BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 17 August 2000

Case Number: T 1071/97 - 3.3.2

Application Number: 90305744.6

Publication Number: 0399843

IPC: A61K 9/107

Language of the proceedings: EN

Title of invention:
Adjuvant formulation comprising a submicron oil droplet emulsion

Patentee:
CHIRON CORPORATION

Opponents:
SmithKline Beecham Biologicals SA
Akzo Nobel N.V.

Headword:
Vaccines/CHIRON

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2), 111, 113, 125

Keyword:
"Third and fourth auxiliary requests: admissibility (no), late-filed, fresh cases; first auxiliary request: allowability (no): disclaimer contravenes Article 123(2) EPC"
"Main and second auxiliary requests: novelty (yes): subject-matter of the claims not directly and unambiguously derivable from the cited state of the art; inventive step (no): replacement of the emulsifying agent in the closest vaccines by different known emulsifying agents obvious; sufficiency (yes): the same level of skill has to be applied to the question of inventive step and sufficiency of disclosure, no

evidence provided to support allegation of insufficiency"

Decisions cited:
G 0010/91, T 0020/81, T 0153/85, T 0060/89, T 0917/94, T 0863/96, T 0013/97

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1071/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 August 2000

Appellant: (Proprietor of the patent)
CHIRON CORPORATION
4560 Horton Street
Emmeryville
California 94608 (US)

Representative:
Hallybone, Huw George
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA (GB)

Party under Article 107 EPC: (Former opponent 01)
SmithKline Beecham Biologicals SA
89 rue de l'Institut
1330 Rixensart (BE)

Representative:
Dalton, Marcus Jonathan William
SmithKline Beecham
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP (GB)

Respondent: (Opponent 02)
Akzo Nobel N.V.
Velperweg 76
6824 BM Arnhem (NL)

Representative:
van Wezenbeek, Lambertus A.C.M.
N.V. Organon
P.O. Box 20
5340 BH Oss (NL)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 22 August 1997 revoking European patent No. 0 399 843 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
B. J. Schachenmann

Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 399 843, which was granted in respect of European patent application No. 90 305 744.6 with a first set of 32 claims for all designated states, except ES and GR, and a second set of 30 claims for ES and GR.

II. Respondent (opponent 02) and the party under Article 107 EPC (former opponent 01, see paragraph VII below) originally filed oppositions against the grant of the patent and requested that it be revoked in its entirety pursuant to Article 100(a) and (b) EPC on the grounds of lack of novelty (Articles 52(1); 54 EPC), and inventive step (Articles 52(1); 56 EPC) and insufficiency of disclosure (Article 83 EPC). The grounds of opposition were supported, *inter alia*, by the following citations:

(1) L. F. Woodard and R. L. Jasman, "Stable oil-in-water emulsions: preparation and use as vaccine vehicles for lipophilic adjuvants", published in Vaccine, vol. 3, June 1985, pages 137 to 144,

(2) EP-A-0382 271,

(3) M. Sing et al. "Parenteral Emulsions as Drug Carrier Systems", published in J. Parenteral Science & Technology, vol. 40, No. 1, 1986, pages 34 to 40.

III. The patent was revoked pursuant to Article 102(1) EPC by a decision of the opposition division posted on 22 August 1997. The decision was based on the main and

auxiliary requests filed during the oral proceedings. Each request included an amended set of 32 claims for all designated states, except ES and GR, and an amended set of 30 claims for ES and GR.

IV. The stated ground for the revocation of the patent was that neither the main request nor the auxiliary request involved an inventive step over citation (1). The essence of the reasoning in the decision of the opposition division was as follows:

Since the feature in claim 1 requiring that at least 80% of the oil droplets were less than 0.5 µm in diameter was neither explicitly nor implicitly disclosed in any cited document, the claimed subject-matter in the patent in suit met the requirement of novelty.

On the other hand, citation (1) disclosed the use of stable oil-in water emulsions as vaccine vehicles for lipophilic adjuvants and taught that, when oil-in-water emulsions were stable, the droplet-size was considerably reduced so that at least some droplets were in sub-micron range. Since moreover the cited document provided evidence that such oil-in-water emulsions *per se* had a significant intrinsic adjuvant activity, the skilled person would have reasonably expected the claimed emulsions to exhibit the same significant intrinsic activity.

Citation (1) admittedly did not disclose that in stable emulsions 80% of the oil droplets were less than 0.5 µm in diameter. However, no reasonable argument or evidence was provided to show that this distinguishing feature was unexpectedly associated with some improved

effects or properties of the claimed vaccine adjuvant compositions or the claimed complete vaccine compositions themselves.

V. The appellant filed an appeal against this decision. The statement of grounds for the appeal was accompanied, *inter alia,* by the following document:

(4) L. F. Woodard, “Adjuvant activity of Water-Insoluble Surfactants”, published in Laboratory Animal Science, vol.39, No. 3, May 1989, pages 222 to 225.

VI. In their observations on the grounds of appeal the respondent and former opponent 01 referred, *inter alia,* to the following citations:

(5) EP-A-0 315 153

(6) C. Washington et al., "The production of parenteral feeding emulsions by Microfluidizer", published in Int. J. Pharmaceutics, 44, 1988, pages 169 to 176.

VII. By a faxed letter dated 10 July 2000 former opponent 01 withdrew its opposition.

VIII. In advance of the oral proceedings scheduled for 16 August 2000, the appellant filed on 14 July 2000 a new main request and four auxiliary requests and cancelled all previously filed requests. Each newly filed request included a set of claims for ES and GR and a set of claims for the other designated states.

IX. At the beginning of the oral proceedings, the board

drew the appellant's attention to the disclaimer in amended claim 27 of the main request, the first and second auxiliary requests for all designated states, except ES and GR, and in the corresponding amended claim 18 of both the third and fourth auxiliary requests. In the board's judgment, the disclaimer in question, which was amended so as to read :"wherein said composition does not include a block polymer **or an antigen**", was worded in such a way as to extend the protection conferred by the claims as granted contrary to Article 123(3) EPC.

Further, the board indicated that the range of the amount of the emulsifying agent specified in claim 1 of the first and second auxiliary requests for ES and GR was inconsistent with the corresponding ranges given in claim 1 of the first and second auxiliary requests respectively for the other designated states.

As a consequence of these objections, the appellant submitted in substitution for all previously filed requests a revised main request and revised auxiliary requests 1 to 4, wherein the wording **"or an antigen"** in the disclaimer had been deleted and wherein the above-mentioned inconsistencies had been removed.

Each request included a set of claims for ES and GR and a separate set of claims for the other designated states. Independent claims 1 and 28 of the main request for the designated states, except ES and GR, read as follows:

"1. A process for the production of a vaccine composition, comprising the steps of adding an immunostimulating amount of an antigen to an

immunostimulating amount of an adjuvant formulation, said adjuvant formulation comprising:

(1) 0.5 to 15% by volume of a metabolizable oil and

(2) 0.02 to 2.5% by weight of an emulsifying agent,

wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets wherein at least 80% by number of said oil droplets are less than 0.5 µm in diameter, wherein said composition does not include a block copolymer and wherein said antigen is added to said adjuvant formulation after the preparation of said adjuvant formulation.

28. A vaccine composition obtainable by a process according to any one of claims 1 to 26."

X. The appellant's arguments submitted in writing and during the oral proceedings can be summarised as follows:

The independent claims of all newly filed requests were novel over the prior art submitted in the course of the opposition and opposition appeal proceedings.

The information in Table 7 of (1) concerning the preparation of a vaccine wherein BSA and avridine were added to the saline phase of an intralipid 10% soybean oil emulsion were inadequate for reproducing the experiment precisely and, for that reason, for determining the precise percentages of the various components and particularly the diameter of the oil droplets. Although the respondent had asserted that

intralipid 10% was a commercially available product the formulation of which had not been changed over the years, the conflict of evidence in citations (3) and (6) regarding the droplet size could only make sense if intralipid 10% was a variable product.

Citation (1) did not provide a direct and unambiguous teaching of a process involving adding an antigen to the aqueous phase of an oil-in-water emulsion with a droplet size of substantially less than 0.5 µm containing 0.02 to 2.5% by weight of an emulsifying agent. The second auxiliary request additionally distinguished the claimed vaccine composition from the prior art of (1) by limiting the emulsifier to 1% by weight maximum.

The ranges of oil and emulsifier specified in the present requests were not disclosed in citation (2) either, nor did (2) teach that substantially all the droplets had a particle size of less than 0.5 µm.

As far as inventive step was concerned, the teaching of (1) was contrary to the claimed invention. Thus (1) taught that stable emulsions were required and this was achieved with a 1:1 oil/emulsifier ratio. The present invention on the other hand employed relatively low levels of emulsifier.

Moreover,(1) taught that the antigen must be added to the internal oil phase, whilst the claimed invention required the antigen to be placed in the external aqueous phase.

Further,(1) did not disclose the significance of droplet size for adjuvanticity. The opposed patent

demonstrated the advantages of reducing droplet size to the sub-micron range. The effects of reduced droplet size were particularly evident in large mammals. However, (1) focussed on mice only, so this surprising effect could not have been foreseen in any way.

Citation (5) provided the skilled person with the teaching that the use of a block co-polymer as the emulsifying agent was indispensable for obtaining adjuvant systems and vaccine compositions on the basis of oil-in-water emulsions with a sub-micron droplet size and good adjuvanticity and immunogenicity. Hence, the person skilled in the art had no reason to remove the block co-polymer. For the skilled person it was therefore not possible to predict what would be the result if one were to attempt to omit the block co-polymer from the adjuvant and vaccine compositions disclosed in (5).

XI. The respondent disagreed, relying essentially on the following arguments:

Citation (1) disclosed also vaccines which were produced by first manufacturing the emulsion and, secondly, by admixing the antigen. Indeed the intralipid soybean emulsion 10%, with the BSA added to the external phase, was one of the most potent vaccines produced in (1) and had a particle size of less than 0.5 µm. Thus claims 1 and 28 were not novel over (1).

The teaching of (2) specifically disclosed a process for making a vaccine comprising the manufacture of a sub-micron oil-in-water emulsion, comprising a metabolisable oil and emulsifier, followed by the addition of antigen. Citation (2) was therefore also

novelty-destroying under Article 54(3) EPC.

Citation (5) described methods of producing a vaccine composition comprising manufacturing an oil-in-water emulsion, comprising a block co-polymer and wherein the droplet size was less than 0.5 µm, and subsequently mixing the antigen with oil-in-water emulsion, prior to administration. There were growing concerns in the art about the reactogenicity and toxicity of block co-polymers. Thus it would be obvious for a person skilled in the art to find an alternative emulsifier. The skilled person would have known that other sorts of emulsifiers referred to in the patent in suit could readily be substituted for the block co-polymers used in (5). For example, MTP-PE (N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-[1,2-dipalmitoyl-sn-glycero-3-(hydroxyphosphoryloxy)]ethylamide, which was used in all the examples of the contested patent, was an attractive candidate to replace the block co-polymer because of its well known adjuvant activity and simultaneous emulsifying properties rendered by the phosphatidylethanolamine tail.

Article 83 EPC required the application to disclose the invention in a manner sufficiently clear and complete for it to enable the invention to be performed by a person skilled in the art in the whole range claimed. In order for the description to be sufficient in relation to the claimed subject-matter, the person skilled in the art should be able to make any sub-micron metabolisable oil emulsion and mix it with the antigen to get a good vaccine. This was not the case in the contested patent.

XII. The appellant requests that the decision under appeal

be set aside and the patent maintained in amended form on the basis of the main request or one of the auxiliary requests 1 to 4.

The respondent requests that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request; auxiliary requests 1 to 4: admissibility

2. The first question to be decided in relation to the amended sets of claims in the main request and auxiliary requests 1 to 4 is whether such alternative set of claims should be admitted for consideration in this appeal.

2.1 As is apparent from paragraphs VIII and IX *supra*, all five sets of claims forming the present main and the auxiliary requests 1 to 4 were in fact filed **about one month before** the date set for oral proceedings and were subsequently amended during oral proceedings. Hence, the filing date of the present requests is:

- more than two years and six months after the statement of grounds of appeal (12 January 1998) was filed;

- more than twenty months after the observations (7 September 1998) of former opponent 01 on the grounds of appeal were filed; and

- about eighteen months after the observations

(18 November 1998) of respondent (opponent 02) on the grounds of appeal were filed.

All these requests were accordingly filed late. The claims of each of the requests on file differ **in various aspects** and, moreover, to **differing extents** from those considered at first instance and from those which were filed with the grounds of appeal.

2.2 In relation to appeal proceedings, the normal rule is as follows: if an appellant wishes that the allowability of one or more alternative sets of claims, which differ in subject-matter from those considered at first instance, to be considered by the board when deciding on the appeal, such alternative sets of claims should be filed **with the grounds of appeal, or as soon as possible thereafter.** When deciding on an appeal during oral proceedings, the board, making use of its discretional power according to Article 111(1) EPC, may disregard alternative claims which have been filed at a late stage if such claims relate to subject-matter which has not been made available to the department of first instance for proper consideration.

The above principles are in accordance with Article 11(1) and (3) of the Rules of Procedure of the Boards of Appeal (RPBA) and were set out clearly and concisely in the "Guidance for parties to appeal proceedings", issued by the EPO and published in the Official Journal (OJ EPO 1996,342). These statements refer specifically to the submission of amendments, but are clearly applicable to the submission of alternative sets of claims by auxiliary requests. An auxiliary request is a request for amendment which is contingent upon the main request being held to be unallowable.

2.3 The admissibility of all late-filed requests is subject to the general principle applied in case T 153/85 (OJ EPO 1988, 1) to the facts of that case. This principle, namely that it is for the public good that legal conflicts be brought to an early close ("expedit rei publicae ut sit finis litium"), is a legal maxim that is said to belong to the laws of all countries (Black's Law Dictionary; 6th Edition). Decision T 153/85 was merely a specific application, pursuant to Article 125 EPC, of the above maxim in that it provided guidelines for the admissibility of late-filed requests: the board may justifiably consider late-filed requests to be inadmissible, if the amendments incorporated into the claims of these requests are such that a decision on the allowability of the alternative claims cannot be arrived at, at the end of oral proceedings, causing the final decision itself to be reserved although the appeal is closed (cf. continuation of the appeal in writing or referral to the department of first instance for consideration of subject-matter introduced into the claims for the first time at the appeal stage). At a late stage all the accumulated objections under the EPC must be taken into account, when the board reaches a decision on the admissibility of the alternative claims.

2.4 In the present case, the **main request** is essentially based **on** the first auxiliary request filed with the grounds of appeal but specifies in claim 1 the range of percentages of metabolisable oil (0.5 to 15% by volume) and emulsifying agent (0.02% to 2.5% by weight) in the adjuvant formulation. In addition, the oil droplet diameter has been decreased to 0.5 µm. The definition of the adjuvant composition in claim 27 has been similarly amended.

The **first auxiliary request** consists of the above main request, with claim 1 further limited by a disclaimer to exclude BSA as the antigen.

The **second auxiliary request** consists of the above main request with claim 1 further limited to specify a narrower percentage of emulsifier present in the adjuvant formulation (0.05% to 1% by weight).

It follows from the above that the main, first and second auxiliary requests essentially differ from the first auxiliary request filed with the grounds of appeal by a **restriction** of the claims to narrower ranges of percentages of metabolisable oil and emulsifying agent and a further **limitation** of the maximum oil droplet diameter. Apart from the fact that narrower ranges were already claimed in dependent claims 6 and 9 of the application as filed, the amendments mentioned above do **not change** the particular purpose and character of the claimed invention as set out in the application as filed and, therefore, did not prevent the present case from being ready for the final decision at the conclusion of the oral proceedings. In the circumstances of the case, the board decided during the oral proceedings to admit for consideration the main, first and second auxiliary requests.

2.5 On the other hand, the **third auxiliary request** has been amended by specifying that the metabolizable oil is **fish oil** and the emulsifying agent is a **polyoxyethylene sorbitan mono-, di- or triester** and/or **a sorbitan mono-, di- or triester.**

Similarly, the **fourth auxiliary request** limits the claims to a specific adjuvant formulation comprising **5%**

by volume of squalene and **1% by weight of Tween 80 and/or Span 85.**

The discovery at the core of the claimed invention is said in the application as filed to be the finding that oil-in-water emulsions of small average droplet size exhibit in general high adjuvant activity, to the extent that such emulsions alone may be used as the active adjuvant component of antigenic compositions for the treatment or prophylaxis of infection with pathogens. The antigenicity of the claimed adjuvant compositions is said to be primarily dependent on the droplet size, while the individual components of said compositions were already well-known in the art for use as components of vaccine adjuvant compositions (see eg page 5, lines 10 to 34).

Compared with the invention as disclosed in the application as filed and claimed in the patent as granted, the gist of the invention was shifted in the third and fourth auxiliary requests in a different direction. The essence of the invention set out in these requests appears to reside in the **selection,** from the various options disclosed in the state of the art, of a specific, possibly advantageous sort of metabolisable oil on the one hand, and a specific, possibly beneficial sort of emulsifier on the other, and in their particular combination to increase conceivably the immunogenicity of the vaccine composition. A selection invention of this scope was neither claimed in the application as filed nor in the patent as granted and was therefore never subject to examination by the departments of first instance during examination or opposition proceedings. Thus, if the third or fourth auxiliary request had been admitted

into the proceedings, the consequence would necessarily have been continuation of the appeal in writing or referral of the case to the department of first instance for further prosecution, in order to comply with the respondent's rights set out in Article 113(1) EPC and to give the parties an opportunity to have considered all the important elements of the case by two instances, as provided for in the EPC.

2.6 In the present case, having regard to what is set out above, the board rejects the appellant's **third and fourth auxiliary requests**, in view of the fact that they were filed only one month before the oral proceedings, without any proper justification for such late filing; and also in view of the board's finding, mentioned above, that these requests amount to fresh cases which were not available as such to the department of first instance for proper consideration.

The appellant's argument that the third and fourth auxiliary requests were filed in reply to new evidence submitted by the respondents at the appeal stage, so that their rejection would unjustifiably disadvantage the appellant, is unsound. In the circumstances of the present case the appellant had ample time before the first instance and during the appeal proceedings to consider and formulate the full range of claims that it might have desired, well prior to the oral hearing (see point 2.1 above).

Main request; first and second auxiliary requests: allowability of amendments:

3. The amendments, which have been incorporated during opposition and opposition appeal proceedings into the

claims of the main and the second auxiliary requests for the designated states, except ES and GR, are adequately supported by the originally filed documents as required by Article 123(2) EPC. The same applies to the consequentially amended claims of the main and the second auxiliary requests for ES and GR.

3.1 With reference to the wording of the disclaimer in claims 1 and 27 of both the main and the second auxiliary requests, the respondent (opponent 02) objected **for the first time during oral proceedings before the board** under the terms of Article 123(2) EPC to the validity of these requests.

Since this disclaimer remained unchanged during opposition and opposition appeal proceedings and the amendments to the claims, which were introduced in the course of these proceedings, are clearly allowable under the terms of Article 123(2) EPC and have, moreover, **no effect at all on the scope and meaning of the disclaimer,** the board takes, in the circumstances of the case, the view that the objection to the disclaimer represents in fact the introduction of a fresh ground of opposition (Article 100(c) EPC), which could not be considered for the first time during oral proceedings before the board, without the appellant's agreement (see G 10/91 (OJ EPO 1993, 420, especially Reasons, point 18). Since the appellant (patentee) did not agree, this fresh ground for opposition could not be introduced into the proceedings either by the respondent or by the board of appeal of its own motion.

3.2 Unlike the amendment of the disclaimer in the main and second auxiliary requests, the first auxiliary request has further been amended by the insertion of an

additional disclaimer at the appeal stage to exclude bovine serum albumin (BSA) as the antigen from the vaccine compositions according to claims 1 and 28.

According to the established jurisprudence and practice of the boards of appeal, excluding protection for part of the subject-matter of the claimed invention as covered by the application as filed or the patent as granted by disclaiming a certain anticipation in the state of the art, which is not referred to in the originally filed documents, is acceptable under the terms of Article 123(2) EPC only if the following conditions are met:

(i) the subject-matter disclaimed must be precisely defined and strictly limited to the actual scope of the anticipation, and

(ii) said anticipation must be a so-called "chance anticipation", which means that it would be regarded as **accidentally** falling within the terms of the claim(s) of the application or the patent in question (see eg T 917/94 of 28 October 1999, especially Reasons, point 4; T 863/96 of 2 April 1999, especially Reasons, point 3.2; T 13/97 of 2 November 1999, especially Reasons, points 2 and 3).

Condition (ii) specifically refers to cases where the anticipation is of a chance nature in that what is disclosed in the prior document could accidentally fall within the wording of the claim(s) of the application or the patent to be assessed for novelty **without there being a common or related technical field, or a common technical problem or solution**. In other words, the

prior document must form part of an entirely remote and unrelated state of the art which the skilled person, faced with the assessment of inventive step, would normally never take into consideration. In each case, a particularly careful comparison has to be made between what can fairly be considered to fall within the wording of the claim(s) and what is effectively shown in the document.

3.3 When carrying out the comparison in the present case it is found that the relevant disclosure in citation (1) relates to stable oil-in-water emulsions, their preparation and use as vaccine adjuvants and complete vaccine compositions and, accordingly, to exactly the same technical field solving exactly the same technical problem as the claimed invention. More specifically, the particular anticipation, which is intended to be excluded from protection in claim 1 of the first auxiliary request by disclaiming the use of BSA as an antigen, relates to a known vaccine composition comprising an oil-in-water emulsion of sub-micron droplet size as the adjuvant. That vaccine is disclosed in (1) by the method of its preparation (*"Antigen (BSA) and avridine were shaken into Intralipid, a 10% soybean oil emulsion"* - see (1), page 138, right-hand column: "Experiment 2", lines 5 to 6) and by its composition and its antibody response to BSA ("*Intralipid soybean oil emulsion (10%): BSA and avridine added to saline phase, ELISA absorbance: 0.842"* - see page 142, Table 7).

Since, as shown above, the state of the art referred to in citation (1) is highly relevant to the claimed subject-matter in the patent in suit, condition (ii) is clearly not met. Accordingly, the disclaimer excluding

BSA is not allowable within the framework of Article 123(2) EPC and, consequently, the **first auxiliary request** as a whole is not acceptable.

Main request and second auxiliary request: novelty (item 4); the closest state of the art (item 5); the problem and the solution (item 6);

4. In their written submissions and during oral proceedings, the respondent and former opponent 01 disputed the novelty of the vaccine composition according to claim 28, the process for its preparation according to claim 1 and the adjuvant composition of claim 27 of both the main and secondary auxiliary requests over the state of the art disclosed in either citation (1) or (2).

4.1 The feature in claim 1, requiring that the claimed vaccine composition be produced by adding the antigen to the adjuvant formulation after the preparation of said adjuvant formulation, excludes *a priori* from the scope of present claim 1 the preparation of all the vaccine compositions disclosed in (1), except the one wherein BSA and avridine are added to the saline phase of an intralipid 10% soybean oil emulsion (see (1): page 138, right-hand column: "Experiment 2", lines 5 to 6 referring to page 142, Table 7).

4.2 The supplier of intralipid 10% is said in (1) to be Cutter Laboratories, Fairfield, NJ, USA. The exact composition and oil droplet size of intralipid is, however, nowhere disclosed in citation (1), which was

published in **June 1985**. For completion of the missing specification of the intralipid 10% emulsion in (1), the reader was referred in the written submissions and during oral proceedings to citations (3), published in **February 1986**, and (6), published **in 1988.**

The disclosure of (3) and (6) is consistent inasmuch as both these documents refer to a proportion of 10% soybean oil as the metabolisable oil in the intralipid emulsion and a proportion of **1.2% egg lecithin as the emulsifying agent** (see (3), Table I, point 6; (6), page 141, left-hand column).

There appears, however, to exist a substantial inconsistency between (1) on the one hand, and (3) and (6) on the other, as far as the supplier of the product intralipid 10% [no supplier is identified in (3); Hospital Pharmacy, Queen's Medical Center, Nottingham is the supplier in (6)] and, in particular, the exact oil droplet size of the this product are concerned.

4.3 Although the disclosures in cited documents (3) and (6) relating to the oil droplet size of intralipid 10% were extensively discussed during oral proceedings and there was general agreement that intralipid 10%, as described in (3) and (6), was indeed a sub-micron oil droplet emulsion, the respondent and former opponent 01, in their written and oral submissions, were unable to provide clear and unequivocal evidence that

(i) the product intralipid 10% referred to in the later published documents (3) or (6) was in fact identical with the product used for the preparation of the vaccine composition disclosed in (1); and that

(ii) the product intralipid referred to in (3) or (6) does indeed meet the requirement that "at least 80% of the oil droplets are less than 0.5 µm in diameter, as stipulated for the vaccine compositions in independent claims 1 and 28 of the patent in suit.

Having regard to the foregoing, former opponent 01 and the respondent, who as the opponents have the onus of proof, failed, in the board's judgment, to provide sufficient evidence that all the technical features of present claims 1 and 28 could be inferred **directly and unequivocally** from the disclosure of (1) in the light of the information provided in (3) and (6).

4.4 An adjuvant composition combining all the technical features of **independent claim 27** [which is of identical scope in the main and second auxiliary requests], that is to say an oil-in water emulsion comprising

(1) 1 to 15% by volume of a metabolisable oil,

(2) **0.02 to 1% by weight of an emulsifying agent** and

(3) wherein at least **80% by number of the oil droplets are smaller in diameter than 0.5 µm in diameter,**

is likewise not described in citation (1). There is no disclosure in (1) [or in any of the declarations relating to the prior art of (1), which have been submitted in the course of the proceedings] of an oil-in-water emulsion **with a concentration of emulsifier** (70:30 Tween 80/Span 80) **of 1% by weight or less** (see Tables 2, 3, 6, 7), wherein at least 80% by number of the oil droplets are smaller in diameter than 0.5 µm.

4.5 As is already apparent from the observations in foregoing points 4.2 and 4.3 the disclosure of (3) or that of (6) does not anticipate all the technical features of claim 27 either.

4.6 Referring now to citation (2), the statement on page 5, lines 5 to 9, was cited by the respondent under Article 54(3) EPC against the novelty of independent claims 1 and 28. Apart from the fact that neither the particular range of the proportion of metabolisable oil nor that of the emulsifying agent, as specified in claim 1 of both the main and the second auxiliary requests, can be derived from (2), the general disclosure in (2) referring to the rather broadly defined particle size as being *"preferably smaller than 20 µm and more particularly smaller than 1 µm* " (see page 5, lines 8 to 9) does not, in the board's judgment, anticipate the more specific feature in claim 1 requiring that 80% by number of the oil droplets be less than 0.5 µm in diameter.

4.7 In view of the above observations, the board concludes that the cited state of the art does not contain sufficient information to enable the person skilled in the art to derive the subject-matter of the main or the secondary auxiliary requests from it **directly and unambiguously**, including any features implicit therein. Accordingly, novelty within the meaning of Article 54(1) EPC is acknowledged.

5. For an objective assessment of inventive step, it is established EPO practice to determine the closest prior art to the invention, as claimed in the broadest claim.

5.1 Claim 28 of both the main and the second auxiliary

requests is directed to "**a vaccine composition** obtainable by a process according to any of claims 1 to 26" and is therefore considered to be the broadest claim on file, as it covers **the product *per se* of the process of claim 1.**

Thus, having regard to the requests as amended at the appeal stage, on the one hand, and the state of the art known from the documents available in the proceedings on the other, it has to be decided, in the board's judgment, whether citation (1), relied on by the opposition division in the decision under appeal as the closest state of the art, or citation (5), already cited in the application as filed (see page 17, lines 9-16) and referred to in the appeal proceedings, comes closer to the claimed subject-matter of the patent in suit.

5.2 Citation (5) describes, *inter alia*, a process for preparing a **vaccine composition** comprising the steps of

(i) preparing an immunopotentiating amount of **an oil-in-water adjuvant emulsion** by cycling said emulsion through a **Microfluidizer**® about 2-10 times, until the particle size reaches the desired level, preferably a diameter less than 800nm, preferably **less than 300nm (0.3 µm)**, most preferably **less than 200nm (0.2 µm),** followed by

(ii) adding an immunostimulating amount of an antigen to said adjuvant emulsion after the preparation of said adjuvant emulsion (see especially page 10, lines 39 to 44).

In a particularly preferred embodiment the particular

adjuvant formulation is used in (5) in the form of an oil-in-water emulsion comprising

1-10% of squalane or squalene as the metabolizable oil, 1-10% of Pluronic^{R} (a linear polyoxypropylene-polyoxyethylene (POP-POE) block-copolymer) and **0.2% Tween^{R}** as the **emulsifying agents, isotonic buffered saline as the continuous phase, 0.00001-10% N-acetylmuramyl-L-threonyl-D-isoglutamine** as a separate **immunostimulating agent**, wherein substantially all of the oil droplets have a diameter less than 800nm, **preferably less than 300nm** (see especially page 5, lines 20 to 25).

Further, citation (5) refers to a method for inducing an immune response in **any animal having an immune system,** comprising administering a vaccine composition consisting of the above defined adjuvant formulation to which the desired antigen has been added (see page 6, lines 44 to 48).

5.3 As is apparent from the observations in foregoing point 5.2, the essential difference between **the vaccine composition** according to the prior art of (5) and that of claim 28 in both the main and the secondary auxiliary requests lies in the omission of the block copolymer or its replacement by a different emulsifying agent in the same or a very similar proportion. In this respect it should be emphasised that present independent claims 1, 27 and 28 are **not** limited to vaccines or adjuvants comprising oil-in-water emulsions themselves but encompass the addition of separate **immunostimulating agents**, for example **N-acetylmuramyl-L-threonyl-D-isoglutamine**, in the range of **0.00001-10%**

(see patent specification: page 7, lines 36 to 38; page 9, line 9).

5.4 Hence, comparison of the claimed invention with the prior art of (5), as outlined in points 5.2 and 5.3 *supra*, establishes that the components as such and their proportions used in the known vaccine compositions and the process used for their preparation are described in (5) in great detail. The technical realisation of the process, including the proportions of the individual components used and the generation of the submicron oil-in-water emulsions using the **microfluidiser technique**, are in fact **identical** with those used in the contested patent (see especially page 11, lines 1 to 9). Further, the particle size of the oil droplets, which is said in the patent in suit to be the key criterion for the improvement of the immunogenicity of the claimed vaccine composition, is already precisely disclosed in (5) and is likewise substantially **identical** in the cited document and in the patent in suit.

5.5 In view of the fact that citation (5) describes the components, the technical and physical parameters and the method of preparing the known vaccine compositions more precisely and in greater detail than is the case in (1), the board comes to the conclusion that compared with (1), optionally in combination with (3) and (6) (see points 4.2 and 4.3 *supra*), the prior art of (5) comes closer to the claimed subject-matter in the main and second auxiliary requests.

6. To assess inventive step, it is necessary to define the technical problem to be solved by the claimed invention vis-à-vis the closest state of the art according to

citation (5).

6.1 The appellant has failed to persuade the board with the argument presented during oral proceedings that the problem to be solved vis-à-vis the cited state of the art was to provide an adjuvant formulation suitable for stimulating immune response in large mammals. In this context, the appellant relied on the argument that certain adjuvant formulations with or without molecular antigens (vaccines), which were shown in the state of the art to be effective in stimulating the immune response in lower animals, such as guinea pigs, were not as effective when the same formulations were tested in large animals, such as goats and baboons.

6.2 During oral proceedings, the appellant argued, *inter alia*, that it was the merit of the present inventors of having recognised for the first time the problem that vaccines, which were found to be effective in stimulating the immune response in lower animals, were possibly not as effective in larger animals. This finding would point in the direction of a so-called "problem invention".

However, any person skilled in the art, faced with the problem of providing an adjuvant formulation or a complete vaccine suitable for stimulating immune responses to a particular antigen in larger animals or human subjects, would routinely start with tests in lower animals and, if the results were positive, go on investigating the immune response in larger animals, before the vaccine was released for clinical trials and investigations. Since this is the normal sequence of testing the effects and efficiency of a medicament, for example a vaccine, and the evaluation of the results of

such tests must be considered as the normal task of the skilled person, the board cannot share the appellant's view that a contribution to inventive step could possibly be seen in the **obvious recognition** that the extent and intensity of the immune response of a certain vaccine determined in lower animals may potentially differ from that found in larger animals.

6.3 The alleged advantage of the claimed vaccines over the state of the art according to (1), namely that of being suitable for stimulating the immune response to molecular antigens in humans and other large mammals, was purported to be proven by the results of the comparative example in the patent in suit (see page 11, line 35, to page 24, line 1). Contrary to the appellant's submission during oral proceedings, this comparison in the patent in suit **is not pertinent at all**, since it does **not** include the vaccine compositions according to the closest state of the art. What has effectively been shown in the comparative experiments included in the contested patent is merely the finding that some more or less arbitrarily-chosen vaccines, which were effective in stimulating the immune response in lower animals, such as guinea pigs, were not as effective when the same vaccines were tested in large animals, such as goats and baboons.

In order to support effectively the alleged advantage of the claimed invention over the closest prior art, it should, however, have been proven by the submission of appropriate comparative evidence that vaccines **in accordance with the claimed invention** would in fact be effective in stimulating the immune response in larger animals, while **the structurally closest vaccines disclosed in the state of the art** would not be as

effective. Apart from the fact that this comparison with the closest state of the art was **not** made and the alleged advantages are accordingly not supported by sufficient evidence, citation (5) already emphasises the usefulness of the known vaccine compositions for inducing an immune response in any animal having an immune system (*loc. cit.*).

Such alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the claimed invention (see decision T 20/81, OJ EPO 1982, 217, especially Reasons, end of point 3).

6.4 In view of the above observations and in the absence of evidence showing any advantageous effects associated with the claimed vaccines over the closest state of the art, the only remaining problem the claimed invention according to both the main and the secondary auxiliary requests seeks to solve may be seen as that of finding alternatives to the vaccine compositions disclosed in (5). The desirability as a therapeutic goal of providing suitable alternatives to certain medicaments, such as vaccines, to increase the options available to doctors in their daily practice for curing or preventing diseases in different subjects, is commonly acknowledged in the art.

The solution to the problem lies essentially in the omission of the block copolymer or, preferably, in its replacement by a different emulsifying agent. In view of the results obtained in the examples of the patent in suit and in the absence of any evidence to the contrary, the board is satisfied that the problem, as defined above, is plausibly solved.

Main request: inventive step

7. It remains to be examined whether, in view of the technical problem to be solved, the requirement of inventive step is met by the claimed vaccine composition and the method of its preparation.

7.1 The skilled practitioner, starting from the vaccine compositions disclosed in (5) and seeking a solution in the state of the art to the above-defined problem, would consider the closely related prior art disclosed in citation (1). This document provides him with the information that effective vaccine compositions with potent immunogenicity are readily obtainable by a process which is in every aspect analogous to those of (5) and claim 1 of the patent in suit, even if the **block copolymer is totally omitted** and is replaced by **a different emulsifying agent** conventionally used for the stabilisation of oil-in-water emulsions having a droplet size in the range disclosed in (5) and claimed in the patent in suit.

More specifically, (1) discloses that the preparation of a vaccine composition by shaking BSA and avridine (as the additional immunostimulating agent) into a commercially available, stable 10% intralipid oil-in-water soybean emulsion containing 1.2% by weight of a conventional emulsifier, ie egg lecithin, resulted in an **entirely equivalent substitute** for a vaccine which was prepared by the addition of BSA and avridine to the internal oil phase before mixing the phases of an oil-

in water emulsion comprising 5% of hexadecane as the metabolizable oil and 5% by weight of a 70:30 Tween 80/Span 80 emulsifier (see especially page 141, the paragraph bridging the left-hand and right-hand columns; page 142, Table 7).

7.2 The skilled person would have immediately noticed from the disclosure of citations (1) and (5) that, in sharp contrast to the interpretation the appellant sought to impose on the cited state of the art, neither the addition of the antigen to the internal oil phase of the emulsion nor the use of certain block-copolymers as emulsifying agents were indispensable technical prerequisites for the preparation of effective vaccine compositions with both an oil droplet diameter of less than 500nm (0.5 µm) and simultaneously an excellent immunogenicity. Hence, the skilled person with this knowledge would be strongly motivated to solve the technical problem defined above by replacing the block co-polymer in the vaccine compositions disclosed in (5) by other known emulsifiers of the same or a similar type (also referred to in the patent in suit as surfactants or detergents - see page 4, line 44) or other metabolisable oil/emulsifier (surfactant) combinations so as to arrive at the present invention.

Apart from the fact that the provision of alternatives to known medicaments is a well-established desideratum in the medical field, the appellant did not refute during oral proceedings the respondent's submission that at the priority date of the patent in suit concerns about the possible reactogenicity and toxicity of the type of block co-polymers used in (5) were growing.

7.3 The appellant also did not contest the respondent's submissions that there are a variety of parameters that have to be taken into account to produce vaccine compositions exhibiting satisfactory immune response to a particular antigen. These are, for example, choice of oil, choice of surfactant or surfactants, conditions of manufacture and the relative proportions of the ingredients. In spite of the undisputed need to adhere to a variety of different parameters for the preparation of the claimed vaccine composition, the disclosure of the claimed invention in the patent in suit illustrates the appellant's intention to leave it more or less to a person with sufficient skill in the art to choose a suitable oil component, a suitable emulsifier surfactant and an effective combination of both these components from rather long lists in the specification for the purpose of preparing effective vaccine compositions according to claim 28.

7.4 The board adopts the view expressed in decision T 60/89 (OJ EPO 6/1992, 268, see especially Reasons, point 3.2.5) that the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure within the meaning of Article 83 EPC and inventive step within the meaning of Article 56 EPC have to be considered. The specialist with the knowledge and skills mentioned in foregoing point 7.3 seeking to solve the problem would have known that the block co-polymers preferably used in (5), for example the one designated L 101, belong to the class of non-ionic surfactants and would thus be able to find suitable alternatives.

Notwithstanding this, if he was nevertheless seeking instructions - should he really need them - in the

state of the art as to how he could find further alternatives to the emulsifying agents (surfactants) used in (5) and (1), he would have certainly been interested in further publications of the authors of (1) and would have come across citation (4). This document provides an extensive list of emulsifiers and surfactants which may be used in oil-in-water emulsions to arrive at effective vaccine compositions. Table 1 (see page 223, right-hand column) compares the antibody responses produced by different adjuvant formulations **including block co-polymer L 101** and the non-ionic surfactants of "Class F". Any of these class F surfactants could be used with a reasonable expectation of success as a suitable substitute for the block co-polymer in vaccine compositions. It is derivable from the data provided in Table 1 of (4) that the surfactants listed in class F resulted without exception in adjuvant systems for vaccines that induced higher antibody responses than those containing the preferred block co-polymer L 101 used for the vaccine compositions in (5).

7.5 To summarise, once the possibility of replacing the block co-polymers as emulsifying agents in vaccine compositions based on sub-micron oil-in-water emulsions disclosed in (5) by different types of emulsifying agents, without impairing the immunogenicity of the vaccines, became obvious, determination of suitable emulsifying agents, oil components and suitable combinations of metabolisable oil and emulsifier within the whole range claimed in the patent in suit to obtain effective vaccine compositions, was a matter of routine experimentation for the specialist endowed with the high level of skills mentioned above and familiar with the relevant state of the art.

Second auxiliary request: inventive step

8. The only difference between the vaccine compositions of claim 28 and the process of their production according to claim 1 of the second auxiliary request and the subject-matter of the corresponding claims of the main request resides in the limitation of the amount of emulsifier present in the vaccine composition from 1.2% by weight maximum, as disclosed in citations (1) and (5) (see point 5.2 above), to 1% maximum. The minor reduction of the upper value of the range of the proportion of the emulsifying agent from 1.2% to 1% cannot be considered to be of an inventive nature but rather results from routine experiments. At least there is no indication in the patent of a specific, surprising effect related to that specific narrower range.

Main request and second auxiliary requests: sufficiency of disclosure (item 9), conclusions (item 10)

9. The ground for opposition under Article 100(b) is based on Article 83 EPC and was dealt with in point 7.3 to 7.5 above in connection with inventive step by reference to Decision T 60/89 (loc. cit.). Moreover, former opponent 01 and the respondent, which as the opponents have the onus of proof, failed to provide **sufficient evidence** in the course of the entire opposition and opposition appeal proceedings that the skilled person would indeed be unable to perform the claimed invention over the whole area claimed on the basis of the disclosure in the patent in suit. In any case, since the appeal has to be dismissed for other reasons, insufficiency as a ground for opposition is no

longer of relevance to the present case.

10. In view of what has been said above, the board finds that the vaccine composition according to claim 28 of both the main and the secondary requests does not involve an inventive step, contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC. The process according to claim 1 of both requests is a pure analogy process in view of the disclosure in (5) and, accordingly, also lacks an inventive step in the absence of patentable products obtainable by the said process.

Since a decision can only be taken on each request as a whole, there is no need to look into the patentability of the other claims. The above conclusions apply *mutatis mutandis* to the separate set of claims for ES and GR.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Dainese P. A. M. Lançon