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D E C I S I O N
of 26 May 2004

Case Number: T 0884/99 - 3.3.2

Application Number: 88400521.6

Publication Number: 0290296

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:
Liposomal formulations with a high antineoplastic agent/lipid ratio

Applicant:
THE LIPOSOME COMPANY, INC.

Opponent:
Alza Corporation

Headword:
Liposomal formulations/THE LIPOSOME COMPANY

Relevant legal provisions:
EPC Art. 87(1), 123(2), 54(3), 56

Keyword:
"Main request, priority validly claimed - no, novelty - no"
"First auxiliary request, originally disclosed - no"
"Second auxiliary request, novelty - yes, inventive step - no"

Decisions cited:
G 0002/98

Catchword:
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Case Number: T 0884/99 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 26 May 2004

Appellant: (Opponent)	Alza Corporation 1900 Charleston Road Mountain View, CA 94039-7210 (US)
Representative:	Howard, Paul Nicholas Carpmaels & Ransford 43 Bloomsbury Square London WC1A 2RA (GB)
Respondent: (Proprietor of the patent)	THE LIPOSOME COMPANY, INC. One Research Way Princeton Forrestal Center Princeton, NJ 08540 (US)
Representative:	VOSSIUS & PARTNER Postfach 86 07 67 D-81634 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 7 July 1999 concerning maintenance of European patent No. 0290296 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
P. Mühlens

Summary of facts and submissions

I. The respondent is proprietor of European patent No. 0 290 296 which was granted with two sets of 44 claims for contracting states AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE and ES, GR respectively on the basis of European patent application No. 88 400 521.6, filed on 4 March 1988 and claiming priority of 5 March 1987 from US 0 22 154.

Claim 1 as granted for the contracting states except ES and GR reads as follows:

"A liposome composition which comprises a lipid bilayer, an ionizable antineoplastic agent, wherein the antineoplastic agent:lipid ratio (w/w) is from 0.1:1 to 3:1; and a buffer combination comprising ;

a) an aqueous medium internal to the liposomes having a first pH, and

b) an aqueous solution external to the liposomes having a second pH, such that there is a pH gradient across the bilayer of the liposome,

wherein when the ionizable antineoplastic agent is cationic, the internal aqueous medium is a citric acid buffer and the first pH is acidic with respect to the second pH, and wherein when the ionizable antineoplastic agant is anionic, the internal aqueous medium is a sodium carbonate buffer and the first pH is basic with respect to the second pH."

II. Oppositions were filed against the granted patent by the appellant (opponent 1) and opponent 2. The patent was opposed under Article 100(a) EPC for lack of

novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC because it contained subject-matter which had not originally been disclosed.

The following documents were cited inter alia during the proceedings before the opposition division and the board of appeal:

(O1) WO 89/04656 (Article 54(3) EPC; priority date 18 November 1987; designated states AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

(O2) Nichols, J.W.; Deamer, D. W.; Catecholamine Uptake and Concentration by Liposomes Maintaining pH Gradients; Biochimica et Biophysica Acta, 455 (1976), 269 to 271

(O3) WO 86/01102

III. Opponent 2 withdrew its opposition in advance of the oral proceedings before the opposition division.

IV. The opposition division held that, account being taken of the amendments made by the proprietor, the European patent met the requirements of the Convention (Article 106(3) and 102(2) EPC).

The wording of corresponding claim 1 for the contracting states except ES and GR is:

"A liposome composition which comprises a lipid bilayer, an ionizable cationic antineoplastic anthracycline,

wherein the antineoplastic agent:lipid ratio (w/w) is from 0.1:1 to 3:1 ; and a buffer combination comprising ;

a) a citric acid buffer internal to the liposomes having a first pH, and

b) an aqueous solution external to the liposomes having a second pH, such that there is a pH gradient across the bilayer of the liposome,

wherein the first pH is acidic with respect to the second pH."

The opposition division considered the lower limit of the agent:lipid ratio of 0.1:1 - like all other features of the amended set of claims - to be originally disclosed in the application as filed and hence Article 123(2) EPC to be met.

As to Article 83 EPC, the opposition division expressed the view that the skilled person, by taking his own common general knowledge in the field of making and loading liposomes, would be able to carry out the invention, even at the extreme ends of the disclosed agent:lipid ratio.

Concerning Article 54 EPC, the opposition division was of the opinion that the priority date was valid for the patent in suit. Since document (O1) had a priority date after the priority date of the patent in suit and since no other document was cited in the context of novelty, the subject-matter claimed in the main request was new over the state of the art.

As to Article 56 EPC, the opposition division found that the subject-matter of claim 1 was a non-obvious alternative to the liposomes of (O3) and even exhibited a non-obvious technical effect in the form of its paradoxical release behaviour, in that liposomes with a high drug-to-lipid ratio had a slower release rate than liposomes having a lower drug-to-lipid ratio.

V. The appellant (opponent 1) lodged an appeal against said decision.

Its submissions can be summarised as follows:

The claims amended before the opposition division had to comply with Article 84 EPC. Claim 1 of these, with respect to the agent:lipid ratio, was intrinsically unclear in the absence of a specified liposome size.

As to Article 83 EPC, it stated that, with respect to over 90% of the claimed range for the agent:lipid ratio, there was no teaching given in the contested patent, how the skilled person could achieve the corresponding liposome compositions.

It still considered the priority of the patent in suit not to be valid and its teaching therefore not to be new over document (O1).

Moreover, the subject-matter of the patent in suit was obvious to the person skilled in the art having regard to documents (O3) and (O2).

VI. In preparation for the oral proceedings, the board drew the attention of the parties in writing to decision G 2/98 OJ 2001, 413, which had been published in the meantime, and informed them that the novelty of the subject-matter of the patent in suit should be discussed in view of document (O1).

VII. With a letter dated 21 May 2004 the respondent submitted a new main request and two auxiliary requests:

The wording of claim 1 of the main request for the contracting states except ES and GR now differs from the result of the proceedings before the opposition division only in the word "anthracycline" having replaced the word "agent" in the expression "agent:lipid ratio".

Claim 1 of the first auxiliary request for the contracting states except ES and GR reads as follows (relevant amendments to claim 1 of the main request put in bold letters by the board):

"A liposome composition which comprises a lipid bilayer, an ionizable ~~**cationic**~~ antineoplastic **agent selected from doxorubicin and daunorubicin**, wherein the antineoplastic **agent**:lipid ratio (w/w) is from **0.2**:1 to 3:1, and a buffer combination comprising:

a) a citric acid buffer internal to the liposomes having a first pH, and

b) an aqueous solution external to the liposomes having a second pH, such that there is a pH gradient across the bilayer of the liposome,

wherein the first pH is acidic with respect to the second pH."

Claim 1 of the second auxiliary request reads like claim 1 of the first auxiliary request with the only difference that it refers to an "agent:lipid ratio" of 0.3:1 instead of 0.2:1.

All sets of method claims for contracting states ES and GR are amended correspondingly.

VIII. On 26 May 2004, oral proceedings took place before the board, in the presence of the representative of the proprietor (respondent). The duly summoned appellant (opponent 1) had informed the board in advance that it did not wish to attend the hearings.

IX. The respondent's arguments in written form and during the oral proceedings may be summarised as follows:

(a) Main request

The claim as granted already contained the limitation of (w/w) agent:lipid ratio. Accordingly, the objection under Article 84 EPC should be refused.

With respect to Article 54(3) EPC it was no longer contested that document (O1) had to be taken into account for novelty.

However, it was submitted that there was novelty over (O1) because citric acid as a buffer system for the liposome composition was mentioned there only in a long list of acidic substances (see (O1), particularly page 9, lines 15 to 33).

Moreover, all data relating to the agent:lipid ratio disclosed in (O1) were outside the range claimed in the patent in suit:

The value of 10 mg/100 mg drug:lipid disclosed in (O1) represented only the upper limit of anthracycline added to the liposomes and since entrapment of the drug can only be achieved close to 100%, the lower limit of the agent:lipid ratio of 0.1:1, claimed in the patent in suit, could not be reached by carrying out the teaching of document (O1). Additionally, entrapment of close to 100% would only be achievable for the preferred range of ratios from 0.05:1 to 0.033:1 for the added drug, and this was far away from 0.1:1.

As regards Article 56, the closest state of the art was (O3). The problem was to maximise the agent:lipid ratio of the liposomes and to minimise the leakage rate during the storing time before application. Having regard to (O3), the subject-matter of the patent in suit involved an inventive step, since there was nothing to indicate that there would be any possibility of improving the corresponding liposome composition by changing the buffer and especially not by taking citric acid.

To the extent that citric acid had been used to achieve the uptake of cationic drugs in liposomes in (O2), the results were very disappointing and would discourage the person skilled in the art from using it for other systems.

(b) Auxiliary request 1

With regard to the priority document and to the application as filed, the original disclosure of a lower limit for the agent:lipid ratio of 0.2:1 could be derived from the corresponding values of numerous examples lying between 0.2:1 and 0.29:1, especially from example 12 (priority document) and example 13 (application as filed) respectively. Thus, (O1) was no longer an Article 54(3) document and novelty had to be considered over (O3).

The teaching of (O3) only referred to glutamate as a buffer and agent:lipid ratios were lower than 0.2:1.

Therefore, the subject-matter of the patent in suit was new over (O3) and for the requirement of inventive step reference was made to the main request.

(c) Auxiliary request 2

There was good evidence of a disclosure of the lower limit of the agent:lipid ratio now figuring as 0.3:1, both from the application as filed and from the priority document. With regard to novelty and inventive step the same arguments applied as for the other requests.

X. The appellant (opponent 1) had requested in writing that the decision under appeal be set aside and that the patent be revoked.

XI. The respondent (patentee) requested that the appeal be dismissed and that the patent be maintained on the basis of one of the main, first or second auxiliary requests filed with letter dated 21.05.04.

Reasons for the decision

1. The appeal is admissible.

2. *First and second auxiliary requests: admissibility*

In comparison with the claims as granted, the subject-matters of these requests are restricted to a narrower range of agents and agent:lipid ratios. Moreover, the corresponding amendments a priori must be considered to be occasioned by the situation coming from publication of decision G 2/98 of the Enlarged Board of Appeal.

Accordingly, these requests fulfil the requirements of Rule 57a EPC and they are admitted into the procedure.

3. *Main request, first and second auxiliary requests; Articles 84 and 83 EPC:*

3.1 *Article 84 EPC*

The contested subject-matter was already contained in the patent as claimed and thus there is no need to examine in the appeal proceedings.

3.2 *Article 83 EPC*

In the absence of evidence, showing that liposome compositions presenting agent:lipid ratios higher than 0.3:1 cannot be produced, the board can only conclude that the teaching of the patent as granted in this respect fulfils Article 83 EPC.

4. *Main request*

4.1 *Article 123(2) and (3) EPC*

The features contained in the two sets of claims of the main request may be derived from the application as filed (see originally filed claims 1, 3, 7 to 18, 20, 22 to 25, 27, 31 to 42 and 52, together with description page 2, paragraph 2; page 1, line 12; page 10, lines 19 to 22; page 7, lines 32 to 33; page 15, lines 9 to 38, and page 16, line 18, to page 17, line 16). Moreover, they do not extend the scope of the claims as granted, since only further restricting features from the disclosure of the patent have been added to claim 1 and embodiments that existed in parallel have been cancelled.

4.2 *Article 54 EPC*

Document (O1) represents the state of the art with respect to Article 54(3) EPC.

This prior art discloses a composition containing liposomes (claim 24 together with claim 1, lines 2 to 5) and

- comprising a lipid bilayer (see page 10, line 26),

- an ionizable cationic antineoplastic anthracycline (daunorubicin, see claim 21 with reference to claim 1),
- wherein the antineoplastic agent:lipid ratio (w/w) is from 0.1:1 to 3:1 (10 mg/100 mg drug:lipid, ie 0.1:1, see line 1 of page 12 together with page 11, lines 33 to 34 referring especially to an anthracylic antineoplastic agent);
- and a buffer combination comprising a citric acid buffer internal to the liposomes having a first pH (see claim 21, second line), and
- an aqueous solution external to the liposomes having a second pH, such that there is a pH gradient across the bilayer of the liposome, wherein the first pH is acidic with respect to the second pH (see claim 21, second line, together with claim 1, especially section c.).

As regards the validity of the agent:lipid ratio of 0.1:1, it should be noted that according to the disclosure of (O1) the anthracyclic antineoplastic agent has to be added to the vesicle-containing medium in amounts of up to **about** 10 mg/100 mg lipid in order to ensure entrapment as close as possible to 100% (see page 11, line 33, to page 12, line 3; bold letters introduced by the board). Since the "close to 100% entrapment" reads for the whole range from 1 mg/100 mg agent:lipid to 10 mg/100 mg agent:lipid and not only for the preferred range, and since the term "about" also discloses use of slightly more than 10 mg agent per 100 mg lipid, an agent:lipid ratio of 0.1:1 will indeed be reached.

Therefore, the subject-matter of claim 1 of the main request is anticipated by the teaching of document (O1).

5. *Auxiliary request 1*

Claim 1 contains a lower limit of 0.2:1 for the agent:lipid ratio. This value cannot be derived from the application as filed.

On the one hand, there is no possibility of obtaining an exact value of 0.2 from the examples, not even from example 13, and on the other, the teaching of example 13 cannot be generalised.

5.1 It may be that,

- even when in example 13 only the absolute weight of 200 mg total lipid in whatsoever a volume of 150 mM citric acid is given (see page 45, lines 6 to 7 of the application as filed) instead of the concentration of 200 mg total lipid/ml buffer and
- even when diluting this sample "2 times with unbuffered saline" normally results in a further unknown concentration of lipid, because the quantity of saline is not known (the term "diluted 2 times" must prima facie mean any dilution achieved in two steps, especially when the term "diluted 2 fold" used in example 12 means a dilution to double the original volume),

reference to example 12, given in example 13, is able to make clear that, in example 13 empty VET_{200}s are produced with a defined concentration of finally 100 mg total lipid/ml buffer.

But even if - despite the described uncertainties - the person skilled in the art should assume by said reference to example 12 that such a well defined solution of 100 mg total lipid/ml buffer is to be produced by the teaching of example 13 and then is used to be adjusted to pH 7.5 with 1.0 N NaOH and to take an aliquot for adding doxorubicin, the result cannot be a solution of an exact 0.2:1 ratio of doxorubicin:lipid.

Adjusting pH can only be achieved by adding some volume of 1.0 N NaOH and by adding the said volume of 1.0 N NaOH, the concentration of lipid in the aliquot must become lower than 100 mg total lipid/ml buffer (in example 16, for instance, 0.275 ml of 1M Na_2CO_3 is added to 1.0 ml of liposomal suspension). Consequently, by adding 70 mg doxorubicin to the aliquot of 3.5 ml, the resulting liposome composition must represent a higher agent:lipid ratio than 0.2:1 and not 0.2:1.

Thus, the lower limit of the agent:lipid ratio in claim 1, as far as it should be derived from example 13, cannot be 0.2:1.

5.2 Moreover, in example 13 a very special mixture of lipids, namely EPC/EPG/cholesterol (0.95/0.05/1.0 mole ratio), is used. Therefore, the results of this example cannot be generalised to a claim referring to any mixture of lipids, being able to build liposomes, as current claim 1 would suggest.

5.3 Finally, even in the context of all examples together a generalisation to a range of agent:lipid ratios between 0.2:1 and 3:1 would not be possible, because all these examples only refer to agent:lipid ratios between about

0.2:1 and 0.29:1 (see letter from the respondent dated 19 July 2000, page 5, paragraph 4).

5.4 Accordingly, auxiliary request 1 cannot be allowed under Article 123(2) EPC.

6. *Auxiliary request 2*

6.1 Article 123(2) and (3) EPC

With respect to the two sets of claims of auxiliary request 2, the board is convinced that there are no objections concerning Article 123(2) EPC because a lower limit of the agent:lipid ratio of 0.3:1 is disclosed in the application as filed (see page 10, lines 19 to 22) and restriction to the use of doxorubicin and daunorubicin is disclosed in original claim 3.

Auxiliary request 2 also meets the provisions of Article 123(3) EPC because its subject-matter is restricted compared to the subject-matter of the patent in suit.

6.2 Article 54 EPC

Since the lower limit for the agent:lipid ratio of 0.3:1 is expressly disclosed in the priority document (see page 8 of the description, last paragraph, lines 4 to 6), the claimed priority is valid for the subject-matter of auxiliary request 2. With regard to this request, reference (O1) is not a prior art document.

Novelty is given in view of (O3), since in this document citric acid is not used as a buffer.

Furthermore, none of the other documents cited in the proceedings discloses all the features of the subject-matter of the patent in suit. Therefore it is new over the prior art.

6.3 Problem-and-solution approach for assessing inventive step

6.3.1 The patent in suit concerns "Liposomal formulations with a high antineoplastic agent/lipid ratio".

Document (O3) represents the closest state of the art.

According to its claim 6, the subject-matter of this prior art is also a liposomal formulation. It shows nearly all the features of the subject-matter of claim 1 of auxiliary request 2 (see (O3), claims 6 and 7 together with the part B version of example 1 on page 24 (referring to page 19, line 28), figures 7A and 7B and page 23, line 1).

High adriamycin (=doxorubicin) uptake and low release rate are already achieved by the liposomal formulations disclosed in (O3) (see for instance figure 7A for EPC-vesicles at 20°C).

6.3.2 In the light of this prior art, the technical problem underlying the patent in suit can only be seen in the provision of another liposomal formulation containing doxorubicin or daunorubicin as ionizable antineoplastic anthracycline.

The solution to this problem is the provision of the liposome composition exhibiting the features of claim 1 of the second auxiliary request, especially containing citric acid as a buffer system.

The patent in suit does not provide evidence for liposome compositions exhibiting an agent:lipid ratio higher than 0.29:1. However, in the absence of any experimental evidence supplied by the appellant the problem must be regarded as plausibly solved.

6.3.3 In order to supply just another liposomal composition containing an ionizable cationic anthracycline, the skilled person will take into account the teaching of document (O2).

(O2) is a basic publication about the possibility of loading liposomes with ionizable cationic drugs, using catecholamines as model drugs and citric acid as buffers. Even if there were relatively low concentrations of the drugs and the author wrote about some problems of obtaining a stable gradient of pH using EPC-based liposomes, its statement of a 10-20-fold accumulation over controls (see page 271, paragraph 3) was a good basis for further experiments.

The teaching of (O2) would not keep the person skilled in the art from using citrate-buffer systems for these experiments, because he did not attribute the problems to the buffer and he knew at the priority date of the patent in suit, for instance, that improvements with regard to stability of the pH gradient and to lowering of the leakage rate could be achieved by using

cholesterol together with EPC (see for instance (O3), figures 7A and 7B).

6.3.4 Additionally, all experimental data with respect to the liposome compositions of claim 1 of auxiliary request 2 rely on liposomal compositions exhibiting agent:lipid ratios lower than those claimed, and so for them neither a higher drug uptake nor a lower release rate is evident.

Accordingly, the board can only conclude that the subject-matter of claim 1 of auxiliary request 2 does not involve an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Townend U. Oswald