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D E C I S I O N
of 30 October 2003

Case Number: T 0552/00 - 3.3.4

Application Number: 94911894.7

Publication Number: 0689454

IPC: A61K 39/39

Language of the proceedings: EN

Title of invention:
Vaccine compositions containing 3-0 deacylated monophosphoryl lipid A

Patentee:
SMITHKLINE BEECHAM BIOLOGICALS S.A.

Opponent:
Wyeth Holdings Corporation

Headword:
3D-MPL/SMITHKLINE

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87 to 89, 114, 123

Keyword:
"Late submission - admitted"
"Added subject-matter - main request - (no)"
"Extension of protection - main request - (no)"
"Priority right - main request - (yes)"
"Novelty - main request - (yes)"
"Inventive step - main request - (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0552/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 30 October 2003

Appellant I: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 19 April 2000 concerning maintenance of European patent No. 0689454 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
V. Di Cerbo

Summary of Facts and Submissions

I. European Patent No. 0 689 454, filed on 14 March 1994 and claiming a first priority from 23 March 1993 (GB 9306029) was granted on the basis of a set of 31 claims, claims 1, 2, 3 and 27 of which read:

"1. A vaccine composition comprising an antigen in conjunction with 3-O-deacylated monophosphoryl lipid A (MPL) and a suitable carrier wherein the particle size of the MPL does not exceed 120nm."

"2. A vaccine composition as claimed in Claim 1 in which the particle size of the MPL is in the range 60-120nm."

"3. A vaccine composition as claimed in Claim 1 or Claim 2 in which the particle size of the MPL is less than 100nm."

"27. A clear sterile solution of 3-O-deacylated monophosphoryl lipid A."

II. The patent was maintained by the opposition division pursuant to Article 102(3) EPC on the basis of the claims of the fourth auxiliary request, whereas the main request and the auxiliary requests I to III were considered to contravene the requirements of Articles 84 and/or 123(2)(3) EPC. None of these requests corresponded to the set of claims as granted.

III. Both the patentee (appellant I) and the opponent (appellant II) lodged an appeal against the decision of the opposition division.

IV. Appellant I filed with his statement of grounds for appeal (letter of 4 August 2000) a main request and auxiliary requests I to IV. Amendments to claims 2 and 3 of the main request were submitted with the letter of 4 May 2001.

V. With letter of 11 April 2003 appellant I withdrew the main request and auxiliary request I filed with the statement of grounds of appeal and declared auxiliary request II as the new main request and auxiliary request III as the new auxiliary request.

VI. Oral proceedings were held on 29 April 2003, at the beginning of which the dependency of the claims of the main and auxiliary requests was amended. The amended main and auxiliary requests were accordingly considered as having been submitted during the oral proceedings. The main request consisted of 28 claims, claims 1 to 3 of which read:

"1. A vaccine composition comprising an antigen in conjunction with 3-O-deacylated monophosphoryl lipid A (3D MPL) and a suitable carrier wherein the particle size of the 3D-MPL does not exceed 120nm."

"2. A vaccine composition as claimed in Claim 1 in which the particle size of the 3-O-deacylated monophosphoryl lipid A is in the range 60-120nm."

"3. A vaccine composition as claimed in Claim 1 in which the particle size of the 3-O-deacylated monophosphoryl lipid A is less than 100nm."

VII. The following documents are cited in this decision:

(1) E. Ribi et al., Immunology and Immunopharmacology of Bacterial Endotoxins, Plenum Publ. Corp., New York, 1986, pages 407 to 419

(2) WO 93/19780

(3) GB 9206786.7 (first priority document of document (2) of 27 March 1992)

(4) GB 9206789.1 (third priority document of document (2) of 27 March 1992)

(5) WO 92/11291

(6) WO 92/16231

(7) WO 92/06113

(10) P.J. Baker et al., Infection and Immunity, 1990, Vol. 58/9, pages 2862 to 2868

(11) P.J. Baker et al., Infection and Immunity, 1988, Vol. 56/5, pages 1076 to 1083

(12) B. Frisch et al., Eur. J. Immunol, 1991, Vol. 21, pages 185 to 193

(13) M. Friede et al., Molecular Immunology, 1993, Vol. 30, pages 539 to 547

(14) C.W. Fifield and T.J. Leahy, in "Disinfection, Sterilization and Preservation", S.S. Block editor, Lea and Febiger ed., Philadelphia, 1983, pages 125 to 153

(16) G.L. Gustafson and M.J. Rhodes, Biochemical and Biophysical Research Communications, 1992, Vol. 182/1, pages 269 to 275

(17) M.A. Tomai et al., Journal of Biological Response Modifiers, 1987, Vol. 6, pages 99 to 107

(24) R. Bomford et al., AIDS Research and Human Retroviruses, 1992, Vol. 8/10, pages 1765 to 1771

(25) Declaration of Dr N. Patel dated 16 August 2000

(26) Declaration of Dr J.P. Prieels dated 15 January 1999

(27) Declaration of Dr N. Garcon dated 24 January 2000

(28) Declaration of Dr P. Desmons dated 21 December 1999

(29) Declaration of Dr P. Desmons dated 25 January 2000

(30) Letter of Ms P.L. Sager dated 27 April 1999

(31) Declaration of Dr A.G. Johnson dated 12 September 1999

(32) Declaration of Dr. M. Friede dated 6 January 2000

(33) Declaration of Dr M. Hagen dated 17 December 1999

(34) Declaration of Dr J. Holland dated 25 August 2000.

VIII. The arguments of appellant I can be summarized as follows:

Admissibility of the appeal

- the new main and auxiliary requests cannot be considered as virtually identical to the claims as granted, since claim 27 of the latter had a much wider scope of protection; therefore, the withdrawal of the claims as granted did not affect the admissibility of the appeal.

Admissibility of the main and auxiliary requests

- the new main and auxiliary requests caused no inconvenience or surprise, since they were filed with the letter of 4 August 2000, ie almost three years before the oral proceedings.

- the new main and auxiliary requests were an attempt to overcome the objections of the opposition division and a reaction to the conclusions reached by decision G 2/98 (OJ EPO 2001, 413) on the question of priority.

Article 83 EPC

- the particle size limits were not to be given a strict interpretation because of the variability of the biological systems and of the imprecision

inherent to the particle size detection methods and/or detectors (cf document (28)).

- the description of the patent in suit (for instance, on page 2, line 20) showed that a strict interpretation of the size limits was not contemplated and the claims were to be read in the light of the description.

- the detector determined the intensity of the light scattering due to the particles and converted this value in the "number" and "volume" of the particles. However, documents (25) and (33) showed that the amount of particles with a size greater than 120nm was below the power of detection of the detector, even if a slight "intensity" peak was seen. Therefore, the skilled person, seeing a small "intensity" peak, would not have concluded to a failure in reproducing the teaching of the patent in suit. If he would have nevertheless reached such a conclusion, he could have without any undue burden filtrated the obtained preparation.

- whether or not the design of the flow cell was critical, was beyond the point, since the flow cell was not mentioned in the claims as an essential feature and could be purchased. The same applied to the detector.

Article 54 EPC

- document (12) did not use 3-O-deacylated monophosphoryl lipid A (3D-MPL), but monophosphoryl lipid A (MPL) as shown by the mention on page 191 (left column) of reference "29" which corresponded to document (1) on file, said document being the publication describing the preparation of MPL from LPS (lipopolysaccharide). This was confirmed by document (32). Further, document (12) was concerned with liposomes, in which MPL was dissolved and not present as a particle. Thus, the particle size indicated referred to the liposomes and not to the MPL particles.

- document (2) had two aspects: particles with a size below 100nm and particles with a size ranging from 80 to 500nm. The first aspect was only to be considered, if the entitlement of the patent in suit to its first priority was not acknowledged. However, in this case, document (2) was also not entitled to its priority, since its disclosure was of an even poorer quality than that of the patent in suit. As far as document (2) had an overlap with the patent in suit in the range 80 to 120nm, document (27) showed that in fact the mean size of the particles of document (2) was 375nm.

Article 56 EPC

- the closest prior art was document (6), although documents (5) and (7) could as well be considered as such, since the disclosures of these three

documents were similar. The technical problem to be solved was to improve the adjuvancy of 3D-MPL and the solution given by the patent in suit was to reduce the particle size below 120nm. This solution was not suggested in document (6) and resulted in an improvement of adjuvancy, stability and sterilization possibility. In particular, there was an unexpected shift from a Th2 to a more Th1-type immune response (document (27)). A combination with documents (16) or (17) was of no value, since none of these documents, which were only concerned with MPL, suggested a particle size as in the claims of the main and auxiliary requests. Equally unsuitable was the combination with document (24) which concerned GMDP, ie an adjuvant structurally unrelated to MPL.

IX. The arguments of appellant II can be summarized as follows:

Admissibility of the appeal filed by appellant I

- the claims as granted were voluntarily withdrawn by the patentee prior to the oral proceedings before the opposition division. Since the claims of the new main and auxiliary requests are virtually identical to the claims originally granted, they cannot be the subject-matter of the appeal proceedings given that, because of the above mentioned withdrawal, appellant I cannot be considered as adversely affected by the decision of the opposition division, as far as these requests were concerned (decision T 528/93 (23 October 1996)).

Admissibility of the main and auxiliary requests

- both requests were submitted only about two weeks before the oral proceedings (and, in their last version, during the oral proceedings), thus resulting in an inconvenience for appellant II.

- the new auxiliary request had not been considered by the opposition division, so that appellant I could not be considered as adversely affected by the decision of the opposition division, as far as this request was concerned.

- the new main and auxiliary requests were no *bona fide* attempts to answer the objections of the opposition division.

Article 83 EPC

- the Examples 1 and 2 of the patent in suit did not enable the person skilled in the art in view of the limits mentioned in claims 1 to 3, ie "does not exceed 120nm", "in the range 60-120nm" and "less than 100nm". This was confirmed by the experiments disclosed in documents (25) and (33).

- the measured size of the particles depended on the detector used, as shown in documents (25) and (33).

- the design of the flow cell used in Example 2 was according to document (29) an important factor, on which the patent in suit was silent.

- the patent in suit did not provide the skilled person with any teaching for eliminating the particles with a size below 60nm.

- the claims did not need to be interpreted in the light of Article 69 EPC, since they were clear for the skilled person and made technically sense as requested in decision T 190/99 (6 January 201). Furthermore, a strict interpretation of the limits mentioned in the claims was supported by the description, for instance on page 3, line 43 or on page 4, lines 48 to 50.

- Table 1 of the patent in suit was no proof that particles were obtained with a size in agreement with the limits mentioned in claims 1 to 3 of the main and auxiliary requests, since it related to the mean particle size and did not give information on the form of the size distribution curve which could be very flat.

- since the skilled person expected a diminution of the particle size to result in an increase of the adjuvancy of 3D-MPL, it was important to have a clear-cut upper limit.

- the claims and Examples 2 of the patent in suit stated that the upper limit of 120nm was reached without the use of an ultrafiltration step.

Article 54 EPC

- document (2) described the use of 3D-MPL particles with a size below 100nm for the preparation of a vaccine containing an antigen from hepatitis virus and a carrier (ie alum).

- document (2) further described the use in the preparation of a vaccine against hepatitis virus of 3D-MPL particles with a size ranging from 80 to 500nm, which overlapped the size ranges mentioned in the patent in suit.

- documents (12) and (13), the latter being a continuation of the study of the former, obtained MPL from Ribi Immunochemical Research. Document (30) showed that in May 1990, ie well before the publication dates of documents (12) and (13), 3D-MPL had replaced MPL. Documents (12) and (13) described MPL-containing liposomes with a size of 90nm, which were encompassed by the claims of the patent in suit, particularly in view of the fact that claim 1 of the main and auxiliary requests used the expression "in conjunction" to define the relation between antigen, carrier and MPL in the vaccine and claim 5 of the main request stated that the carrier was any "*other lipid based vehicle*".

Article 56 EPC

- the closest prior art, document (6), disclosed the preparation of herpes simplex virus (HSV) vaccine formulations using 3D-MPL as adjuvant and alum as

carrier. The technical problem to be solved was to improve the adjuvant properties of 3D-MPL. The solution provided by the claims of the main and auxiliary requests was based on the use of small 3D-MPL particles with an upper size not greater than 120nm. However, there was either no direct comparison between "large" and "small" 3D-MPL particles in the Tables of the patent in suit or, when such a comparison was made, the results obtained with the small particles were similar to those given by the large ones of the prior art (documents (31) and (34)). Therefore, the solution provided in the claims of the main and auxiliary requests did not solve the technical problem.

X. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main or the auxiliary request filed at the oral proceedings.

XI. Appellant II (opponent) requested that the decision under appeal be set aside and that European patent No. 0 689 454 be revoked.

XII. After discussion of the case, the Chairwoman declared the debate closed and announced that the decision will be issued in writing.

Reasons for the Decision

Admissibility of the appeals

1. The appeal of appellant II is admissible, since it complies with Articles 106 and 108 EPC and with Rules 1(1) and 64 EPC.

2. The objection put forward by appellant II, concerning the admissibility of the appeal filed by appellant I, is based on the assumption that the new main and auxiliary requests are virtually identical to the claims as granted. Since the latter was withdrawn prior to the oral proceedings before the opposition division, appellant I could not be considered as being adversely affected, pursuant to Article 107 EPC, by the decision under appeal.

3. In the Board's view, appellant II's assumption is not convincing.

4. Indeed, as far as the main request is concerned, whereas claims 1 to 26 are identical with claims 1 to 26 as granted, claim 27 corresponds to claim 29 as granted, at the end of which "*and a carrier*" has been added and claim 28 to claim 28 as granted with addition of "*until the particle size does not exceed 120nm adsorbing the 3-O-deacylated monophosphoryl lipid A solution to aluminium hydroxide, and adding antigen*". There is no claim corresponding to granted claims 27, 30 and 31 in the main request. Therefore, the claims of the new main request are not identical with those granted by the first instance.

5. The claims of the main request are hence not only formally different from the claims as granted, but also in their "substance", since, in particular, the broad granted claim 27 has been deleted. Therefore, their submission in the appeal proceedings does not amount to a simple re-introduction of the claims as granted.

6. The deletion of the term "*in general*" from the claims of the main request is an attempt to overcome an objection under Articles 84 and 123(3) EPC having led the opposition division to reject the claims of the main and auxiliary requests I and II (pages 4 to 6 of the decision of the opposition division). The claims of the main request are hence *bona fide* attempts to overcome objections of the opposition division.

7. On the other hand, the subject-matter of the main request (ie 3D-MPL particles with a size below 120nm, in the range 60-120nm or below 100nm, their use for the preparation of a vaccine, methods related thereto and use thereof) is similar to that of the requests considered by the opposition division. Therefore, even though the opposition division has not based their decision on the claims of the main request presently on file, they have nevertheless given a decision on their subject-matter, so that appellant I can be considered as being adversely affected by the decision under appeal.

8. The Board thus concludes that the appeal of appellant I complies with Articles 106 to 108 EPC and Rules 1(1) and 64 EPC.

Article 114(2) EPC

9. The admissibility of the main and auxiliary requests already on file before the oral proceedings was questioned by appellant II. These requests were in fact filed (although as auxiliary requests II and III, respectively) with the letter dated 4 August 2000 and, therefore, were known to appellant II since three years. Accordingly, no inconvenience can be derived to appellant II from the mere fact that two weeks prior to the oral proceedings these requests were declared as main and auxiliary requests, respectively.

10. During the oral proceedings, appellant I filed two new sets of claims, as main and auxiliary requests. In the Board's view, these late-filed requests are admissible, since they only contain few amendments to the wording of the main and auxiliary requests already on file, amendments which can be considered as a direct consequence of the discussion during oral proceedings.

Main request

Articles 84, 123(2)(3) EPC

11. No objection has been raised by appellant II in view of these Articles. The Board also considers that the claims of the main request are clear, have a basis in the application as filed and do not extend the scope of protection.

Article 83 EPC

12. Appellant II objected that the patent in suit does not enable the skilled person, using his/her common general knowledge, to prepare 3D-MPL particles as defined in claims 1 to 3. To confirm their objection, appellant II submitted experimental data (documents (25) and (29)) showing that, using the method and apparatus of the patent in suit, preparations in which all the 3D-MPL particles had a size less than 120nm could not be achieved. The same result was even obtained with better detectors than that of the patent in suit. Further, appellant II objected to the assumption that the claims should be interpreted in a way larger than that suggested by their formulation.

13. The patent in suit and documents (25), (29) and (33) show that 3D-MPL particles with a size below 100nm, below 120nm or in the range 60-120nm, as requested by claims 1 to 3 of the main request, can be obtained, when the conditions of Example 1 are followed and that increasing the time of sonication, as suggested in the patent in suit, also increases the amount of particles exhibiting the required size. However, documents (25), (29) and (33) show that ***not all*** the particles exhibit the required size.

14. As stated in decision T 190/99 (cf supra section IX), claims should be considered in a way which rules out interpretations which are illogical or which does not make technical sense and in a manner to arrive at an interpretation which is technically sensible and takes into account the whole disclosure of the patent.

Following this principle, the Board is convinced that the essential element of the disclosure of the patent in suit lies in the teaching that lowering the size of the 3D-MPL particles increases their adjuvancy, which is not precluded by the presence of some few percent of particles with a size greater than the upper limit of 120nm or lower than the lowest one of 60nm mentioned in claims 1 to 3. Furthermore, the Board is also convinced that the skilled person at the priority date of the patent in suit would have encountered no difficulty in separating the particles with the sizes required by the claims from that having a size greater than 120nm or less than 60nm using his/her common general knowledge, because document (14), a textbook reflecting the common general knowledge of the skilled person and published about 10 years before the priority date of the patent in suit, shows that ultrafiltration is the method of choice for such a purpose.

15. Therefore, the patent in suit fulfils the requirements of Article 83 EPC, even if a strict interpretation is given to the upper (120nm) and lower (60nm) limits mentioned in claims 1 to 3, since it discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art using his/her common general knowledge.

Articles 87 to 89

16. Before considering the novelty objection raised by appellant II against the claims in view of document (2), the question of whether the patent in suit enjoys the priority right of its first priority GB 9306029 (23 March 1993) has to be dealt with. Indeed, document

(2) has a priority (27 March 1992), which lies before that of the patent in suit, and has been filed (24 March 1993) and published (4 October 1993) after said priority date, but before the filing date of the patent in suit (14 March 1994). As a consequence, if the patent in suit does enjoy the priority right of GB 9306029, then document (2) is a prior art document in the sense of Article 54(3) EPC which can only be considered for novelty objection. On the contrary, if the patent in suit does not enjoy said priority right, then document (2) is a prior art document in the sense of Article 54(2) EPC and can be considered for both novelty (Article 54 EPC) and inventive step (Article 56 EPC) objections. Of course, following the objection raised by appellant I (cf *supra* section VIII), it should also be determined whether document (2), in the context of the patent in suit, enjoys its priority right, because if it does not, whereas the patent in suit does, then document (2) cannot ***at all*** be taken into consideration.

17. The question of the priority right is dealt with in Articles 87 to 89 EPC which state that a European patent application is only entitled to priority in respect of the same invention as was disclosed in a previous application. Opinion G 2/98 (cf *supra section VIII*) indicates that the concept of the "same invention" should be given a narrow interpretation.

18. The subject-matter claimed in claims 1 to 3 (ie the vaccine composition using 3D-MPL particles with a size less than 120nm, in the range 60-120nm or less than 100nm, respectively) is disclosed in Example 1 of the patent in suit. Example 1 of the first priority

document is the same as Example 1 of the patent in suit and, as the latter (cf points 12 to 15), enables the skilled person to produce 3D-MPL particles with a size as required in claims 1 to 3. Therefore, the patent in suit is entitled to the priority date of the first application as far as the subject-matter disclosed in Example 1 is concerned. The relevant date for the assessment of the prior art in the sense of Article 54(2) EPC is thus **23 March 1993** for any subject-matter corresponding to that disclosed in Example 1. The consequence of this is that document (2) is a prior art document under Article 54(3) EPC which can only be taken into consideration for novelty objection, provided it enjoys its priority right.

Article 54 EPC

19. Document (2) discloses in Example 5 (Part A, Experiment III and Part B, Experiment II) MPL particles with a size less than 100nm. However, documents (3) and (4), the priority documents of document (2) do not contain said Example 5 and do not appear to disclose elsewhere in their specifications its subject-matter in a way sufficiently clear and complete for it to be carried out by the skilled person. Therefore, in the context of the patent in suit, the Board concludes that document (2) does not enjoy its priority right for this feature and considers that the relevant date for document (2), as far as this feature is concerned, is the filing date, ie 24 March 1993, which is posterior to the first priority date of the patent in suit, so that document (2) cannot be taken into consideration in view of particles with a size less than 100nm.

20. Document (2) also discloses in Example 1 the use of 3D-MPL particles with a size ranging from 80 to 500nm for a purpose identical to that of the patent in suit and is entitled to its first priority date for this feature, which is disclosed in Example I of documents (3) and (4). The lower part of the disclosed range overlaps with the sizes given in the claims of the main request. The established case law (Case Law of the Boards of Appeal of the European Patent Office, 4th edition, 2001, pages 82 and 83) suggests that for determining whether a technical teaching has been made available to the public the question should be asked whether the person skilled in the art would seriously contemplate applying the technical teaching of the prior art document in the range of overlap. In the present case, the range defined in document (2) is large, since it extends from 80nm to 500nm and the region of overlap (80nm to 120nm) represents less than 10% of the whole range and is placed at the lowest end of it. The information which can be retrieved from document (2) for preparing the 3D-MPL particles (page 7, lines 6 to 9) is scarce and undifferentiated insofar as it does not provide the skilled person with any guidance for preparing particles with a specific size within this broad range. Document (2) only teaches to continue the sonication until the desired size is obtained (page 7, lines 6 to 9), but does not indicate any particularly preferred sub-range within this "80 to 500nm" range. In the absence of any precise guidance from document (2), the skilled person would follow the protocol suggested by Ribi Immunochem Research (the supplier of MPL and 3D-MPL), which according to document (27) gave particles in the range 115 to 951nm with a mean size of about 375nm. Furthermore, the skilled person knows that the

size distribution of the particles follows a Gauss-curve and would hence assume that the lower and upper limits of the range defined in document (2) only represent both ends of said Gauss-curve. Therefore, the Board is convinced that document (2) does not seriously contemplate applying the technical teaching described therein in the range of overlap, which cannot be considered as having been made available to the public in the sense of Article 54 EPC.

21. Document (12) discloses the use of liposomes containing MPL to trigger an immune response to a hexapeptide antigen. The particles obtained have a diameter of 90nm (page 187, left column, last paragraph). However, the Board is convinced that document (12) uses MPL and not 3D-MPL. The reasons therefor are that, when MPL is defined in document (12) as an adjuvant (page 189, left column, 3rd paragraph), "reference 29" is mentioned, which corresponds to document (1) on file. Document (1), however, deals with the preparation of MPL (not 3D-MPL) from LPS (lipopolysaccharide). Further, document (30) states that Ribi Immunochem Research (the supplier of both MPL and 3D-MPL) replaced MPL by 3D-MPL, without changing the trade name and the accession number, in **May 1990**. Moreover, document (12) was, according to page 192 (left column, line just before the heading "References"), received for publication on **20 August 1990**. The Board has serious doubts whether the study described therein and the writing of the publication could have been made within a period of three months or even less, since document (26) shows that 3D-MPL was not available before June 1990. Finally, the subject-matter of document (12) is, in the Board's view, different from that of the patent in suit, since MPL is

not said to be used as particles, but appears to be dissolved within the liposomes (page 186, right column first paragraph, lines 10 to 12) in which it is introduced as a solution in chloroform. On the contrary, in the patent in suit, when liposomes are used (claim 5), 3D-MPL is in the form of a particle.

22. Therefore, the Board is convinced that no prior art document on file describes 3D-MPL particles with a size as requested in claims 1 to 3, so that these claims, independent claims 26 and 28 also mentioning said size features and dependent claims 4 to 25, 27 and 29 meet the requirements of Article 54 EPC.

Article 56 EPC

23. The Board, in agreement with the appellants, considers that each of documents (5), (6) or (7) can be considered as the closest prior art, since these documents teach essentially the same, ie the use of 3D-MPL as an adjuvant to produce vaccine compositions. Document (5) states on page 29 (lines 20 to 35) that "*submicron particles*" have been used and document (7) defines on page 9 (lines 19 and 20) said submicron particles as having a size between 100 and 400nm. Document (6) is silent about the size of the said 3D-MPL particles.

24. The technical problem to be solved in view of each of these documents can be defined as improving the adjuvant properties of 3D-MPL.

25. The solution given in claims 1 to 3, respectively, is the reduction of the size of the 3D-MPL particles below 120nm, to a range from 60 to 120nm or below 100nm.

26. The first question in view of the assessment of inventive step is whether the skilled person would have been led to this solution in an obvious manner by the cited prior art. The second question is whether, as argued by appellant II, this problem has been solved, ie whether the patent in suit shows that the 3D-MPL particles with reduced size display improved adjuvant properties.

27. None of documents (5), (6) and (7) suggests that a reduction of the 3D-MPL particle size would be of any advantage. They only use particles with a size distribution following a Gauss-curve, the extremities of which are represented by 100nm and 400nm and hence centred on a mean size of about 250nm.

28. Document (12) does not use 3D-MPL as particles and the size mentioned refers to that of the carrier particles (liposomes)(cf *supra* point 21).

29. Document (24) concerns an adjuvant (GMDP) which is structurally unrelated to MPL and there is no evidence that its mode of action could be similar to that of 3D-MPL. Therefore, its teaching cannot be extrapolated to 3D-MPL particles.

30. Document (16) even teaches away from the use of small size MPL particles, since it states on page 274 (last paragraph) that MPL is rapidly cleared. This being confirmed by document (10) on page 2866 (bridging

sentence between the left and right columns) and document (11) on page 1081 (left column first sentence). A rapid clearance is inappropriate for an adjuvant in presenting the antigen to the immune system of the host.

31. Document (17) only stresses the adjuvant properties of MPL (not 3D-PL) without making any comment on the particle size.

32. The Board does not share the conclusion of document (31) considering that the skilled person would expect a reduction of the size of the 3D-MPL particles to result in improved adjuvant properties, since it was not established at the priority date of the patent in suit whether or not the mechanism of action of 3D-MPL involves a ligand/receptor interaction.

33. Therefore, the Board is convinced that the first question mentioned above (cf *supra* point 26) has to be negatively answered, since no cited prior art document considered alone or in combination with other documents or the common general knowledge leads in an obvious manner to the solution disclosed in the claims of the main request.

34. As far as the second question is concerned, Experiment 2 of the patent in suit, which is concerned with the primary HSV2 (herpes simplex virus 2) disease, shows in Table 3 that, having regard to all the parameters used, the use of small size 3D-MPL particles results in a better adjuvancy than the control. Experiment 1 confirms this teaching and extends it to a comparison with the large size particles, showing that all the parameters used for the comparison (ie the

antibody titres, the median lesion severity, the PI index and the lesion score incidence) give better values with small size particles.

35. A similar conclusion can be drawn from Table 4 dealing with the recurrent HSV2 disease.

36. Table 9 (large particles) is to be compared with Table 12 (small size particles): at low 3D-MPL particle concentrations, higher total IgG titres are obtained with small particles and at every 3D-MPL particle concentration higher IgG2a titres are obtained with small particles.

37. The comparison between Table 13 (large 3D-MPL particles) and Table 14 (small 3D-MPL particles) shows that small 3D-MPL particles favour the IL-2 synthesis more than the larger ones do, whereas the influence of the small particles on the synthesis of IFN- γ is lowered. This shows a shift in the quality of the immunological response which is unexpected in view of the prior art documents on file.

38. Therefore, the Board, in contradiction to document (34), does consider that the patent in suit shows that the reduction of the particle size to the values given in the claims results in an improvement of the properties of said particles, so that the second question (cf *supra* point 26) must be answered positively.

39. Thus, the Board is convinced that the claims of the main request cannot be derived in an obvious manner from the closest prior art (documents (5), (6) or (7)) considered alone or in combination with other cited

prior art documents and that the solution disclosed in these claims does solve the technical problem underlying the patent in suit. Therefore, the claims of the main request fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain European patent No. 0 689 454 on the basis of the claims of the main request submitted during the oral proceedings of 29 April 2003 and a yet to be adapted description.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey