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Datasheet for the decision of 21 November 2022

Case Number: T 2623/18 - 3.3.07

Application Number: 13157613.4

Publication Number: 2601933

IPC: A61K9/107, A61K39/12, A61K39/39

Language of the proceedings: EN

Title of invention:
Hydrophilic filtration during manufacture of vaccine adjuvants

Patent Proprietor:
Seqirus UK Limited

Opponents:
SOCIETE D'EXPLOITATION DE PRODUITS POUR LES INDUSTRIES CHIMIQUES - SEPPIC
GlaxoSmithKline Biologicals S.A.

Headword:
Hydrophilic filtration during manufacture of vaccine adjuvants/NOVARTIS

Relevant legal provisions:
RPBA Art. 12(4)
RPBA 2020 Art. 13(1), 13(2)
EPC Art. 56

Keyword:
Admission of the main request (Yes)
Admission of a new document (Yes)
Admission of arguments regarding clarity (No)
Admission of arguments regarding inventive step (Yes)
Main request - Inventive step (No)

Decisions cited:
T 0247/20, T 2591/18, T 1344/16

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Case Number: T 2623/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 November 2022

Appellant: (Opponent 1)	SOCIETE D'EXPLOITATION DE PRODUITS POUR LES INDUSTRIES CHIMIQUES - SEPPIC 75, quai d'Orsay 75321 Paris Cédex 07 (FR)
Representative:	Alatis 3 rue Paul Escudier 75009 Paris (FR)
Appellant: (Opponent 2)	GlaxoSmithKline Biologicals S.A. P.O. Box rue de l'Institut 89 1330 Rixensart (BE)
Representative:	Thornley, Rachel Mary GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor)	Seqirus UK Limited Point 29 Market Street Maidenhead, Berkshire SL6 8AA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 31 August 2018 concerning maintenance of the European Patent No. 2601933 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	L. Basterreix

Summary of Facts and Submissions

I. European patent No. 2 601 933 was based on application EP 13 157 613.4, which is a divisional application of the earlier application EP 10 807 661.3 (publication number 2 506 832). It was granted on the basis of a set of 19 claims.

II. The patent had been opposed under Article 100(a) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step and extended beyond the content of the application as filed and the parent application.

III. The appeal of the opponents lies from the decision of the opposition division to maintain the patent as amended. The decision was based on 8 sets of claims filed with letter of 27 June 2018, as main request and auxiliary requests 1-7.

Claim 1 of auxiliary request 7 reads as follows:

"1. A method for manufacture of a pharmaceutically acceptable composition comprising a squalene containing oil-in-water emulsion vaccine adjuvant, comprising steps of:
(i) formation of a first emulsion having a first average oil droplet size;
(ii) microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size of 500 nm or less which is less that the first average oil droplet size; and
(iii) filtration of the second emulsion using a hydrophilic double-layer filter which has a first

hydrophilic polyethersulfone membrane layer having a pore size ≥0.3 µm, and a second hydrophilic polyethersulfone membrane layer having a pore size <0.3 µm, thereby providing a vaccine adjuvant."

IV. The documents cited during the opposition proceedings included inter alia the following:

D5: Dixit (Sartorius) - Membrane filtration in the biopharma industry
D6: Dixit (Sartorius) - The importance of prefiltration
Dll: Allison - Squalene and Squalane Emulsions as Adjuvants (1999)
D13: Ott- The Adjuvant MF59: A 10-Year Perspective (2000)
D15: Ott - MF59 Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines (1995)
D17: Cardona (Pall) - Biopharm article - Pleated Membrane Filters Improve Process Economics

V. According to the decision under appeal, the main request and auxiliary requests 1-7 were admitted into the opposition proceedings. The opposition division considered that these requests were a reaction to the objections raised by opponent 02's Rule 116 EPC submissions. The main request and auxiliary requests 1-6 did not meet the requirements of Article 123(3) EPC.

Auxiliary request 7 met the requirements of Articles 123(3), 76(1), 123(2) and 84 EPC.

With regard to inventive step, D11, D13 and D15 were found to be equally suitable as starting point. D13 was chosen since it was the only document describing filtration through two membranes. The differences

between claim 1 and D13 were the use of a double layer filter, the use of polyethersulfone membrane layers, and the first membrane layer having a pore size ≥ 0.3 µm. The data provided in example 4 of the patent showed a higher yield recovery for the emulsions prepared with the specific filters claimed. The problem to be solved was the provision of an improved manufacturing process for squalene-containing oil-in-water emulsions. The solution was not obvious in view of D13, D15, D11, D5, D6 or D17.

When starting from D15 or D11 as alternative closest prior arts, the conclusion was the same.

VI. Opponents 01 and 02 (hereinafter appellant 01 and appellant 02) filed an appeal against said decision.

VII. With a letter dated 24 May 2019 the patent proprietor (hereinafter the respondent) filed a new main request. The subject-matter of the independent claim 1 of the main request reads as follows, the difference(s) compared with the request maintained by the opposition division shown in bold:

"1. A method for manufacture of a pharmaceutically acceptable composition comprising a squalene containing oil-in-water emulsion vaccine adjuvant, comprising steps of:
(i) formation of a first emulsion having a first average oil droplet size **by circulation of the first emulsion component through a homogenizer a plurality of times**;
(ii) microfluidization of the first emulsion to form a second emulsion having a second average oil droplet size of 500 nm or less which is less that the first average oil droplet size; and

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

VIII. With a letter dated 10 February 2021, the appellant 02 submitted a new evidence:
D30: International Journal Of Cosmetic Science, 4, 207-218, 1982, "Influence du processus d'homogénéisation sur la stabilité des émulsions"

IX. Oral proceedings took place on 21 November 2022 in the presence of the appellants and the respondent.

X. The arguments of the appellants may be summarised as follows:

Admission of the main request and D30 into the appeal proceedings

According to appellant 02, the new main request should not be admitted into the appeal proceedings. The purpose of the present proceedings was not to provide the respondent with a chance to solve issues that he did not manage to solve in the parent case T 1344/16. The respondent did also not provide any reason why this request had not been filed during the opposition proceedings. Moreover, the request was not clearly allowable.

D30 was filed by appellant 02 in response to the filing of the new request and should be admitted.

Admission of the arguments of appellant 01 regarding clarity and inventive step objections filed with the letter dated 4 July 2022 (sections B and C)

According to appellant 01, the arguments on inventive step were a simple reformulation of the already presented arguments. The objection on lack of clarity was a new objection, since raised after the file was taken over by the new representative, but was admissible.

Main request - Inventive step

The closest prior art was D13. There was no evidence that step i) provided any effect. According to paragraph [0042], too many cycles of homogenization produced re-coalescence and a decrease of stability of the emulsion. No effect was demonstrated in paragraph [0043] which was a simple statement. The examples did neither provide any evidence of an effect. For instance, there was no mention of use of a homogenizer in the examples of the patent, in particular no comparative data (with and without homogenizer), and therefore no evidence that there was an actual advantage associated with circulating the first emulsion through a homogenizer a plurality of times.

Moreover, the use of homogenizers for preparing emulsions was well established in the field (cf. D30).

Consequently, the homogenization feature had no effect, and the problem was the provision of an alternative process. The claimed solution was an arbitrary feature which was obvious. Accordingly the claimed subject-matter was obvious in view of D5.

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

Admission of the main request into the appeal proceedings

The main request was an attempt at overcoming the deficiencies highlighted in decision T 1344/16 on the related case EP 2 506 832. The amended claim was based on auxiliary request 7 as maintained by the opposition division and included a further narrowing amendment. The present appeal was the earliest opportunity to file this request.

Admission of the arguments of appellant 01 regarding clarity and inventive step objections filed with the letter dated 4 July 2022 (sections B and C)

The appellant 01's submissions of 4 July 2022 contained arguments relating to the new feature of circulation through the homogenizer which were not present in the appellant 01's grounds of appeal. These arguments constituted an amendment to the appellant 01's case more than 3 years after the filing of the appeal and the reply thereto by the respondent. Said arguments comprised new objections under Article 76(1) EPC, about clarity and inventive step.

Main request - Inventive step

In view of the decision in T 1344/16, the respondent saw D13 as the closest prior art. The distinguishing features of claim 1 of the main request over D13 were the formation of the first emulsion by circulation of the first emulsion components through a homogenizer a plurality of times in combination with the use of a

double-layer hydrophilic polyethersulfone filter in which the first membrane layer has a pore size > 0.3 um.

Paragraph [0043] of the specification highlighted how the circulation of components in a homogenizer led to downstream advantages, specifically for the filtration step. This paragraph explained how circulation reduces both the number of large oil droplets and the average droplet size in the homogenised emulsion of step (i). These reductions led to an improved microfluidisation performance (step (ii)) and an improved filtration performance (step (iii)). Therefore, improved filtration performance was linked to the use of circulation in the homogenisation step.

Moreover, the patent examples also showed an improvement when compared to D13. Specifically, figure 3 of D13 provided data for the number of large particles during microfluidisation and following filtration of the oil-in-water emulsion. The number of large particles in figure 3 before filtration was $32x10^6$ /ml, and this was reduced to $0.2x10^6$ /ml after filtration, i.e. the filter leads to ~160x reduction in large particles. In contrast, [0163] and [0165] of the patent stated that filters 'A' and 'B' (both of which met the criteria specified in claim 1) consistently provided a 1000X reduction in large particles.

Therefore, improved filtration performance was also linked to the specific filter choice of claim 1.

Therefore, the combination of circulation through the homogeniser with the specific filter of claim 1 provided improved filtration results and the objective technical problem of claim 1 vis-a-vis D13 was the

provision of a process for making a pharmaceutically acceptable composition comprising a squalene-containing oil-in-water emulsion vaccine adjuvant, wherein the process included a filtration step having improved filtration performance.

None of the cited documents taught or suggested that the combination of circulation through the homogeniser a plurality of times and the specific filter of claim 1 would improve filtration results. Therefore, the subject-matter of claim 1 was inventive.

XII. Requests

Appellant 01 and appellant 02 requested that the decision under appeal be set aside and the patent be revoked.

Appellant 02 further requested that the main request not be admitted into the appeal proceedings and, should the main request be admitted into the proceedings, that document D30 also be admitted.

The respondent requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed with letter of 24 May 2019. The respondent also requested that the additional arguments of appellant 01 regarding clarity and inventive step objections filed with the letter dated 4 July 2022 (sections B and C) not be admitted into the proceedings.

Reasons for the Decision

1. Admission of the main request

1.1 The new main request has been filed in reply to the statement of grounds of appeal, at the earliest stage of the appeal proceedings.

In comparison to claim 1 of the request maintained by the opposition division, i.e auxiliary request 7 filed on 27 June 2018, claim 1 of the main request has been further restricted by the incorporation of a new feature, i.e. **" by circulation of the first emulsion component through a homogenizer a plurality of times"**.

This amendment finds a basis in the description of the patent application, on page 6, lines 20-22.

1.2 According to the respondent, the new main request was filed to overcome the deficiencies highlighted in the decision T 1344/16 of the Board of Appeal with regard to the assessment of inventive step. Said decision concerned the parent application of the present patent. The decision was issued on 6th May 2019, hence after the oral proceedings before the opposition division for the present case held on 11 July 2018.

1.3 In the Board's view, it is acceptable to limit the subject-matter of a request to take into account of the development of the jurisprudence, in the present case the technical decision T 1344/16, even if this request had been maintained by the opposition division. Moreover, it was reasonable to assume that the appellants could have mentioned decision T 1344/16 later in the appeal proceedings, and that this citation would have necessitated a reaction.

In the exercise of its discretion, the Board decides to admit the new main request for the reasons presented above (Article 12(4) RPBA 2007).

2. Admission of D30 into the appeal proceedings

This document has been filed by appellant 02 with a letter dated 10 February 2021, in response to the reply to the statement of grounds of appeal by the respondent. This filing is a direct response to the submission of a new main request, which is seen as a substantial case amendment. The document is indeed relevant to the amendment brought to claim 1, with regard to the assessment of inventive step.

Consequently, D30 is admitted into the appeal proceedings (Article 13(1) RPBA 2020).

3. Admission of the arguments submitted by appellant 01 regarding clarity and inventive step in sections B and C of its letter dated 4 July 2022

3.1 In its letter dated 4 July 2022, appellant 01 provided arguments relating to the main request regarding Article 76(1) EPC (Point A of the letter), lack of clarity of the new feature "by circulation of the first emulsion components through a homogenizer a plurality of times" (section B of the letter), and inventive step (section C of the letter).

3.2 The admittance of the submissions presented under sections B and C were objected to by the respondent under Article 13(2) RPBA 2020.

3.3 The Board notes that the arguments filed with the letter dated 4th July 2022 were filed after the parties had been summoned to oral proceedings and after the Board had issued a preliminary opinion on 4th April 2022. Accordingly, Article 13(2) RPBA 2020 applies. The provision of Article 13(2) RPBA 2020 indicates that: "Any amendment to a party's appeal case made...after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned."

In the Board's view, an amendment to a party's appeal case is a submission which is not directed to the requests, facts, objections, arguments and evidence relied on by the party in its statement of grounds of appeal or its reply. In other words: an amendment to a party's appeal goes beyond the framework established therein (Cf. decision T 247/20, point 1.3 or T 2591/18 point 2). Parties must however be allowed to refine their arguments, even to build on them provided they stay within the framework of the arguments, and of course the evidence, submitted in a timely fashion in the written proceedings.

3.4 The objection of lack of clarity raised by appellant 01 in section B of its letter of 4th July 2022 is a fully new objection raised at a late stage of the appeal proceedings.

According to Article 13(2) RPBA 2020, such late filed objection or argument can only be admitted under exceptional circumstances, which have been justified with cogent reasons by the party concerned. This is not the case with regard to the objection for lack of clarity. It furthermore could and should have been

filed much earlier in the appeal proceedings, since the main request was filed by the respondent with its letter dated 24 May 2019.

Consequently, the arguments submitted by appellant 01 regarding clarity constitute an amendment to the case and are not admitted into the appeal proceedings (Article 13(2) RPBA 2020).

3.5 With regard to the arguments on inventive step presented in section C of the appellant 01's letter of 4th July 2022, appellant 01 brought in summary the following arguments:
- point C-I) dealt with the choice of the closest prior art, which is D13,
- point C-II) identified the distinguishing features between the claimed subject-matter and the disclosure of D13,
- point C-III) related to the technical effect linked with the distinguishing features,
- point C-IV) defined the technical problem solved by the claimed invention,
- point C-V) dealt with the evaluation of the inventive step, in view of document D5.

Appellant 01 presented essentially the same arguments in its statement of grounds of appeal with regard to the set of claims held allowable by the opposition division. In this context it also discussed the content of document D13 as the closest prior art and the content of document D5. The arguments on inventive step presented in the letter of 4 July 2022 are therefore essentially an adaptation of previous arguments to take into account of the modification introduced in the new main request.

Hence, the Board takes the view that the arguments regarding inventive step presented by the appellant 01 in its letter dated 4th July 2022 and objected to by the respondent do not amount to an amendment of the appellant's appeal case. Therefore, the Board has no discretion not to admit them into the proceedings (Article 13(2) RPBA 2020).

Consequently, the submissions made by appellant 01 in its letter of 4 July 2022 are part of the appeal proceedings.

4. Main request - Inventive step

4.1 The claimed invention relates to the manufacture of oil-in-water emulsion adjuvants for vaccines.

4.2 The opposition division considered that document D13 was the closest prior art.The Board concurs with this decision.

D13 relates to the MF-59 emulsion adjuvant, which is an oil-in-water emulsion comprising squalene, polysorbate 80 and sorbitan trioleate. D13 discloses the method of preparation of the emulsion by mixing the components in an in-line homogenizer to obtain a coarse emulsion, microfluidization of the coarse emulsion to obtain a microemulsion, and filtration (p. 213-217, and page 214, first par.). Figure 1 shows a manufacturing process for a 50 L scale wherein the microemulsion is filtered twice through two 0.22 µm unidentified filters, namely a first filtration to remove large particles and a second filtration for sterilization.

D13 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 (see page 214, point 3.2).

Figures 2 and 3 of D13 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 in size remaining according to the number of passes in the microfluidizer. Figure 3 shows in particular that the number of particles >1.2 µm in size 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 (par. [0110] of the specification).

The **circulation of the first emulsion component through a homogenizer a plurality of times in step i)** and **the nature of the filter as specified in step iii)** constitute the distinguishing features between the subject-matter of claim 1 of the main request and the disclosure of D13.

4.3 According to the respondent, the problem is the provision of a process for making a pharmaceutically acceptable composition comprising a squalene-containing oil-in-water vaccine adjuvant, wherein the process includes a filtration step having improved filtration performance.

The opposition division defined the problem in its decision as the provision of an improved manufacturing process for squalene-containing oil-in-water emulsions.

4.4 As a solution to these problems, claim 1 of the main request proposes a method comprising inter alia a step (i) wherein a first emulsion is formed **by circulation of the first emulsion component through a homogenizer a plurality of times** and a step iii) of filtration of the second emulsion **using a hydrophilic double-layer filter which has a first hydrophilic polyethersulfone membrane layer having a pore size ≥0.3 µm, and a second hydrophilic polyethersulfone membrane layer having a pore size <0.3 µm.**

4.5 According to the respondent, the filtration results shown in examples 1-4 of the patent and as disclosed in paragraph [0043] show an improvement when compared to D13.

It must therefore be determined whether such improvement is credible and to what extent each distinguishing features might be involved in such improvement.

4.5.1 With regard to the feature that the first emulsion is circulated a plurality of times through the homogenizer, the Board observes there is no evidence on file that this step improves the filtration performance.

Indeed, the examples of the contested patent are completely silent with regard to the homogenization step. They do not mention that the first emulsion has been obtained via a plurality of re-circulation and focus mainly on the microfluidization step ii) and the filtration step iii). Moreover, the description clearly indicates that any improvement of the process is exclusively linked with the use of the specifically claimed type of filters (see paragraphs [0163], [0165],

[0169] of examples 1-3 and example 4). Thus, there is no evidence supporting the respondent's position that the circulation of the first emulsion through a homogeniser a plurality of times has beneficial effects on the process.

Paragraph [0043] mentions that "*circulation through the homogenizer is advantageous because it can reduce the average size of the oil droplets in the first emulsion*", in particular "*because it can reduce the number of oil droplets having a size >1.2 µm*". The passage lists other effects, namely that the circulation "*can provide advantages in downstream process(es)*", "*can lead to an improved microfluidization process which may then result in a reduced number of oil droplets having a size>1.2 µm in the second emulsion*" and "*can improve filtration performance*".

The conditions under which such improvements occur are however neither disclosed in the cited passage nor are they present in claim 1 of the main request, despite the fact that description of the patent highlights in paragraphs [0038]-[0042] the criticality of several parameters in the use of the homogenizers, in particular the speed of the rotor, the flow and shear rate, the temperature and the number of circulation cycles.

Moreover, the homogenization by a plurality of circulations has even possible drawbacks as mentioned in paragraph [0042], that would in fact have a contrary effect and lead to a decrease of performance of the process. Said paragraph [0042] indicates indeed that "*too many cycles may be undesirable as it can produce re-coalescence...Thus the size of the oil droplets may*

be monitored if homogenizer circulation is used to check that a desired droplet size is reached and/or recoalescence is not occurring".

Hence, in view of the above, it cannot be concluded that a step (i) wherein the first emulsion is formed by circulation of the first emulsion component through a homogenizer a plurality of times is associated with an improvement of the filtration.

4.5.2 With regard to the use of a double-layer filter as defined in claim 1, the situation appears to be identical to the case of the parent application (cf. T 1344/16).

As for that case, the Board accepts 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 (see T 1344/16, point 2.5).

4.5.3 The problem is therefore as posed by the respondent, i.e. the provision of a process for making a pharmaceutically acceptable composition comprising a squalene-containing oil-in-water vaccine adjuvant, wherein the process includes a filtration step having improved filtration performance.

4.6 It remains to determine if the claimed solution is obvious, namely whether a skilled person would have formed the first emulsion by circulation of the first emulsion component through a homogenizer a plurality of times, and whether a skilled person would have used a filter as defined in step (iii) of claim 1.

4.6.1 D13 discloses a homogenization as first step in the preparation of a vaccine adjuvant in emulsion form. The use of homogenizers for preparing emulsions was well established in the field, as shown by D30. In view of D30, the skilled person would also be able to adapt the homogenization process in order to provide a stable emulsion (see D30, "Synopsis" or "Summary" on page 207).

In the Board's view,the circulation of the first emulsion through a homogenizer a plurality of times, in the absence of any technical effect associated thereto, must be regarded as an arbitrary choice over a single circulation. Adapting the parameters of the homogenization step, such as modifying the number of circulations through the homogenizer, appears as a routine procedure that a skilled person would normally perform in order to obtain a stable emulsion.

4.6.2 With regard to the filters, the Board considers that the substitution of a filter in a known process by a newly available and more efficient filter is an obvious measure for a skilled person.

At the priority date of the contested patent, some of such newly commercially available filters were the filters as claimed, which correspond to the filters described in D5.

D5 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 D5). D5 describes in particular the Sartopore® double layer filters 2XLG 0.8/0.2 and 2XLI 0.35/0.2 (see D5, 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 µm final layer is said to provide highly reliable bacterial retention (see D5, last page, left-hand and middle column).

In view of the commercial brochure D5, the skilled person faced with the technical problem defined above, would find a clear incitation to try the newly available filters presented therein because they are presented as being more effective than 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 D13.

In view of the predicable improvements as to the efficiency of the claimed filter, their use in the process of claim 1 is obvious for a skilled person.

4.7 It follows that the main request does not meet the requirements of Article 56 EPC

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated