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Datasheet for the decision of 16 February 2022

Case Number: T 0313/19 - 3.3.07

Application Number: 10710427.5

Publication Number: 2396032

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Language of the proceedings: EN

Title of invention:
INFLUENZA VACCINES WITH REDUCED AMOUNTS OF SQUALENE

Patent Proprietor:
Seqirus UK Limited

Opponent:
Sanofi Pasteur Inc.

Headword:
Influenza vaccines with reduced amounts of squalene/SEQIRUS

Relevant legal provisions:
EPC Art. 83, 114(1), 54, 56

Keyword:
Sufficiency of disclosure - (yes)
Admission of novelty as a new ground of opposition (No)
Inventive step - (yes)

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Case Number: T 0313/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 February 2022

Appellant: (Opponent)	Sanofi Pasteur Inc. 1 Discovery Drive Swiftwater, PA 18370 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Seqirus UK Limited Point Level 3, 29 Market Street Maidenhead, Berkshire SL6 8AA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 November 2018 rejecting the opposition filed against European patent No. 2396032 pursuant to Article 101(2) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 2 396 032 was granted on the basis of a set of 7 claims.

Independent claim 1 as granted read as follows:

"1. An influenza virus vaccine for use in raising an immune response in a patient of 6 to <36 months of age comprising:
(i) hemagglutinin from at least two influenza A virus strains and at least two influenza B virus strains wherein the concentration of hemagglutinin per strain is at least 25µg/ml, and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is ≤10mg/mL and the minimum amount of squalene per dose is 0.5mg, and wherein the influenza B virus strains include a B/Victoria/2/87-like influenza B virus strain and a B/Yamagata/16/88-like influenza B virus strain, and wherein the vaccine has a unit dose volume of 0.2-0.3mL or 0.5mL."

II. The patent was opposed under Article 100(a) and (b) EPC on the grounds that its subject-matter lacked inventive step and was not sufficiently disclosed.

III. The appeal of the opponent lies from the decision of the opposition division to reject the opposition.

IV. The documents cited during the opposition proceedings included the following:
D1: WO 2008/128939
D2: WO 2008/068631
D3: WO 2008/043774

D4: WO 2007/052155
D5: Schneider M.M. et al: "Antibody response to tetravalent influenza subunit vaccine in patients infected with human immunodeficiency virus type 1", International Journal of Antimicrobial agents, Elsevier Science, Amsterdam, vol. 6, no. 4, 1 April 1996, pages 195-200
D6: Della Cioppa Giovanni et al, "Trivalent and quadrivalent MF59((R))-adjuvanted influenza vaccine in young children: a dose and schedule-finding study.", Vaccine, vol. 29, no. 47, November 2011, (2011-11-03), pages 8696-8704
D7: Schultze V. et al: "Safety of MF59(TM) adjuvant", Vaccine, vol. 26, no. 26, 19 June 2008, pages 3209-3222, XP022710569, Elseveier LTD, GB
D8: T. Jefferson et al: "Vaccines for preventing influenza in healthy children (Review)", Cochrane Database Syst Rev., 16 April 2008; (2), pages 1-195, XP055436549, England
D9: Vesikari Timo et al: "Enhanced Immunogenicity of Seasonal Influenza Vaccine in Young Children Using MF59 Adjuvant", Pediatric Infectious Disease Jour., Lippincot Williams & Wilkins, US, Vol. 28, no. 7, 1 July 2009, pages 563-571, XP009166530
D10: Allyn Bandell et al: "Protective efficacy of live attenuated influenza vaccine (multivalent, Ann Arbor strain): a literature review addressing interference", Expert Review of Vaccines, Vol. 10, no. 8, 1 August 2011, pages 1131-1141, XP055396776, GB
D11: Enlarged Table 3 of D6
D12: Sigma catalogue excerpt for squalene
D13: Sigma catalogue excerpt for alpha-tocopherol
D14: Taro Maeda et al: "Failure of inactivated influenza vaccine to protect healthy children aged 6-24 months", Pediatrics International, vol. 46, no. 2, 1 April 2004, pages 122-125, XP055515102.

V. According to the decision under appeal, the technical effect of "raising an immune response in a patient of 6 to 36 months of age" had been plausibly achieved, in particular in view of the prior art D9. The claimed invention was sufficiently disclosed.

Novelty as a new ground of opposition was not admitted since D1 and D2 were considered to be *prima facie* not relevant.

With regard to inventive step, D1 was considered to represent the closest prior art and the claimed subject-matter differed in that:
a) at least 25 µg HA per strain was present and
b) it had a lower than standard squalene concentration of 10 mg/ml, whereby the squalene amount was between 0.65 and 5 mg per dose, with an unit dose of 0.2-0.3 ml or 0.5 ml.
Since there was no disclosure in the granted patent of a technical effect, the problem was the provision of an alternative tetravalent ABBA influenza vaccine, suitable for raising an immune response in a patient 6 to 36 months of age. The claimed solution was not obvious.

VI. The opponent (hereinafter the appellant) filed an appeal against said decision.

VII. In his reply to the statement of grounds dated 23 August 2019 the patent proprietor (hereinafter the respondent) filed auxiliary requests 1 to 35.

VIII. A communication from the Board, dated 10 November 2021, was sent to the parties.

IX. With a letter dated 13 January 2022, the respondent filed corrected auxiliary requests 5, 11, 17, 23, 29 and 35.

X. Oral proceedings took place on 16 February 2022.

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

Main request - Sufficiency of disclosure

The claims of the contested patent were not limited to a specific medical use but they did include the use of the influenza virus vaccine in raising a protective immune response against the four influenza strains. The aspect of raising a protective immune response in a patient of 6 to <36 months of age by administering the claimed vaccine only once was not sufficiently disclosed and it was not credible that a single administration will result in a protective immune response in this immunologically naive patient group; the skilled person would not have expected that an immune response is obtained against all four influenza strains when the vaccine is administered only once to patients of 6 to <36 months of age. Furthermore, there was not a single reproducible example in the patent application as filed that would plausibly demonstrate that a protective immune response against the four influenza strains could be obtained after a single dose administration. The teaching of D9 could not be taken in account, since not representative of the common general knowledge at the relevant time, and published after the priority date of the patent. Thus, the requirements of Article 83 EPC were not met.

Main request - Novelty

The claimed subject matter of the contested patent was *prima facie* anticipated by D1 or D2. A pointer for the combination of all features could be found in D1. Given that each of the features recited in claim 1 of the contested patent was mentioned as a preferred embodiment, the skilled person would seriously contemplate an ABBA influenza vaccine according to claim 1, comprising 15 µg HA per strain and an oil-in water emulsion adjuvant with submicron oil droplets, comprising 0.5 mg squalene, in a dose volume of 0.5 ml. Such a vaccine would be considered suitable for "raising an immune response" in children of 6 to <36 months of age, according to the statement on page 43 of D1.

Main request - Inventive step

D1 had the most structural features in common and related to a similar purpose as the contested patent. In addition, D1 explicitly and specifically pointed out that “the adjuvanted quadrivalent influenza vaccine offered the advantage of enhanced prophylaxis for naive children as its superior efficacy compared to unadjuvanted vaccines”. No technical effect was derivable from the patent application as filed that could be attributed to the specific combination of all the features of claim 1, namely the dose volume, the squalene concentration, and the claimed HA concentration. The objective technical problem vis-a-vis D1 had to be formulated as the provision of an alternative oil-in-water adjuvanted ABBA vaccine suitable for human use. D1 contained a preclinical evaluation of adjuvanted ABBA vaccines in naive C57BL/6 mice (see Example IX), which credibly demonstrated the

protective effect of the disclosed vaccine. Naive mice, as used in Example IX, had not been primed with influenza virus to mimic the situation in immunologically naive subjects. Hence, the skilled person would have reasonably expected that there is a protective effect in immunologically naive human subjects, such as young children aged 6 to <36 months. The claimed solution was not inventive.

XII. The arguments of the respondent may be summarised as follows

Main request - Sufficiency of disclosure

It was plausible that an immune response against influenza virus infection was generated, because the vaccine contains adjuvant and at least four influenza virus strains. The skilled person would have considered it entirely plausible that at least the influenza A strains in such a composition would be able to elicit an immune response against influenza in a patient 6 to <36 months of age. No serious doubts had been provided to suggest that such an effect of raising an immune response against influenza could not be achieved by the claimed compositions. The plausibility of such effects was also supported by the prior art. For example, it was known from the prior art that even unadjuvanted, trivalent vaccines containing two A strains and one B strain (AAB) could raise an immune response in patients 6-24 months of age (see D14). This was confirmed by D8, D6 and D7. The examples of the patent also explained precisely how the skilled person could put the invention into effect.

Main request - Novelty

The lack of novelty objections should not be admitted.

There was no *prima facie* lack of novelty over D1. The cited passages of D1 were arbitrarily assembled from a patchwork in an attempt to arrive at the claimed subject-matter, in the absence of any pointer for their combination. At least three combined selections with regard to the HA concentration, the dose volume and the squalene concentration had to be made from D1 in order to arrive at subject-matter having these three features in claim 1. The selection of submicron droplets was neither unambiguously disclosed specifically in combination with the other selected features of claim 1.

There was neither *prima facie* lack of novelty over D2. Several selections in relation to the amount of HA, presence or absence of adjuvant, and composition of the adjuvant would have been required to arrive at the claimed subject-matter based. Moreover, D2 failed to provide any direct and unambiguous disclosure of an ABBA vaccine according to the claims in which the concentration of squalene is in the claimed range of <10mg/mL.

Main request - Inventive step

The claimed subject-matter was not an obvious alternative starting from D1 because:
- the provision of even alternative ABBA vaccines suitable for raising an immune response in young children was not a focus of D1; the whole focus of D1 was on using adjuvanted compositions so that lower amounts of influenza antigen may be used

- D1 provided no pointer towards the combination of features in the claims
- D1 when considering ABBA vaccines actually taught away from the claimed subject-matter in that it urged the use of only 2.5 µg HA per strain per dose in an ABBA vaccine suitable for raising an immune response in children (the dose volume of which is not specified).

XIII. Requests

The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked. The appellant also requested that auxiliary requests 5, 11, 17, 23, 29 and 35 filed with letter of 13 January 2022 not be admitted into the appeal proceedings.

The respondent (patent proprietor) requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained according to the set of claim filed as auxiliary requests 1-4, 6-10, 12-16, 18-22, 24-28, 30-34 with letter of 23 August 2018 and auxiliary requests 5, 11, 17, 23, 29 and 35 filed with letter of 13 January 2022.

The respondent mentioned that if the Board was not inclined to admit auxiliary requests 5, 11, 17, 23, 29 and 35 as filed with letter of 13 January 2022, it would maintain previous versions of these auxiliary requests as filed with letter of 23 August 2018.

Reasons for the Decision

1. Main request (patent as granted) - Sufficiency of disclosure

1.1 Claim 1 of the main request relates to an influenza vaccine comprising hemagglutinin from at least two influenza A virus strains and at least two influenza B virus strains (ABBA strains or vaccine) "for use in raising an immune response in a patient of 6 to 36 months of age".

The Board concurs with the respondent that the claims should be interpreted as purpose-limited product claims pursuant to Article 54(5) EPC. Claim 1 relates indeed specifically to an "influenza virus vaccine", containing hemagglutinin from at least four influenza virus strains in association with a vaccine adjuvant, which is a clear indication that the composition is a medicament. The association of such features defining the medicament with features defining a method falling under Article 53(c) EPC, namely "for raising an immune response" provides the basis for the interpretation of the claim under Article 54(5) EPC.

The Board cannot follow the reasoning of the opposition division that the subject-matter of claim 1 was not covering a medical indication pursuant to Article 54(5) EPC, because "*the indication of "raising an immune response in a patient of 6 to <36 months of age" in claim 1 incorporates both specific and unspecific immune response*", the specific response being directed to the influenza A and B strains antigens, and the unspecific response being generated by the adjuvant. Thus, in the opinion of the opposition division, in case of absence of a specific response against the

influenza antigens, claim 1 would cover only a non-medical use.

The Board concurs in this regard with the respondent (paragraph 3.4 of its reply) that this claim construction, wherein only unspecific responses to the adjuvant are elicited by the vaccine, is not that of a skilled person with a mind willing to understand. Indeed the claim relates to "influenza virus vaccine" containing hemagglutinin from at least four influenza virus strains. There is no reason to assume that such a vaccine would elicit only a non-specific response.

1.2 According to the appellant, a skilled person would not be able to prepare the claimed invention, since it is doubtful that a protective immune response can be obtained with the ABBA strains in children that are immunized for the first time, in particular after only a single administration. Such specific immune response was not made credible in the application as filed, in view of the absence of experimental data, and is particularly doubtful with regard to the B strains. The appellant cites furthermore the experimental results of the post-published document D6 in support of its arguments.

1.3 According to the jurisprudence of the Boards, the requirements of sufficiency of disclosure are met if the patent in suit contains sufficient information to enable the skilled person to carry out the invention, i.e when at least one way is clearly indicated in the patent specification enabling the skilled person to carry out the invention, and when the disclosure allows the invention to be performed in the whole area claimed without undue burden, applying common general knowledge. Post-published evidence can possibly be

taken into account to back-up the findings in the patent.

1.4 In the present case, the subject-matter of claim 1 relates to a vaccine composition specifically "for use in raising an immune response in a patient of 6 to <36 months of age". This wording does not require the achievement of any particular level of effectiveness in terms of immune response. In particular the claimed invention is neither directed specifically to a "seroprotection or a seroconversion". The technical effect to be achieved, i.e. "for use in raising an immune response in a patient of 6 to <36 months of age" remains indeed broadly defined.

Moreover, the claimed invention is also not restricted to any dosage regimen, such as a limitation to a single administration, and the description of the specification discloses explicitly that the "treatment can be by a single dose schedule or a multiple dose schedule" and that "multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule" (see paragraph [0095] of the specification). Thus, in case of insufficient immune response after a single dose the skilled person would be taught by the description to use multiple doses. The same passage of the description teaches furthermore in detail the possible multiple dose time schedule, giving therefore also sufficient information on this point.

1.5 It is undisputed that the description of the patent does not disclose experimental data demonstrating the effectiveness of the vaccine in raising an immune response in a patient of 6 to <36 months of age has been achieved.

The description of the patent discloses indeed the administration of a trivalent influenza AAB vaccine to adults and indicates in paragraphs [0111] and [0112] that all three CHMP criteria were met for the influenza A and B strains without giving any detailed experimental results.

There is a further example of an administration of a ABBA vaccine to patients of 6 to <36 months of age, wherein at least several groups of patients were injected a composition as claimed (see Groups F, I, J and N, paragraph [0107]). Said example does however not specify any result with regard to the immune response obtained.

1.6 There are however no serious doubts substantiated by verifiable facts supporting the appellant's position that the claimed effect of raising an immune response in a patient of 6 to <36 months of age is not achieved.

Indeed in the Board's view there is no reason to doubt of the effectiveness of a tetravalent ABBA vaccine in young children having regard to the presence of evidence that an immune response in this group of patients is provided by other kind of influenza vaccines, such as in particular AAB influenza vaccine or single strain influenza vaccines A or B, as shown by some cited prior art documents (see below). The effect claimed in the patent does furthermore not go against any prevailing opinion in the prior art cited by the parties in the proceedings.

For instance, D14 describes a study published in 2004 in which children aged 6-24 months were administered a unadjuvanted trivalent AAB influenza vaccine in two doses (see “Immunization” on page 123). As explained on

page 124 (right hand column), the responses varied with the vaccine immunogen, but sero responses of infants and young children to the influenza vaccines were identified.

D8 describes numerous studies in which young children were vaccinated with various influenza antigen vaccines, such as the studies of Ritzwoller 2005 (page 9) in patients 6-23 months of age using AAB vaccines which were licensed for that age group.

D7 also explains that it was recommended by the Advisory Committee on Immunization Practices (ACIP) that children 6-23 months of age be vaccinated with trivalent inactivated influenza vaccine and further explains in this section that the adjuvanted trivalent AAB vaccine FLUAD had been tested for safety and immunogenicity in young children, including patients 6-59 months of age (see Section 5.3.6).

D2 discloses on pages 3 and 4 tetravalent vaccines ABBA. D2 further specifies that the vaccines according to the invention may be used to treat children from the age of 6 months, and vaccines containing antigen from more than one influenza B virus strain are particularly useful for treating patients in the 0-15 years old group (see pages 32, 33). D1, which represents the closest prior art of the appellant in the assessment of inventive step, also considers tetravalent ABBA vaccines for young children (see page 42, lines 13-18).

1.7 This prevailing opinion is further confirmed by the post-published documents D6 and D9.

D9 indicates the existence of a long-lasting and broad immune response in young children vaccinated by two

doses of an ABA trivalent influenza vaccine adjuvanted with MF49 (see Abstract or Figure 2).

D6 discloses the study of the administration of trivalent and tetravalent MF-59® adjuvanted (squalene oil-in-water submicron emulsion) influenza vaccine in young children; the tetravalent vaccine is a ABBA vaccine of the same type as claimed in claim 1 of the main request. The document mentions that for the first B strain, only the adjuvanted formulation met the CHMP criteria after the first administration, while for the second B strain this was reached after the second vaccination only. Hence, after two vaccinations by a tetravalent vaccine all CHMP criteria were met, which confirms the efficiency of the adjuvanted ABBA vaccine in children (see page 8699, paragraph bridging the two columns and Table 3).

1.8 Consequently, the requirements of sufficiency of disclosure are met by the main request.

2. Main request - Novelty

2.1 During the oral proceedings before the opposition division, the opponent requested to introduce the new ground of opposition of lack of novelty of the main request over documents D1 and D2. These documents were however considered *prima facie* not relevant by the opposition division which decided to not admit the new ground of opposition in the opposition proceedings. In particular, the opposition division considered that multiple selections from these documents were necessary to arrive to the claimed subject-matter.

2.2 Claim 1 of the main request comprises *inter alia* the following features defining the composition of the vaccine and the dose:

1) an influenza vaccine with ABBA strains,
2) the concentration of HA per strain is at least 25 µg/ml,
3) an oil-in-water emulsion adjuvant with sub-micron oil droplets, comprising squalene
4) the squalene concentration is less than 10 mg/ml with a minimum of 5 mg per dose,
5) the dose volume is 0.2-0.3 ml or 0.5 ml.

2.3 The Board notes first that both documents D1 and D2 were cited in the notice of opposition in the context of the assessment of inventive step only and not under novelty, namely that the claimed invention was not inventive over D2 as closest prior art in combination with D1.

2.4 D1 relates possibly to influenza vaccines comprising single influenza strain, trivalent composition, quadrivalent compositions or pentavalent composition (see D1, page 41).

Moreover, the amount of HA per strain in D1 in the case of a tetravalent vaccine is given on page 43 and is about 15 µg, or 10 µg, so as to achieve a maximum of 40-45 µg HA per dose (page 43, lines 2-5); the same passage on page 43 mentions that the HA per strain is at about or below 5 µg, or at about 2.5 µg or below (see D1, page 43, lines 1-6). The dose volume is given in Table 1 on page 17 of D1 with volumes of 0,5 ml or 0.7 ml. If a particular dose volume of 0.7 ml is chosen, then none of the HA amounts listed on page 43 falls under the claimed concentration of at least 25

µg/ml. If the dose volume of 0.5 ml is chosen, only the value of 15 µg can fall under the scope of claim 1 of the main request.

In the same Table 1, the concentrations and amounts of squalene can be less than 10 mg/ml with a minimum of 5 mg per dose, as claimed in claim 1 of the main request, only in a few cases and only when a final volume of 0.5 ml is chosen (see tables 1A and 1b).

Submicron droplets are disclosed in D1 only as a possible option (see page 15, line 14).

Consequently, the Board concurs with the opposition that multiple selections for at least features 2)-5) would be necessary to arrive at the claimed subject-matter. A vaccine as claimed in the main request is not derivable directly and unambiguously from D1, which is *prima facie* not relevant for novelty.

2.5 In document D2, the use of a oil-in-water submicron emulsion with squalene is only one of several possibilities given on pages 17-19. The same consideration applies to the amount of HA (see D2, page 1, lines 23-27 and page 2, line 22, page 9, lines 12-14). The influenza antigens have also to be selected among several possibilities, namely among the AABB type, AAABB, AAAABB or AAAB type (see D2, page 5 and 37 and claims 7, 9-15).

Thus, multiple selections are needed to arrive at the subject-matter claimed in claim 1 of the main request. Therefore, the Board agrees with the opposition division that this document is *prima facie* not novelty-destroying.

2.6 Consequently, the opposition exercised correctly its discretionary power in not admitting novelty as a new ground of opposition.

3. Main request - Inventive step

3.1 The claimed invention relates to a vaccine for protecting children aged 6 to under 36 months against influenza virus infection, in particular vaccines that include reduced amounts of squalene.

3.2 The opposition division considered that D1 was the most promising starting point for the assessment of inventive step in its decision. The appellant considered D1 and D2 as possible closest prior art in its written submissions, but considered during oral proceedings that D1 was most suitable, since relating to the same purpose and presenting the most features in common with the claimed subject-matter. The respondent was of the opinion that D14 (or D8) should be the closest prior art.

3.2.1 D14 is a general article about the influenza vaccination of children which reports the weak efficacy of influenza vaccination performed on children under 36 months. The vaccines were unadjuvanted and were divalent AB or trivalent AAB influenza vaccines.
D8 is a general review on the influenza vaccination in children which mentions inter alia the study of D14 on page 16, in particular the composition of the unadjuvanted influenza vaccine used in D14. In view of their disclosure, these documents represent the common general knowledge at the priority date, but they are less close than D1 to the subject-matter of the main request (see below) and therefore do not represent the most promising starting point for assessing inventive

step. During the oral proceedings, the respondent eventually argued on inventive step starting from D1 as the closest prior art.

3.2.2 D1 relates to vaccines against influenza with hemagglutinin from A and B strains, in the form of single strains as well as bivalent, trivalent, tetravalent and pentavalent strains (see from page 41, line 13 to page 42 line 6). A tetravalent influenza vaccine is envisaged on page 42-43, with two A strains, and two B strains such as from B/Victoria and B/ Yamagata. The amount of HA per strain is about 15 µg, and suitably this amount is low, optionally at about 10 µg HA per strain so as to achieve a maximum of 40-45 µg for all strains in the dose (page 42, lines 2 to 5).

D1 mentions explicitly on page 43 (lines 12-13), that the tetravalent vaccine ABBA is particularly suitable for very young children. In this case, the dose of the immunogenic composition is suitably the half of an adult human dose, and will comprise 2.5 µg HA per strain. It is in the form of an oil-in-water emulsion comprising squalene in an amount of between 2.5-3.5 mg, 2-3 mg or 1-2 mg per dose, thus less than the minimum claimed (page 43, lines 15-18). D1 furthermore states (page 43, lines 22 to 25) that a low amount of HA such as below 2.5 µg for children would have the advantage to limit the impact of an addition influenza strain on the global vaccine supply. This passages of D1 do not indicate whether the adjuvant is in the form of submicron droplets, and neither the dose volume, which makes it impossible to determine the concentration of the different components of the vaccine.

D1 discloses in the paragraph bridging pages 16-17 that the human dose is comprised between 0.25 and 1.5 ml and

for paediatric population, a human dose may be less than 0.5 ml, for example between 0.25 and 0.5 ml. Hence, the selection of a children dose of 2.5 µg per strain (10 µg in total) with a dose of 0.5 ml cannot lead to a final concentration of 25 µg/ml as claimed (10 µg in total for 0.5 ml, thus 20 µg/ml), and it would be necessary to select a dose of less than 0.4 ml to arrive at the claimed concentration, such as 0.3 ml or 0.2 ml. Such a low dose volume would however contain a concentration of squalene which could be higher than the claimed 10 mg/ml, when the amount of squalene is 2.5-3.5 mg or 2-3 mg per dose.

On page 17, Table 1 of D1 gives several adjuvant compositions which have a minimum of 0.5 mg of a squalene adjuvant per dose and less than 10 mg/ml when a dose of 0.5 ml is chosen(B, E, F, C, H, G, D, J-P, Q-X). This Table does however not specify which influenza strain might be incorporated in the composition.

The possibility to have an adjuvant emulsion in the form of submicron droplets is also mentioned in D1, on page 15, lines 14-20.

Example IX (page 100) discloses the use of a specific ABBA vaccine with 1.5 µg HA in 0.1 ml, hence 15 µg/ml, for the immunisation of mice. One group of mice is treated with a adjuvanted composition QIV AS03 half diluted, corresponding to an amount of 5.35 mg/ml of squalene (see Table 3 on page 76). Said adjuvant is a submicron oil-in-water emulsion.

Consequently, no matter which part of the disclosure of D1 is used as starting point, multiple selections among the dose volume, the amounts and concentration of HA

and/or of the adjuvant, as well as the submicron size of the emulsion droplets, are always necessary to arrive at the claimed subject-matter; when starting in particular from the disclosure on page 43, it is necessary to make a selection among the concentration of HA per strain, the submicrom size of the emulsion droplets, the squalene concentration and its minimum amount, as well as the dose volume.

3.2.3 D2 discloses several types of influenza vaccines, such as AAAB and ABBA, with a preference for the tetravalent ABBA vaccines with the same B strains as claimed, which are however not necessarily adjuvanted, even less adjuvanted with a squalene-containing oil-in-water emulsion at the concentration required by the claims (see page 4, lines 23-25). D2 does not contain any specific teaching that when the composition is an ABBA vaccine, and contains squalene, the squalene should be present at a concentration of <10mg/mL, much less that the same composition should also have an HA concentration per strain of at least 25pg/ml.

Several HA concentrations are disclosed in D2 in the form of multiple alternatives ranging from 15 µg per dose, or less than 15 or 10 µg, or even more than 30 µg per dose (see page 1 or page 9). Even in light of the 0.5ml and 0.25ml dose volumes recited in D2 (see page 13, lines 32-33), the skilled person would have to choose between various HA concentrations falling within or outside the claim, without any pointer as to which is preferred in the context of ABBA vaccines.

Multiple options of adjuvants are disclosed in D2, among which a submicron emulsion comprising squalene (see pages 14-16) without any indication that such

emulsion is preferred and without specification of the amounts of squalene.

The treatment of children is mentioned in D2, with alternative patients to be treated going from 6 months, less than 1 year old, 1-5 years old, 5-15 years old, 15-55 years old and at least 55 years old (see page 32).

3.2.4 Consequently, the disclosure of D2, D8 and D14 is technically more remote from the claimed subject-matter, while D1 clearly relates to the same purpose. Therefore the Board does not see any reason to deviate from the decision of the opposition division as regards the choice of the closest prior art, which is document D1.

3.3 According to the appellant, the problem is the provision of a further influenza vaccine as defined in its written submission or an alternative influenza vaccine as defined during oral proceedings.

According to the respondent, the problem is the provision of a further adjuvanted oil-in-water emulsion vaccine which increases protection against A or B strains of influenza virus in children under 36 months.

According to the opposition division, the problem is the provision of an alternative tetravalent ABBA influenza vaccine, suitable for raising an immune response in a patient of 6 to <36 months of age.

3.4 The solution to any of these problems is an influenza vaccine as claimed, comprising in particular:
1) HA strains, wherein the concentration of HA per strain is at least 25 µg/ml,

2) an oil-in-water emulsion adjuvant with sub-micron oil droplets,
3) squalene with a concentration less than 10 mg/ml and a minimum of 5 mg per dose,
4) a dose volume of 0.2-0.3 ml or 0.5 ml.

3.5 The respondent relied on document D6 to show that the problem was solved. This document shows indeed the efficiency of such vaccine after two administrations to children (see point 1.7 above). In view of this document, the Board, in line with the conclusion of the opposition division, considers that the problem of providing an alternative vaccine suitable for raising an immune response in young children has been solved.

3.6 It remains to determine whether the claimed solution is obvious.

There is no indication in D1 that an ABBA vaccine having the features defined in claim 1 of the patent would be effective in raising an immune response in young children.

D1, when considering more particularly ABBA vaccines for children actually teaches away from the claimed subject-matter in that it urges the use of only 2.5 µg HA or less, per strain and per dose, without specification of the dose volume; this low amount of HA strains makes it impossible to reach the claimed 25 µg/ml. The focus of D1 is indeed particularly on using adjuvanted compositions with higher amounts of adjuvant so that lower amount of influenza antigen may be used (see page 43, lines 3-6).

A suggestion towards the claimed solution can neither be found in the examples of D1, in particular example

IX of D1. Example IX is a preclinical evaluation of adjuvanted and non-adjuvanted trivalent or tetravalent vaccines in naive and primed mice, and does therefore not relate to the vaccination of children. In any case, the dose volume used in this example is 100 µl, and the amount of HA is 1.5 µg which results in a concentration which is less than the claimed concentration. Only one of the 7 treated groups is treated with a vaccine comprising a squalene emulsion in submicron droplet size. However, it comprises 5.35 mg of squalene at a concentration of 10.7 mg/ml (See Group 6 of Table 21 and Table 3 page 76), i.e. a concentration which is higher than the maximum concentration allowed by claim 1. Hence, the teaching of this example, as the rest of D1, does not lead the skilled person seeking to provide a vaccine capable of raising an immune response in children <36 months to a vaccine having the features defined in claim 1.

Consequently, the main request is inventive.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated