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Datasheet for the decision of 21 March 2019

Case Number: T 1344/16 - 3.3.07

Application Number: 10807661.3

Publication Number: 2506832

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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 AG

Relevant legal provisions:
RPBA Art. 13
EPC Art. 56

Keyword:
Inventive step - All requests (no)

Decisions cited:

Catchword:

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Case Number: T 1344/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 March 2019

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
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 24 March 2016 revoking European patent No. 2506832 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 2 506 832 was granted on the basis of a set of 18 claims.

Independent claim 1 as granted read as follows:

"1. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:
(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and
(iii) filtration of the second emulsion using a hydrophilic asymmetric membrane, thereby providing a vaccine adjuvant."

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

III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on two sets of claims filed as main request with letter dated 23 July 2015 and auxiliary request 21 filed with letter dated 22 December 2015.

IV. The documents cited during the opposition proceedings included the following:
D1: G. Ott 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 211-228
D2: G. Ott et al (1995), "MF-59 Design and Evaluation of a safe and potent adjuvant for human vaccines", Vaccine Design,: The subunit and adjuvant approach, Ed. M.F. Powell and M.J. Newman, Plenum Press, Chapter 10, pages 277-296
D3: WO 2006/100110 A1
D6: Cardona M. et al, (2006), Filtration designs remove proceesing bottlenecks for high yield biotech drugs, printout from BioPharmInternational.com
D9: Dixit M. (2008), Membrane Filtration in the Biopharm Industry, Filtration+Separation, October, 18-21
D11: Lidgate D.M. et al, (1992), "Sterile Filtration of a parenteral Emulsion", Pharm. Res., 9(7), 860-863
D12: Allison A.C., Squalene and squalene emulsions as adjuvants, Methods, 19, 87-93, 1999.
D13: ProductNews (2003), "High Filtration Area Membrane Filters Available in European Market", September page 12
D20: Data Sheet Millipore Corporation, 2006, Durapore CBR 0.2 micron Bioburden Reduction filters
D22: Data Sheet Millipore Corporation, 2009, Durapore 0.1 micron and 0.22 micron Hydrophilic Filters
D26: Lidgate D:M et al, 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 313-324

V. According to the decision under appeal, D12 was considered as the closest prior art by the opposition division for the assessment of inventive step, while the opponent considered D1, D2 or D3 as potential closest prior art in its notice of opposition.

D12 disclosed emulsion formulations comprising naturally occurring squalene or hydrogenated squalene (squalane) in final concentration of 5% (w/v) in an aqueous phase stabilized with polysorbate 80 (see page 88 and page 91). The opposition considered that squalane fell within the generic term squalene as defined in claim 1 of the main request.

The subject-matter claimed in claim 1 of the main request differed in that the hydrophilic membrane used in the terminal filtration was asymmetric.
In the absence of any effect shown by the examples of the contested patent and of any comparison with the closest prior art, the problem was defined as the provision of alternative filters for 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 use of a hydrophilic asymmetric membrane was seen as obvious in view of D6 or D9.

Auxiliary request 21 was not inventive for the same reasons as the main request.

VI. The proprietor (hereinafter the appellant) filed an appeal against said decision. With its statement of gounds of appeal dated 3 August 2016, it submitted a main request and auxiliary requests 1 and 2. The main request corresponded to auxiliary request 21 filed during the opposition proceedings.

Independent claim 1 of the main and auxiliary requests 1 and 2 read as follows, difference(s) compared with claim 1 as granted shown in bold:

a) Main request

"1. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:
(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and
(iii) **prefiltration and** filtration of the second emulsion **using a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are** hydrophilic asymmetric **porous polyethersulfone** membranes, thereby providing a vaccine adjuvant."

b) Auxiliary request 1

"1. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant **comprising (i) squalene, polysorbate 80 and sorbitan trioleate or (ii) squalene, an α-tocopherol and polysorbate 80,** said method comprising steps of:
(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and
(iii) **prefiltration and** filtration of the second emulsion **using a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are**

hydrophilic asymmetric **porous polyethersulfone** membranes, thereby providing a vaccine adjuvant."

c) Auxiliary request 2

"1. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant **comprising squalene, polysorbate 80 and sorbitan trioleate,** said method comprising steps of:
(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and
(iii) **prefiltration and** filtration of the second emulsion **using a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are** hydrophilic asymmetric **porous polyethersulfone** membranes, thereby providing a vaccine adjuvant."

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

VIII. A communication from the Board, dated 22 January 2019 was sent to the parties. In this communication, it was stated in particular that the closest prior for assessing inventive step should be D1, and that there was no improvement shown by the claimed invention of the different requests over the teaching of D1. The Board was in particular of the opinion that the outcome of experiments of example 4 of the patent could not be taken in account in the assessment of inventive step. The Board concluded that none of the requests on file

appeared to be inventive over D1 in combination with D6 or D9.

IX. With a letter dated 25 February 2019, the appellant submitted new auxiliary requests 3 and 4.

Independent claim 1 of these auxiliary requests read as follows, difference(s) compared with claim 1 as granted shown in bold:

a) Auxiliary request 3

"1. A method for the manufacture of a squalene-containing oil-in-water emulsion vaccine adjuvant, comprising steps of:
(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less, **in which at least 80% by number of the oil droplets have an average size of 200 nm or less**; and
(iii) **prefiltration and** filtration of the second emulsion **using a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are** hydrophilic asymmetric **porous polyethersulfone** membranes, thereby providing a vaccine adjuvant."

b) Auxiliary request 4

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

(i) formation of a first emulsion having an average oil droplet size of 5000 nm or less;
(ii) microfluidization of the first emulsion to form a second emulsion having an average oil droplet size which is 500nm or less; and
(iii) **prefiltration and** filtration of the second emulsion **using a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are** hydrophilic asymmetric **porous polyethersulfone** membranes, and **wherein the avrerage oil droplet size after filtration is less than 220 nm**, thereby providing a vaccine adjuvant."

X. With a letter dated 13 March 2019, the opponent (hereinafter the respondent) submitted a new item of evidence:
D34: Catalogue from Sartorius Biotech, 2007

The respondent also filed experimental data corresponding to the data filed by the appellant with letter dated 2nd May 2017, completed by missing further data filed by the appellant in the opposition proceedings of the divisional application of the present patent.

XI. Oral proceedings took place on 21 March 2019.

XII. The arguments of the appellant may be summarised as follows:

As regards inventive step, D1 failed to disclose the nature of the filter which might be used to achieve the results shown in Figure 3. D1 was therefore non-enabling. On the contrary, the patent disclosed the

filter characteristics which could be used to achieve the results given in the examples; if the skilled person used a filter as defined in claim 1 of the main request then he would achieve the technical effects of the invention, but these effects could not be achieved by following the deficient disclosure of D1. The claimed invention therefore achieved a clear technical improvement relative to D1.

Moreover, the patent's examples showed an improvement when compared to the results in Figure 3 of D1. Paragraphs [0158] and [0160] of the patent specification state that filters 'A' and 'B', both of which meeting the criteria specified in claim 1, consistently provided a ~1000x reduction in the number of large droplets. Thus, the filters of claim 1 provided improved results.
Moreover, the results of example 4 of the patent and the experimental data provided with the letter of 2nd May 2017 confirmed this improvement.

The problem vis-a-vis D1 had to be defined as an improvement. The problem could be defined as the provision of a process for making a squalene-containing oil-in-water emulsion which enabled the achievement of low numbers of large oil droplets and which improved the yield of the final composition. The prior art gave no pointers to selecting this type of filter material for reducing the number of large oil droplets in such emulsions. On the contrary, if the skilled person tried to put D1 into effect then he would need to choose a filter material, for which he had a totally free choice, and could choose any of the various filters discussed in several documents and known at the priority date of the patent. All said documents presented indeed their filters as being the bests on

the market, and there would be no incitation to rather choose the filters described in D6 or D9; the choice of the filters disclosed in D6 or D9 could only be seen with an a hindsight.

Moreover, rather than making a random selection, the skilled person might have searched for materials that had previously been used for this type of emulsion. This search could lead them to inter alia D12, so they would choose a single-layer 0.22 µm hydrophilic symmetric PVDF membrane. When using these filters, however, the skilled person would have found that they quickly clogg, in view of the presence of large oil droplets, and the skilled person would first look at improving the effect of the microfluidization steps.

The same arguments applied to the auxiliary requests.

XIII. The arguments of the respondent may be summarised as follows:

Starting from Dl, the skilled person was looking for a specific filter to implement in the method disclosed and taught in Dl. The filter, or filtration step, was a feature common to both the claimed method and the method of Dl. As such, there was no need for any justification, whatsoever, as for the skilled person to decide to focus on the filtration. The question was whether the actual choice of the claimed filter was inventive over the prior art. Any attempt of the patentee suggesting, or implying, that the skilled person would have rather first looked at improving the effect of the microfluidisation step was just a diversion, which should be ignored.

Moreover, the argument as to the reduction in the number of large droplets in examples 1 and 2 of the patent was higher when using the filters 'A' and 'B' than when using the unspecified filters in D1 (lOOOx reduction and 220x reduction, respectively) was flawed, because the initial number of large droplets was not the same. Therefore, the apparent higher reduction level was simply due to a higher number present in the first place in the source emulsion to be filtered. It could not be attributed to a better filtration capacity.

The distinguishing feature between the method as claimed in claim 1 and the method disclosed in Dl was not associated with any technical effect going beyond the technical effect disclosed and taught in Dl. Whether in Dl or in the patent (from Tables 1 and 2 given in Examples 1 and 2), a similar number of large droplets of a size higher than 1.2 pm , the so-said "large droplets", was obtained after filtration. Accordingly, no improvement could be inferred. The skilled person would have tried the filters disclosed in D6 and D9, and the claimed solution could not be considered as inventive.

XIV. Requests

The appellant requested that the decision under appeal be set aside and that the patent be maintained based on the main request or one of auxiliary requests 1 or 2, filed with letter of 3 August 2016 or one of auxiliary requests 3 or 4, filed with letter of 25 February 2019.

The respondent requested that the appeal be dismissed and that the experimental data filed by the appellant

with letter dated 2 May 2017 not be admitted into the proceedings.

Reasons for the Decision

1. Admission of the experimental data filed by the appellant with letter of 2nd May 2017

The experiments of letter dated 2nd May 2017 have been filed by the appellant a few months after the statement of grounds of appeal, thus at an early stage of the appeal proceedings. They have been filed in response to questions raised during the opposition proceedings. These questions are still relevant in the appeal proceedings.

The experiments of letter dated 2nd May 2017 are therefore admitted into the proceedings (Article 13 RPBA).

2. Main request - Inventive step

2.1 The invention relates to the manufacture of a squalene containing oil-in-water emulsion adjuvant for vaccines by microfluidization and hydrophilic filtration. It relates in particular to improved methods for the production of microfluidized oil-in-water emulsions comprising squalene, such as MF-59, suitable for use on a commercial scale (see par. [0001] and [0005] of the specification). Said improvement is reflected by the number of oil droplets of size> 1.2 µm in the emulsion after filtration which has to be 100 times, ideally 1000 times fewer after filtration (see par. [0008]-[0011] of the specification).

2.2 D12 was considered as the closest prior art by the opposition division in its decision, and was also the choice of the appellant in its statement of grounds of appeal.

2.2.1 D12 discloses the manufacture of oil-in-water emulsion by microfluidization cycles on page 88. Seven cycles of microfluidization allowed the emulsion to have a mean droplet size of 165 nm, with a range of 81-270 nm. The document mentions that "when the number of larger particles is small, it becomes possible to filter the emulsion through a 0.22 µm filter membrane, thus allowing terminal filtration (6)". The reference (6) corresponds to document D26, which itself refers to D11.

It is however clear that the passages mentioned on page 88 of D12 by the opposition division in its decision refer explicitly and specifically to the SAF emulsion adjuvant which is an oil-in-water emulsion of squalane, and not of squalene. This is confirmed by the teaching of the cross-reference documents D26 and D11 which relates also explicitly to said SAF adjuvant comprising squalane, and not to an adjuvant comprising squalene.

The Board cannot follow the argumentation of the opposition division that squalane falls within the generic term squalene as defined in claim 1; squalane is hydrogenated squalene and has to be considered as a different oil, even if it might be considered that the process of manufacture of a microemulsion of squalane could be applicable and extrapolated also to the manufacture of a microemulsion of squalene. The cited passage on page 88 of D12 and the cross-referenced teaching in D26 and D11 therefore cannot be relevant

and taken into account for the selection of the closest prior art.

D12 discloses also further on page 91 a paragraph mentioned "Other Squalene and Squalane Emulsions" which relates to the MF-59 emulsion adjuvant, made from squalene. Said passage mentions that the MF-59 emulsions are prepared by microfluidization without any further details about the process of preparation of said emulsion MF-59 or of the droplet size of the emulsion. D12 presents therefore an incomplete teaching as to the process of preparation of the squalene microemulsion, namely adjuvant MF-59. In the absence of these technical features, it is also not possible to see in this passage of D12 a good starting point for the assessment of inventive step, especially in view of the disclosure of the other documents mentioned initially by the opponent in its notice of opposition.

2.2.2 The choice of the respondent in the opposition proceedings was indeed D1, D2 or D3 as closest prior art.

D1 relates specifically to the MF-59 emulsion adjuvant cited in D12, which is an oil-in-water emulsion comprising squalene, polysorbate 80 and sorbitan trioleate. It gives its method of preparation by mixing, microfluidization, and filtration (p. 213-217). Figure 1 shows a manufacturing process for a 50 L scale wherein the microemulsion is filtered twice through two 0.22 µm unidentified filters (therefore two single layer filters), namely a first filtration to remove large particles and a second filtration for sterilization. It indicates that, after the microfluidization, the filtration removes 99.5% of particles >1.2 µm in size and that the bulk emulsion

contained less than 0.1% of total particles that are >1.2 µm. Figures 2 and 3 of D1 give also details as to the average size of the droplets, which is around 150 nm before and after filtration, as well as the number of droplets >1.2 µm remaining according to the number of passes in the microfluidizer. Figure 3 shows in particular that the number of particles >1.2 µm before and after filtration is on the same scale and even lower than for the emulsions of the present invention, namely around 32 X 10^6 before filtration and 0.15 X 10^6 after filtration (see par. [0107] of the specification EP 2 506 832 B1, and examples 1 and 2). The method of manufacture of the MF-59 microemulsion is therefore identical to the method claimed in claim 1 of the main request, with the only exception that the filters are not identified in D1, i.e neither the type of filter(s), nor its material composition or filtration size, even if it is deductible that said filter is adapted to the filtration of a 50L volume.

2.2.3 The appellant's argument that the disclosure of D1 was non-enabling in the absence of any information as to the type of filter used could not be followed by the Board.

D1 indeed is silent as to the type of filters used, especially as regards its material composition, the only indication given in D1 being that they were single layer 0.22 µm filters. This information appears to be sufficient for a skilled person since such kind of filters is very commonly used in the pharmaceutical field.

Moreover, as shown by D11 and D26, and also as acknowledged by the appellant, one type of filter usually used for this type of vaccine adjuvant was a

0.22 µm single layer filter made from PVDF (polyvinylidene fluoride). An alternative filter for the specific preparation of the MF-59 vaccine adjuvant was also a 0.22 µm polysulfone filter as mentioned in paragraph [0004] of the contested patent, with reference to various documents. The filter used in D1 was therefore most likely a 0.22 µm single layer filter made from an hydrophilic polymer, such as PVDF or polysulfone.

In any case, for the sake of comparison with the claimed invention, it will be sufficient to consider that the filter used in D1 is any kind of 0.22 µm single layer filter.

2.2.4 D2 relates also to the MF-59 emulsion adjuvant and its teaching on pages 288-290 confirms the teaching of D1. Figures 9 and 10 give in particular the droplet size after microfluidization. As for D1, the type of the filter is not indicated.

2.2.5 D3 discloses on page 43 the preparation of an adjuvant which is a squalene in water emulsion, prepared by microfluidization and having a final size between 100 and 200 nm. The final emulsion is sterilised by filtration through an unspecified 0.22 µm filter.

2.2.6 Hence, the technical teaching given by in particular D1, but also D2 and D3 appears to be much more complete than the technical teaching given in D12. Since D1 presents the most complete teaching as regards the process of preparation of the squalene microemulsion MF-59 and since its disclosure presents the highest number of technical features in common with the claimed invention, this document appears clearly as being the closest prior art.

2.3 According to the appellant, the problem was the provision of a process for making a squalene-containing oil-in-water emulsion which enabled the achievement of low numbers of large oil droplets and which improved the yield of the final microemulsion composition.

2.4 As a solution to this problem, claim 1 of the main request proposes a step of prefiltration and filtration of the second emulsion characterized by using a specific type of filter, namely "a double-layer filter comprising a first membrane layer having a pore size >0.3µm and a second membrane layer having a pore size <0.3µm, wherein the first membrane layer and the second membrane layer are hydrophilic asymmetric porous polyethersulfone membranes".

2.5 According to the appellant, evidence supporting the alleged effect was provided in examples 1-3, 4 and the tests provided by the letter of 2nd May 2017.

Even though it might be questionable whether these examples and the tests provided with letter of 2nd May 2017 indeed support the existence of an improvement of the claimed process over the prior art, the Board will, in the appellant's favour, nevertheless start from the assumption that a filter as claimed in claim 1 of the main request does provide an improved result as regards the retention of particles of size >1.2 um, which is reflected by an improvement in the yield of the final microemulsion composition.

This supposed improvement is shown by the filters as claimed over single layer filters used in D1, whatever hydrophilic material may be used in said single layer filters.

2.6 It remains to determine if the claimed solution is obvious, namely whether a skilled person would have substituted a filter used in the manufacturing process of D1, whatever kind of filter it could have been, by the claimed filter in claim 1 of the main request.

2.6.1 The person skilled in the art had at his disposal a certain number of commercially available filters on the priority date of the disputed patent.

Some of such commercially available filters were the filters as claimed, which correspond to the filters described in D9. Such filters, namely the Sartopore® type filters, had been developed and placed on the market shortly before the priority date of the contested patent (see headnotes of D9).

D9 is a commercial brochure which shows graphically that membranes made from polyethersulfone provide generally a better flow rate, throughput or adsorption than membranes made inter alia from PVDF, polyamide or cellulose acetate (see Figures 2-4 of D9). D9 presents particularly "new innovative application specific approaches in membrane filtration", namely the Sartopore® double layer filters 2XLG 0.8/0.2 and 2XLI 0.35/0.2 (see D9, last page, left-hand column). The prefilter layers of the Sartopore filters are said to avoid the need of a prefiltration step and to achieve very high throughputs resulting in 30% higher effective filtration area per 10'' element, and the 0.2 um final layer is said to provide highly reliable bacterial retention (see D9, last page, left-hand and middle column).

In view of the commercial brochure D9, the skilled person would find a clear incitation to try the newly available filters presented therein, especially as they are presented explicitly as being more effective as the commonly used filters through the choice of their constituting component, namely polyethersulfone, and through their double-layer structure. Moreover, said double-layer filters are presented as eliminating the need for a specific prefiltration step for removing the large particles, which constitutes a further predictable advantage over the filters used in the process of D1.

Hence, the substitution of a filter in a known process by a newly available and convincingly presented as more efficient filter is an obvious measure or option for a skilled person. In view of the predicable improvement as to the efficiency of the claimed filter, the use of such filter is obvious for a skilled person.

2.6.2 The appellant argued that a skilled person had the choice among a large palette of commercially available filters, all said commercially available filters being usually presented in their commercial brochures as very or more efficient. Hence, the person skilled in the art would not be in a position to determine whether a commercially available filter is actually more efficient than another on the basis of commercial documentation, and to make choices accordingly. In support of its arguments, the appellant quoted in particular the filters shown in the commercial brochures D20 or D22 which extol the superior qualities of the filters described therein, i.e. PVDF 0.22 µm filters, which could have been the choice of the skilled person.

The Board could not follow the appellant's argumentation in view of the technical pointers disclosed in D9 (see point 2.6.1 above); in view of D9, the improvements which can possibly take place with the use of filters according to claim 1 were predictable improvements.

Moreover, a person skilled in the art remains usually particularly attentive to the most recent developments such as, in the present case, the newly developed filters presented in D9, which as such would already incite the skilled person to try said newly developed filters. The trend as to the choice of polyethersulfone as membrane component of filters and the use of asymmetric pores in the same filters for an improved filtration was also already known from document D6, and would have directed the skilled person to use such kind of filters, rather than the filters disclosed in D20 or D22. The disclosure of both documents D6 and D9 made clear that said recently developed filters had properties which made it plainly suitable for an efficient use in the manufacture of vaccine emulsions.

2.6.3 Moreover, according to the appellant, the choice of the filter as claimed in claim 1 showed a real improvement, which should as such constitute the foundation of the presence of an inventive step.

The Board could also not follow this argumentation, since the existence of an improvement is not necessarily bound with the presence of an inventive step. The existence of an improvement over the closest prior art does indeed not necessarily involve or imply an inventive step, it is rather the unexpected or surprising character of said improvement which does

involve an inventive step. In the present case, the improvement was predicable.

If the reasoning of the appellant were to be followed, the use of any kind of commercially available filter presenting an improvement over single layer filters would be considered as involving an inventive step. As shown by the experimental data of example 4 and of the tests provided by the respondent with letter of 13 March 2019, this would be the case for any double layer filter commercially available, in the same way as for the filter according to the invention.

2.7 The subject-matter of claim 1 of the main request is therefore obvious vis-à-vis document D1 in combination with D9. Consequently, the main request does not meet the requirements of Article 56 EPC

3. Auxiliary requests 1 to 4 - Inventive step

Compared to the subject-matter of claim 1 of the main request, the subject-matter of claim 1 of these requests has been amended by the respective following features:
- "comprising (i) squalene, polysorbate 80, and sorbitan trioleate or (ii) squalene, an α-tocopherol and polysorbate 80" in auxiliary request 1,
- "comprising squalene, polysorbate 80, and sorbitan trioleate" in auxiliary request 2,
- "(ii) microfluidization...in which at least 80% by number of the oil droplets have an average size of 200 nm or less;" in auxiliary request 3,
- "(iii) prefiltration and...and wherein the average oil droplets size after filtration is less than 220 nm..." in auxiliary request 4.

Since all said features are also disclosed in D1, they have no impact on the assessment of inventive step, and the reasoning and decision as to inventive step reached for the main request apply also to these requests.

Consequently, auxiliary requests 1 to 4 also do not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated