

2.1.4 In its decision, the opposition division considered that the term "squalene" of claim 1 was a generic term which comprised the hydrogenated squalene, i.e. squalane (see page 12 of the decision, first paragraph).

2.1.5 The Board does not share the opposition division's view. Instead, it agrees with the appellant that squalene and squalane are two distinct chemical entities. Accordingly, the disclosure of D8 relating to the squalene-containing MF-59 emulsion is a more suitable starting point than the one referring to the squalane-containing SAF adjuvant.

2.1.6 Nevertheless, the Board also notes that D8 discloses the preparation of the MF-59 emulsion in very general terms only, that is apart from microfluidization no further details are provided in this regard.

2.1.7 Document D2, on the other hand, does disclose a more detailed description of the preparation of this emulsion (see pages 213 to 217). It has been cited in the notice of opposition as a further suitable starting point for the assessment of inventive step.

(a) Specifically, figure 1 on page 215 shows a 50l scale manufacturing process for this emulsion that includes i.a. the following steps:

(i) formation of a first, squalene-containing coarse emulsion,

(ii) microfluidization of this first emulsion to form a second emulsion with the desired submicron particle size,

(iii) filtration of the second emulsion through a 0.22 micron filter under nitrogen to remove large droplets,

(iv) sterile filtration of the resulting emulsion through a 0.22 micron membrane.

(b) The microfluidization in step (ii) reduces the average oil droplet size of the emulsion to less than 175 nm (see figure 2).

(c) The MF-59 emulsion obtained by means of this process comprises i.a. squalene, polysorbate 80 and sorbitan trioleate.

Accordingly, the Board considers this document to be a more suitable starting point than D8.

2.1.8 The subject-matter of claim 1 differs from D2 in that the filter used for filtering the emulsion is a hydrophilic double-layer polyethersulfone membrane.

2.2 Objective technical problem and solution

In order to formulate the objective technical problem effectively solved by the claimed subject-matter over the closest prior art, the technical effects associated with the distinguishing feature need to be identified.

2.2.1 In the appellant's view, example 4 of the patent as well as the experimental data provided in its letter of 2 May 2017 demonstrate that the claimed filters provide for larger volumes of a squalene-containing emulsion to be filtered before blocking, i.e. the recovery of the emulsion is better with the claimed filters than with filters falling outside the claim such as the filter used in D8. Therefore, the objective technical problem to be solved by the claimed invention was to select a filter for filtering a squalene-containing emulsion to achieve a high recovery for a prolonged period.

2.2.2 Even though it might be questionable whether the data relied on by the appellant do indeed support the alleged improvement of the claimed process over the process disclosed in D2, the Board will nevertheless assume in the appellant's favour that the filter of claim 1 achieves the alleged technical effect of high recovery for a prolonged period and that the objective technical problem is to be formulated accordingly.

2.2.3 The solution proposed to this problem is the selection of a filter of the type defined in claim 1.

2.3 Obviousness

2.3.1 It remains to be determined whether the skilled person would have replaced a 0.22 micron filter employed in

the manufacturing process of D2 with the filter defined in claim 1 in order to solve the technical problem as posed.

2.3.2 As indicated on page 21, last paragraph, of the decision of the opposition division, hydrophilic filters with a heterogenous double-layer ≥ 0.3 µm / < 0.3 µm configuration were commercially available at the priority date of the patent in suit and were known to have a number of advantages in terms of sterile filtration in the field of biopharmaceutical industries.

2.3.3 Accordingly, the skilled person looking for a solution to the technical problem defined above would consider such filters. He would in particular focus his attention on D15, i.e. a commercial brochure available shortly before the priority date of the patent in suit and bearing the title "Membrane filtration in the biopharm industry".

Page 20 of this document describes different types of membrane filters which were commercially available at the time D15 became publicly available. Many of these are said to be generally pleated from two heterogenous membrane layers, wherein the upstream membrane layer is coarser for larger particulate removal, whereas the downstream membrane is finer to reduce colloidal content and bioburden (see the third column of this page, second full paragraph).

With regard to the membrane materials themselves, D15 teaches that hydrophilic polyethersulfone is the only liquid-service membrane that is good over the entire pH range (see the first three lines of page 21).

D15 then continues by discussing in the paragraph bridging the first two columns of page 21 "new, innovative application specific approaches in membrane filtration" including the Sartopore® double layer filters 2 XLG 0.8/0.2 and 2 XLI 0.35/0.2 polyethersulfone filters. The prefilter layers of these filters are said to be effective in different applications and to achieve very high throughputs resulting in 30% higher effective filtration area per 10" element. The 0.2 final filter layer, in turn, is said to provide highly reliable bacterial retention. The aforementioned paragraph concludes by stating the following:

"This new development promises a quantum leap in membrane filtration compared to the current commercially available double layer membrane filters. These filters have reduced total membrane filters surface area by more than half in some large-scale applications while eliminating the need for prefilters."

2.3.4 In the Board's judgement, the aforementioned passages of D15 give the skilled person a clear incentive to replace the filters used in the process of manufacture disclosed in D2 by a hydrophilic double-layer polyethersulfone filter of the Sartopore® type mentioned in D15 with a reasonable expectation that this filter allows for larger volumes of MF-59 emulsion to be recovered before it becomes blocked.

Hence, the subject-matter of claim 1 of the main request is obvious in the light of D2 taken in combination with D15.

2.3.5 The appellant argued in its appeal brief that the opposition division used hindsight knowledge of the patent to focus on i.a. D15 rather than on other potential choices of filter.

However, this argument cannot succeed in view of the technical pointers disclosed in D15 (see point 2.3.3 above). Accordingly, the Board finds the technical effects brought about by the claimed filters to be predictable improvements which cannot provide for an inventive step.

2.3.6 Consequently, the main request does not meet the requirements of Article 56 EPC.

3. Auxiliary requests 1 to 5 - Inventive step

Claim 1 of each of these requests differs from the subject-matter of claim 1 of the main request, in that:

- the squalene-containing oil-in-water emulsion vaccine adjuvant comprises 2-20 vol% oil in claim 1 of auxiliary request 1;

- the squalene-containing emulsion formed in step (i) of claim 1 of auxiliary request 2 comprises either squalene, polysorbate 80 and sorbitan trioleate or squalene, an α-tocopherol and polysorbate 80;

- the squalene-containing emulsion formed in step (i) of claim 1 of auxiliary request 3 comprises squalene, polysorbate 80 and sorbitan trioleate;

- the squalene-containing oil-in-water emulsion vaccine adjuvant has a pH between 6.0 and 8.0 in claim 1 of auxiliary request 4;

- the volume of the second emulsion filtered in step (ii) of claim 1 of auxiliary request 5 amounts to ≥ 50 litres.

The aforementioned additional features of claim 1 of auxiliary requests 1, 3, 4 and 5 as well as those of the first alternative of claim 1 of auxiliary request 2 already form part of the MF-59 emulsion disclosed in D2 (see in particular point 2.1.7 above and page 91, right-hand column, first paragraph of D8). Hence, they have no impact on the assessment of inventive step.

Accordingly, the subject-matter of claim 1 of each of these auxiliary requests does not fulfil the requirements of Article 56 EPC for the same reasons as set out for claim 1 of the main request.

4. Appellant's request for reimbursement of the appeal fee in accordance with Rule 103(1)(a) EPC

4.1 According to Rule 103(1)(a) EPC, the appeal fee shall be reimbursed if the board of appeal deems an appeal to be allowable, and if such reimbursement is equitable by reason of a substantial procedural violation.

4.2 In the present case, the appeal has been found to be not allowable for the reasons provided above. Moreover, as set out in the Board's communication, the Board cannot acknowledge any substantial procedural violation.

Consequently, the request for reimbursement of the appeal fee has to be refused.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated