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D E C I S I O N
of 18 September 2001

Case Number: T 0989/98 - 3.3.4

Application Number: 92921753.7

Publication Number: 0662839

IPC: A61K 39/00

Language of the proceedings: EN

Title of invention:
Vaccines and antigenic conjugates

Applicant:
THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION

Opponent:
-

Headword:
Antigenic conjugates/OHIO

Relevant legal provisions:
EPC Art. 54

Keyword:
"Novelty (no)"

Decisions cited:
T 0012/81, T 0026/85, T 0305/87

Catchword:
-

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Case Number: T 0989/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 18 September 2001

Appellant: THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 27 April 1998 refusing European patent application No. 92 921 753.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
S. U. Hoffmann

Summary of Facts and Submissions

I. The applicants lodged an appeal against the decision of the examining division issued on 27 April 1998 whereby the European patent application 92 921 753.7 (published as WO-A-94/07530; EP publication No. 0 662 839) was refused. Basis of the rejection were claims 1 to 13 filed with letter dated 11 November 1997.

In the view of the examining division, the subject-matter of claims 1-3, 5 and 7 was not novel having regard to the following document:

(1) US-A-5 006 334.

Furthermore, the subject-matter of remaining claims was considered not inventive in view of the same document.

Claims 1 to 3, 5 and 7 read as follows:

"1. A vaccine comprising:

an antigenic conjugate of a protein reproductive hormone, a fragment of such a hormone, or a peptide substantially immunologically equivalent to such a hormone or fragment;

an adjuvant, and

at least one oil,

the conjugate and adjuvant being dispersed in an aqueous medium to form an aqueous phase and this aqueous phase being emulsified with the at least one oil,

characterized in that the antigenic conjugate comprises the hormone, fragment or peptide conjugated with a chemically-modified diphteria toxoid, and the aqueous phase is emulsified with a mixture of squalene and squalane."

"2. A vaccine according to claim 1 characterized in that the hormone, fragment or peptide is the beta subunit of human chorionic gonadotropin, a fragment thereof or a peptide substantially immunologically equivalent thereto."

"3. A vaccine according to claim 1 characterized in that the fragment or peptide has a sequence corresponding to amino acids 109-145 of the beta subunit of human chorionic gonadotropin, or a sequence substantially immunologically equivalent thereto."

"5. A vaccine according to any one of the preceding claims characterized in that the antigenic conjugate comprises 20-30 peptides per 10^5 daltons of the chemically-modified diphteria toxoid."

"7. A vaccine according to claim 1 further comprising at least one of mannide monooleate and aluminum monostearate."

II. The reasons for the decision given by the examining division in respect of lack of novelty were essentially as follows:

(a) Document (1) disclosed modifications of proteins such as FSH (follicle stimulating hormone) and HCG (human chorionic gonadotropin) with bacterial toxoids in order to increase the antibody response

to the protein;

(b) Examples 32 and 40 described the use in vaccination tests of a conjugate between the HCG fragment 109-145 and the diphteria toxoid comprising 20-30 peptides per 10^5 carriers. The conjugate was administered together with an oily phase comprising squalene and Arlacel A, the latter containing mannide monooleate.

(c) The use in vaccines of a combination of squalene and/or squalane in combination with Arlacel was suggested in column 6, last paragraph and in column 44, lines 39-40.

(d) Although not specifically exemplified, the emulsification of a conjugate of HCG with diphteria toxoid with squalene and squalane was an embodiment seriously contemplated by the skilled reader of document (1) which did not require a selection.

(e) It was further noted, in reply to the applicants' observations during the prosecution of the case, (i) that claim 1 did not exclude the use of Arlacel (mannide monooleate) which was in fact a preferred embodiment of the claimed invention (see claim 7), (ii) that the different results obtained with Arlacel/squalene and Arlacel/squalane in the examples would not have prevented the skilled reader from using a combination of squalene and squalane as suggested by document (1) in the general description, (iii) differently from the case of T 26/85 (OJ EPO 1990, 22) document (1) did not contain any

statement dissuading the skilled reader from using both oils in the emulsifier.

III. The statement of grounds of appeal contained no further claim requests. While admitting that document (1) did indeed disclose the chemically-modified diphteria toxoid, squalene and squalane **separately**, the appellants argued that the manner in which these materials were separately disclosed and the lack of guidance in combining them did not affect the novelty of claim 1 at issue. The concept of the invention was a selection. As stated in T 305/87 (OJ EPO 1991, 429), it was not permissible to combine separate items of a prior art disclosure combining different embodiments. Although referring to the possibility of using a mixture of squalene **and**/or squalane in a vaccine, document (1) did not teach any particular advantage of the "**and**" combination. In the passage of the general description, where such a combination was mentioned, particular emphasis was given to the use of mannide monooleate, not to any variations in the proportions of squalene/squalane. Document (1) never tested the latter two in combination and in column 82, line 62 to column 83, line 1 pointed to significant differences between the results obtained with squalene/Arlacel A and squalane/Arlacel A vehicles, the former being superior. It was admitted that compositions containing Arlacel were indeed preferred embodiments of the present invention. However, nothing in document (1) would have induced the skilled person to abandon the proven superiority of the Arlacel/squalene vehicle by "diluting" it with squalane. The experimental plan of Examples 32 and 33 indicated to the skilled reader that squalene and squalane were essentially equivalent to one another. As in the case of T 26/85 (supra), the

skilled reader would have been dissuaded from operating with a mixture of the two materials. It was further noted that claim 1 required the presence of a chemically-modified diphteria toxoid. While document (1) described the use of both unmodified and chemically-modified diphtheria toxoids, carefully distinguishing between them, Examples 32 and 33 used the unmodified toxoid.

For these reasons, document (1) was not novelty-destroying.

IV. The examining division did not rectify its decision under Article 109(1) EPC, and remitted the appeal to the board of appeal, cf Article 109 (2) EPC.

V. The appellants requested that the decision under appeal be set aside, that novelty of the claimed subject-matter over document (1) be acknowledged and that the application be remitted to the examining division for further prosecution.

Reasons for the Decision

The question of novelty over document (1)

1. The board shares the evaluation of the technical circumstances of the case made by the examining division (cf Section II above) and considers that the appellants' submissions do not add new elements sufficiently convincing to lead to a different decision.

2. Claim 1 at issue is directed to a vaccine wherein an

antigenic conjugate of a protein reproductive hormone with a chemically-modified diphtheria toxoid is emulsified with a mixture of squalene **and** squalane.

3. It is established case law that the teaching of a cited document is not confined to the detailed information given in the examples, but it embraces any information which the skilled person derives from the general description (cf eg T 12/81 OJ EPO 1982, 296, in particular point 7 of the reasons). As pointed out in T 305/87 (supra), and emphasized by the appellants, it is indeed not permissible to combine separate items belonging to different embodiments of the document, **unless of course such combination has been specifically suggested therein** (loc. cit, point 5.3 of the reasons). However, the latter situation applies here.

4. The examining division correctly observed that, although document (1) specifically exemplifies only the use of either squalene or squalane (both in admixture with Arlacel A, ie a mannide monooleate) as an emulsifier for antigenic conjugates of HCG with a diphtheria toxoid, it **explicitly** refers in the general part of the description and in the chapter "Administration of the instant modified polypeptides" to the administration of such conjugates as vaccines with a vehicle comprising a mixture of mannide monooleate with squalene **and**/or squalane (cf column 6, lines 61 to 68 as well as column 44 line 35 to column 45, line 9). This vehicle is said to have the effect of increasing the quantity of antibodies provoked by the antigen when the vaccine is administered to an animal. The skilled reader would consider the "**and**" combination a feasible part of the

whole disclosure of document (1) because it is technically directly related to and consistent with the invention which is described therein. For this, the skilled person does not have to combine together unrelated parts of document (1), and make a selection, as alleged by the appellants. The combination squalene/squalane is specifically suggested by the document and can be performed and tested without any technical difficulty. The appellants admit (cf Section III above) that the experimental plan of the examples, in particular Examples 32 and 33, indicates a substantial equivalence of squalene and squalane. The board agrees therewith and concludes that this confirms the feasibility of the combination as indicated. In the board's judgment, the examining division correctly concluded that the difference in effectiveness of the combination Arlacel/squalene vs the combination Arlacel/squalane would not have led the skilled person to think that the "and" combination indicated in the general part of the description was unpracticable. As a matter of fact, squalane/Arlacel is stated to be an effective emulsifier, although less than squalene/Arlacel. Both are stated to be clinically acceptable in human beings. Thus, as observed by the examining division, there is no dissuasive statement in document (1) in respect of the suggested "and" combination.

5. As for the requirement of claim 1 that a chemically-modified diphteria toxoid be used, the appellants admit that document (1) refers to the use of a chemically-modified diphteria toxoid, but observe that such toxoid is not used in the examples. In this respect, it is again noted that what matters is the general teaching of document (1) as a whole, as it would be read by the

skilled person. The examining division, during the prosecution of the case, never considered the feature "chemically-modified" to be a discriminating feature over the teaching of document (1) as chemical modifications were an integral part of the disclosure of the latter. This is also the position of the board. The appellants have not submitted new arguments which could change it. In fact, document (1) refers explicitly to the chemical modifications of the toxoids which are necessary to achieve conjugation with the polypeptide. In columns 34 to 37 a wide range of techniques which are applicable to both partners of the conjugate are described. This part corresponds to the respective part of the present application (cf page 31 line 25 to page 39, line 39).

6. In the board's view, the appellants' reference to decisions T 26/85 (OJ 1990, 22) and T 305/87 (OJ 1991, 429) does not help their case, as, firstly, document (1) cannot be considered to contain "a reasoned statement dissuading the person skilled in the art" from using squalene **and** squalane, and, secondly, the combination is explicitly suggested.

7. Thus, in agreement with the examining division, and essentially for the same reasons (cf Section II above), the board considers that claims 1 to 3, 5 and 7 lack novelty.

Procedural matters

8. Oral proceedings were **not** been requested by the appellants who informed the board that there were no supplementary requests (see statement of grounds of appeal under the heading "Main Request"). Having

examined the reasons given by the examining division in its decision in the light of the written submissions by the appellants, the board has been able to reach the final decision without the necessity to add further grounds or evidence on which the appellants had to be given an opportunity to comment (cf Article 113 (1) EPC). Thus, no communication was issued prior to the present decision.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairperson:

U. Bultmann U. Kinkeldey