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Aktenzeichen / Case Number / N° du recours : T 52/88 - 3.3.1

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Bezeichnung der Erfindung: Method of making uniformly sized liposomes and liposomes so made
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : A61K 9/50

ENTSCHEIDUNG / DECISION

vom / of / du 5 September 1989

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent / Titulaire du brevet : The Regents of the University of California

Einsprechender / Opponent / Opposant : Parfums Christian Dior

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Articles 54, 56, 111, 114, 123

Schlagwort / Keyword / Mot clé :
"Novelty (yes)"
"Inventive step (yes)"
"Function of appeal proceedings"
"Late filed evidence disregarded"
"Same request made by the Appellant and the Respondent"

Leitsatz / Headnote / Sommaire

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Case Number : T 52/88 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 5 September 1989

Appellant : (Opponent)
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Decision under appeal :
Decision of the Opposition Division of the European Patent Office dated 30 November 1987 rejecting the opposition filed against European patent No. 0 036 676 pursuant to Article 102(2) EPC.

Composition of the Board :

Chairman : K. Jahn
Members : C. Gérardin
J. Stephens-Ofner

Summary of Facts and Submissions

I. The mention of the grant of the patent No. 36 676 in respect of European patent application No. 81 200 162.6 filed on 23 March 1979 and claiming priorities of 24 March 1978 and 23 February 1979 of two earlier applications in the United States of America, was published on 11 July 1984 on the basis of 12 claims.

The two independent claims read as follows:

Claim 1: "A method for the production of liposomes comprising forming liposomes in relatively random sizes and passing the random sized liposomes through an orifice characterized in that the initially random sized liposomes are converted into uniformly sized liposomes by extruding the random sized liposomes through at least one orifice, which said orifice is smaller than the largest of the random sized liposomes."

Claim 2: "A method for the production of liposomes comprising forming liposomes in relatively random sizes and passing the random sized liposomes through an orifice characterised in that the initially random sized liposomes are repeatedly subjected to the said passage by successively passing the liposomes through orifices, the largest of the orifices being smaller than the largest of the random sized liposomes and the orifice used in one said passage being larger than the orifice used in a later said passage to provide liposomes of uniform size."

Claim 12 was directed to a liposome containing encapsulated a bis-anthracycline.

II. On 3 April 1985 the Appellant (Opponent) filed a notice of opposition requesting the revocation of the whole patent on the grounds that the subject-matter of the patent in suit was not novel and did not involve an inventive step with regard to the teaching of FR-A-2 298 318 (document (2)). In addition, it was objected that the process as claimed was not disclosed in a manner sufficiently clear and complete in the description to be carried out by a person skilled in the art. Furthermore, the objection was raised that the scope of the claims extended beyond the content of the European patent application No. 79 300 470.6 (document (1)) which gave birth to the divisional application from which the patent in suit was derived.

III. By a decision of 30 November 1987, which referred to a more detailed intermediate communication of 29 April 1986, the Opposition Division rejected the opposition on the grounds that the requirements of Articles 100(a), (b) and (c) EPC were all met.

IV. The Appellant thereafter lodged a notice of appeal on 29 January 1988 and paid the prescribed fee simultaneously. The Statement of Grounds of Appeal, which was filed on 28 March 1988, only concerned the objections under Article 100(a) and (c) EPC.

During the appeal procedure several new documents, inter alia,

(12) Interactions of liposomes with mammalian cells by R.E. Pagano and J.N. Weinstein, Annual Review of Biophysics and Bioengineering, 1978, 7, 435 to 468

(13) Large volume liposomes by an ether vaporization method by D. Deamer and A.D. Bangham, Biochimica et Biophysica Acta, 1976, 443, 629 to 634

(14) Vesicles of variable diameter prepared by a modified injection method by J.M.H. Kremer, Biochemistry, 1977, volume 16, No. 17, 3932 to 3935

were filed in support of these two objections.

Further, on 5 August 1989 a test report was filed in order to demonstrate that the filtration of a liposome dispersion actually required a positive pressure and that, in absence of a corresponding feature in Claim 1, the process as claimed could not be carried out.

V. During oral proceedings held on 5 September 1989 the Board first raised the point of the late submitted evidence and late-filed documents. In the Board's view, it could not reasonably be expected from the Respondent to provide counter-evidence to these comparative data filed one month before oral proceedings; moreover, the results of this test report actually supported an objection under Article 100(b) EPC, which the Appellant had waived in the appeal procedure. As to the documents themselves, the practice of the Board was to disregard any document filed after the nine month opposition period, unless it was exceptionally relevant. In these circumstances, the Board took the preliminary view that both experimental data and documents were most likely to be disregarded.

In reply to the Board's objection of accidental anticipation based upon the teaching of document (2), the Respondent, having filed and subsequently withdrawn a number of intermediate sets, eventually filed the following final set of claims together with an adapted description:

Claim 1: A method for the production of liposomes of uniform size comprising forming liposomes in relatively random sizes and decreasing their size by extruding the

random sized liposomes through at least one orifice at a pressure of at least about 1 170 bars.

Claim 2: A method according to Claim 1, wherein the or each extrusion is carried out in the presence of a therapeutic agent.

Claim 3: A method according to Claim 2, which includes the additional step of separating liposomes having encapsulated therapeutic agents agent from unencapsulated therapeutic agent.

Claim 4: A method according to any one of the preceding claims, wherein the or a last said extrusion of successive extrusions is the final step in the preparative process.

Claim 5: A method according to any one of the preceding claims, wherein the liposomes are forced through at least one said orifice at a pressure up to 2070 bars.

Claim 6: A method according to any one of the preceding claims, wherein the said liposomes are composed of lipids including phospholipids, macromolecules, cholesterols, amphiphiles, or a mixture thereof.

Claim 7: A liposome made by the method of any one of the preceding claims and incorporating a bis-anthracycline as claimed in European patent No. 4467.

VI. Both the Appellant and the Respondent finally requested the maintenance of the patent, but only in the final form submitted during oral proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. The final version of the claims is the result of extensive and protracted discussions between the parties and the Board during oral proceedings, and represents the parties' agreement on issues that differ significantly from those decided by the Opposition Division. The Board wishes to emphasize that such extensive re-drafting during appeal proceedings, especially during oral proceedings, is highly undesirable and should not normally be allowed for the following reasons.

The essential function of appeal proceedings, written or oral, is to determine whether a decision of first instance was right on its merits. It follows that appeal boards should decide the same or a closely similar case as was decided by the first instance, regarding both the claims of the patent in suit and the documents cited. What is closely similar or identical is a question of degree, depending on the fact of each case. Appeals, therefore, should not be used by the parties as a continuation of first instance proceedings by other means.

In the present case, by introducing new documents together with each statement during the appeal procedure, which documents bear little relation to those filed in the original opposition, the Appellant has produced a virtually new opposition at the appeal stage; this is not the purpose of an appeal. However, following the principles set out in its decision T 416/87 of 29 June 1989 to be published (point 9), the Board decided to exercise its descretion under Article 111(1) EPC by examining the late filed documents, especially documents (12) to (14), and deciding the opposition having regard to these documents, rather than referring it back to the first instance. This course

of action is all the more desirable because the parties are in full agreement that the patent, as finally amended, should be maintained. To remit to the Opposition Division would not only cause delay but also, having regard to the way this case had been handled by the Opposition Division, be uncertain to lead to a resolution of the issues under Article 123(2) EPC.

As far as the late submittal by the Appellant of test reports less than one month before oral proceedings is concerned, such late submittal failed to give the Respondent the opportunity to provide counter evidence. This, in the Board's view, is clearly an abuse of procedure and therefore, the Board, in the exercise of its discretion under Article 114(2) EPC, decided to disregard the late submitted evidence.

3. There are no formal objections on the basis of Article 123 EPC to the final version of the claims.

In Claim 1, the step of decreasing the size of the random sized liposomes by extrusion through at least one orifice is originally disclosed on column 2, lines 15 to 27 (document (1): page 21, lines 8 to 14); as to the lower value of the pressure to carry out the extrusion, it is indicated at column 3, lines 2 to 5 (document (1): page 22, lines 15 to 18).

The presence of a therapeutic agent during extrusion according to Claim 2 can be inferred from the preparation of liposomes mentioned on column 2, line 31 to column 3, line 11 (document (1): page 21, line 18 to page 22, line 22) and, more specifically, from the passage on column 2, lines 41 to 44 (document (1): page 21, lines 26 to 28), where it appears that the addition of drugs occurs early on in the process, thus before extrusion.

In Claim 4, which derives from original Claim 6, it has been specified that the passage is in fact an extrusion, as now required in the main claim and disclosed on column 2, lines 20 to 22 (document (1): page 21, lines 10 to 12).

As to Claims 3, 5, 6 and 7, they merely correspond to previous Claims 5, 7, 9 and 12; in Claim 6 the deletion of the word "about" before the upper limit of pressure is justified in view of column 3, line 12 of the patent in suit (document (1): page 22, line 23) which only finds support in Claim 37 in the two priority documents. This support for the upper limit of the range of pressure is essential in view of document (12), published on 23 May 1978, i.e. between the two priority dates, which discloses the preparation of liposomes by injecting an aqueous suspension of phospholipids through the small orifice of a French press under a not specified high pressure (page 439, paragraph 3).

In conclusion, the new wording of the claims does not result in an extension of the scope of protection with regard to the granted version.

4. As it appears from the requests, during oral proceedings both parties eventually agreed on the fact that the final version of the claims met not only the requirements of Article 123 EPC, but as well those of Articles 54 and 56 EPC. Since the Board shares this opinion too, a detailed argumentation in this respect is not necessary; however, the Board deems it appropriate to summarise the reasons which led to this conclusion.

The introduction of the lower limit of 1170 bar for the extrusion pressure overcomes the accidental anticipation of the patent in suit by the teaching of document (2),

according to which homogenisation is achieved by forcing a phospholipid dispersion through a small orifice under a pressure higher than 200 bar, preferably between 350 and 550 bar (page 3, line 3 to 24).

The subject-matter of the patent in suit involves an inventive step as well, since the extrusion of liposomes under high pressure (process claims) enables the preparation of liposomes of uniform size for the first time (product claim); this result could not be achieved by the conventional homogenisation methods which required a subsequent filtration as in document (2) or a filtration through a Millipore membrane as in documents (13) and (14). Thereby the effectiveness of the drug encapsulated in the liposomes is surprisingly enhanced.

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 the patent with documents filed at oral proceedings (Claims 1 to 7 and description).

The Registrar: The Chairman:

M. Beer K. Jahn