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D E C I S I O N
of 13 November 1998

Case Number: T 0831/94 - 3.3.2

Application Number: 86301513.7

Publication Number: 0219922

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:
Anthracycline antineoplastic agents encapsulated in phospholipid micellular particles

Patentee:
Vestar, Inc.

Opponent:
The Liposome Company Inc.

Headword:
Anthracycline/VESTAR

Relevant legal provisions:
EPC Art. 54(1), 111(1), 123(2)

Keyword:
"Main request - novelty - no"
"First to fourth auxiliary request - rejected - contain subject-matter which extends beyond the content of the application as filed"
"Fifth auxiliary request - remitted - contains subject-matter never discussed before the first instance in the light of the prior art"

Decisions cited:
T 0047/90

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0831/94 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 13 November 1998

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 August 1994 revoking European patent No. 0 219 922 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
J. H. van Moer

Summary of Facts and Submissions

I. European patent No. 0 219 922 concerning anthracycline antineoplastic agents encapsulated in phospholipid micellular particles was granted on the basis of 18 claims contained in European patent application No. 86 301 513.7.

Claim 1 as granted reads as follows:

"1. A composition comprising an anthracycline antineoplastic agent encapsulated in phospholipid micellular particles consisting of anionic and neutral phospholipids and cholesterol, said particles suspended in a low ionic strength aqueous phase containing sugar."

II. Opposition was filed against the granted patent by the Respondent. The patent was opposed for lack of novelty and lack of inventive step under Article 100(a) EPC as well as for insufficiency of disclosure of the invention under Article 100(b) EPC. The ground of opposition under Article 100(b) EPC was withdrawn at the oral proceedings before the Opposition Division.

Of the numerous documents cited during the opposition only the following remain relevant to the present decision:

(8) International Journal of Pharmaceutics, 16 (1983), pages 79 to 92,

(14) US-A-4235871,

(17) Proc. Natl. Acad. Sci. USA, Vol. 75, No. 9, pages 4194 to 4198, September 1978.

III. By a decision delivered orally on 27 July 1994 with the written reasons posted on 23 August 1994, the Opposition Division revoked the patent under Article 102(1) EPC.

The Opposition Division took the view that the subject-matter of claim 1 as granted relating to a composition comprising an anthracycline agent encapsulated in phospholipid micellular particles, lacked novelty in the light of the disclosure in document (8) which was concerned with the preparation and characterization of doxorubicin-containing liposomes. This document did not explicitly state that the said particles were suspended in a low ionic strength aqueous phase; however, since the patent in suit contained neither a definition of ionic strength nor numerical values of ionic strength, the Opposition Division concluded that it was questionable whether such a relative term was suitable as a feature distinguishing the claimed composition from the prior art.

In this respect, the Opposition Division made inter alia reference to documents (14) and (17) as evidence that the 0.8 % solution according to document (8) could also be regarded as being of "low ionic strength".

IV. The Appellant lodged an appeal against the said decision, filed two auxiliary requests attached to the grounds of appeal and indicated that in case the Board of Appeal was contemplating maintaining any part of the Opposition Division's decision, he reserved the right to request oral proceedings.

During the appeal proceedings the Appellant filed fifteen new documents including

(18) Karczmar et al; Biochimica et Biophysica Acta, **557** (1979), pages 306 to 319,

and

(21) Crommelin; Journal of Pharmaceutical Sciences, Vol 73, No. 11, November 1984, pages 1559 to 1562,

in order to show the meaning of the term high and low ionic strenght in the field of liposomes. In the light of the disclosures in the new documents, the Appellant took the view that the term "low ionic strength" in the context in which it was used in the patent in suit should be understood by the skilled person to mean an ionic strength somewhere in the region of 30 mM or less. Accordingly, the isotonic liposome suspension of document (8) due to the presence of 0.8 % NaCl providing an ionic strength of about 150 mM could not be regarded as a low ionic strength aqueous phase. Since document (8) disclosed a value of 85% as the maximum amount of entrapped doxorubicin, the authors of this prior art never achieved the 90% or greater trapping efficiency of the anthracycline agent according to the composition of the patent in suit and particularly not by maintaining 90% of the particles intact after two weeks. Moreover, there was no suggestion in document (8) that a low ionic strength suspending medium containing sugar was possible or desirable. The sugar (lactose) which was present in document (8) was present accidentally in that it happened to be present in the commercially available source of doxorubicin.

After summons to oral proceedings, in a letter dated 13 October 1998, the Appellant informed the parties that: "On the understanding that the respondents (opponents) are also withdrawing their requests for oral proceedings, the applicants withdraw the request for oral proceedings and request that the procedure be continued in writing". New auxiliary requests 3, 4, 5 and 6 were attached to this letter. Claim 1 of

auxiliary request 5 reads as follows:

"1. A composition comprising an anthracycline anti-neoplastic agent encapsulated in phospholipid micellular particles **in the form of unilamellar vesicles about 45 to 55 nanometers in diameter** consisting of anionic and neutral phospholipids and cholesterol, said particles suspended in a low ionic strength aqueous phase containing sugar **and exhibiting a greater than 90% trapping efficiency of the anthracycline anti-neoplastic agent.**"

[Emphasis added in order to indicate features distinguishing this claim from claim 1 as granted (main request)].

V. The Respondent contested the above arguments. In particular it was pointed out that the paragraph "Materials and Methods" on page 80 of document (8) clearly disclosed doxorubicin (an anthracycline antineoplastic agent) entrapment in liposomes containing cholesterol, a phosphatidylserine (an anionic phospholipid) and phosphatidylcholine (a neutral phospholipid), the anthracycline agent being provided in conjunction with a sugar and the particles suspended in an aqueous solution with 0.8% NaCl. As regards the ionic strength of the solution, it was particularly pointed out that having regard to the disclosures in the numerous documents cited during the proceedings only document (14) clearly defined the meaning of "low ionic strength" by referring to a value of 300 mM as low, and that accordingly the said paragraph on page 80 of document (8) disclosing a liposomal anthracycline suspension with an ionic strength of about 150 mM corresponding to the 0.8% NaCl content took away the novelty of claim 1 of the patent in suit.

It was furthermore noted that in addition to objections under Article 100(a) EPC, the amended claims according to the auxiliary requests did not fulfil the requirements of Articles 84, 100(b) and (c) or Rule 29 EPC.

After the summons to oral proceedings, in a letter dated 21 October 1998, the Respondent informed the parties that: "On the understanding that the Patentees are also withdrawing their request for oral proceedings, the Opponent, The Liposome Company, withdraws its request for the oral proceedings...., and requests that the decision be rendered on the written records".

VI. The oral proceedings took place on 13 November 1998 as scheduled. None of the parties attended these proceedings.

VI. The Appellant requested in writing that the decision under appeal be set aside and that the patent be maintained as granted (main request), alternatively on the basis of auxiliary requests 1 or 2, filed on 30 December 1994; or on the basis of one of the auxiliary requests 3 to 6, filed on 13 October 1998.

The Respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. The Appellant made no objection under Article 100(c)

EPC and the Board considers that the requirements of Article 123(2) and (3) EPC are satisfied.

3. Having regard to the Opposition Division's decision, the point at issue is the novelty of the subject-matter of claim 1 as granted corresponding to claim 1 of the present main request.

3.1 Comparing the general procedure for preparing liposomes described in document (8) on page 80 under the heading **"Methods and Materials"**, with the subject-matter of claim 1, the Board sees no reason to doubt the Opposition Division's analysis that, except for the feature that the phospholipid micellular particles are suspended in a low ionic strength aqueous phase containing sugar, this document discloses a composition falling within the scope of claim 1 as granted.

3.2 It is particularly to be noted that the Appellant contested neither that phosphatidylserine and phosphatidylcholine are respectively an anionic phospholipid and a neutral phospholipid, nor that Adriablastine produced by Farmitalia contains doxorubicin and lactose in a ratio of 1:5 and that according to the preparation method at least a part of the lactose will be present in the final composition of (8). The Appellant's statement that the sugar (lactose) in document (8) was present accidentally in that it happened to be present in the commercially available source of doxorubicin is tantamount to admitting the presence of sugar. Where a product claim is to be examined, this statement clearly cannot have any influence on the decision concerning novelty but rather on the question whether or not the claimed subject-matter would involve an inventive step in the light of the prior art disclosure. It was furthermore not disputed between the parties that the presence of 0.8% NaCl in the composition according to document (8)

provides an ionic strength of about 150 mM.

3.3 Accordingly, in the absence of any reference to the ratios of the components in the claimed composition, it only remains to be considered whether the relative term low ionic strength can be regarded **clearly and unequivocally** as a characterising feature distinguishing the claimed composition from the composition of document (8) which also comprises phospholipid micellular particles suspended in an aqueous phase with an ionic strength of 150 mM, or whether on the contrary in the field of phospholipid micellular particles a value of the ionic strength of 150 mM **clearly and unequivocally** does not fall within the technical meaning of low ionic strength.

3.4 Relative terms such as "low" are not necessarily excluded when defining the subject-matter of a product claim. Although in the present case the term low ionic strength finds support in the description of the patent in suit as originally filed on page 8, second paragraph in the reference to "low-ionic media, such as sugar solutions or de-ionized distilled water", the description neither contains numerical values exemplifying low ionic strength aqueous phases, nor does it contain a concrete value delimiting the relative term "low" vis-à-vis other possible relative terms such as "medium" or "high". In this context it is to be noted that ionic strength in accordance with the common general knowledge of those skilled in the field of physical chemistry is defined as the half of the algebraic sum of the concentration values of each type of ion - cationic and anionic ions being taken separately - present in a liquid phase with each of the concentration values multiplied by the square of the corresponding ionic valence status. Therefore, it would be not possible to exemplify the ionic strength of an aqueous phase only by reference to the concentration of

one ionic species out of a group of different species having different ionic valence status present in the aqueous phase. Accordingly, in the circumstances of the present case, the term low ionic strength in claim 1 has to be understood in its broadest sense and not therefore as an absolute numerical feature when comparing the claimed subject-matter with ionic strength values disclosed in the known prior art.

3.5 As regards the relevant prior art for a comparison of so-called "high" and "low" ionic strength values, the Appellant cited document (14), which was deemed by the Opposition Division to support the conclusion that the 150 mM NaCl solution of document (8) represents a low ionic strength aqueous phase. By reference to calculations on the basis of concentration values disclosed in column 5, lines 22 to 33 and column 11, Table 1, of this document, and in contrast to the Opposition Division's conclusions, the Appellant has sought to demonstrate that this prior art does not disclose a buffer solution with a low ionic strength of 0.3 M or 300 mM but 0.3 mM.

The Board, however, cannot follow the Appellant's way of reading or interpreting the disclosure in document (14). The above-mentioned passages indicate as a general rule that "the ionic strength of the aqueous phase has a bearing on the encapsulating efficiency obtained in the methods of the invention". Reference is made to sodium chloride concentrations of 15 mM in line 27 and 500 mM in line 29 in connection with attainable percentage values of encapsulated aqueous phases. In the same context and immediately following in the subsequent sentence starting in line 30, it is more generally stated that

"to maximize the encapsulation of macromolecules, a buffer of low ionic strength (less than 0.3) is preferably employed" and that "the encapsulation efficiency is also dependent on the concentration of lipid or phospholipid present in the 2-phase system".

This is, however, not the only disclosure in document (14) relating to a relationship between varying sodium chloride concentrations and the encapsulation efficiency obtainable under conditions described in this document. Table 1 in column 11, belonging to Example 5, which table has also been considered by the Appellant, shows values of percentage encapsulation depending on 0.5; 0.15; 0.1; 0.04; 0.02 and 0.00 moles of NaCl. This table clearly shows a step of 47.5% to 62.3% encapsulation between 0.04 moles and 0.02 moles of NaCl content and a trend to about the same values for 0.02 moles and below, down to 0.00 moles NaCl in the phase system forming the basis for Example 5. The said step and trend is confirmed by Figure 2 on page 4196 of document (17). Said Figure 2 of document (17) is a graphical representation of the same experimental data as Table 1 of document (14). Accordingly, there is no basis for the Appellant's assumption that the low ionic strength of 0,3 mentioned in document (14) without a reference to M or mM relates clearly and exclusively to 0.3 mM and that a value of 150 mM is clearly and unequivocally outside the scope of claim 1 of the main request containing the mere reference to the low ionic strength of an aqueous phase.

3.6 Since document (14) clearly indicates that the encapsulating efficiency not only depends on the ionic strength of the liquid phases, but also on other parameters such as the phospholipid content, there is no reason to follow the Appellant's argument that the absolute maximum of encapsulation occurs only at "0.00

M NaCl". Moreover, the wording of the passages in document (14) relevant to this matter can only be understood to mean that the reference to a "low ionic strength (less than 0.3)" is intended to show under what experimental conditions it is possible to maximize one of the parameters influencing the encapsulating efficiency.

3.7 This situation is not changed by taking into account the disclosures in further documents on file exemplifying ionic strength values, eg document (18). This document contains on page 306, the front page of this publication, a reference to an ionic strength of 0.01 M being "relatively low" and then goes on to describe conditions "at higher ionic strength" of 0.15 M. In these circumstances, each of the ionic strength values referred to subsequently in this prior art, for example the so-called high and low ionic strength buffers of 0.15 M and 0.01 M respectively, mentioned on page 307, as well as the low ionic strength of 0.01 M and the high ionic strength of 0.15 M according to Table 1 on page 309, must be understood in the same way as being "relatively low" and "higher", but cannot be understood as representing absolute values for high and low ionic strength conditions in aqueous phases.

The Board agrees with the Appellant's analysis that document (21) does not refer in relative terms to a high ionic strength in respect of a value of 150 mM NaCl. However, taking into account the fact that the disclosure in document (14) does not exclude a value of 150 mM being of low ionic strength, document (21) could be regarded as being contradictory to the disclosure in document (14).

3.8 As regards the prior art disclosure, it is to be noted that none of the documents contradict the interpretation of Table 1 in document (14) and Figure 1 in document (17) as given in points 3.5 above, but that at least the disclosures in two documents on file, namely (14) and (21), contradict each other. Taking into account the circumstances of the present case, it can therefore only be concluded that the Appellant failed to show clearly and unequivocally the novelty of the composition of claim 1 of the main request compared with compositions described in document (8), and that having regard to the facts on file, the Opposition Division's arguments cannot be disregarded.

Claim 1 of the main request does not meet the requirements of Article 54(1) EPC.

Auxiliary requests

4. Each of the auxiliary requests 1 to 6 on file can be regarded either as a fair response by the Appellant to overcome the grounds of revocation as set out in the Opposition Division's decision or as constituting a bona fide attempt to overcome objections raised by the Respondent during the appeal proceedings. Since the auxiliary requests also appear to limit the scope of the main request, the Board sees no grounds to exclude these claims from the further procedure.

4.1 Auxiliary requests 1 to 4, however, do not meet the requirements of Article 123(2) EPC.

Each claim 1 of these requests comprises the feature "...phospholipid micellular particles... exhibiting a greater than 90% trapping efficiency...". According to

the description as originally filed, page 6, second full paragraph, such a trapping efficiency is only disclosed for micellular particles in the form of **unilamellar** phospholipid **vesicles 45-55 nanometres in diameter**.

Accordingly auxiliary requests 1 to 4 must be rejected.

4.2 Having regard to the aforementioned passage on page 6 of the description as originally filed, claim 1 of auxiliary request 5 fulfils the requirements of Article 123(2) and (3) EPC.

It is to be noted, however, that the combination of features newly introduced into claim 1 of auxiliary request 5 relating to unilamellar vesicles 45-55 nanometres in diameter and exhibiting a greater than 90% trapping efficiency, has not been discussed in the light of the disclosures in the prior art documents on file, nor did the Respondent have the opportunity to comment in detail on this request. Moreover, the question whether or not the subject-matter of the patent in suit involves an inventive step was not considered in the decision of the Opposition Division.

4.3 Accordingly, it does not seem appropriate at the present stage of the procedure for the Board to carry out an investigation in the state of the art on file on the basis of auxiliary request 5 and possibly auxiliary request 6, both requests not having formed the basis for the decision of the Opposition Division. Apart from the fact that the parties would be deprived of an instance of jurisdiction for this matter, in the circumstances of the present case the Board wishes to point out that the essential function of the appeal proceedings is to determine whether the decision of the first instance was correct (T 47/90, OJ EPO 1991, 486).

4.4 Since it is well known to the parties that the normal purpose of oral proceedings is to bring the case to a conclusion (Article 11(3) RPBA), the parties' failure to attend the oral proceedings, together with the request to continue the proceedings in writing, can be regarded as further support for the decision to remit the case to the first instance. As a consequence it is also meaningful to continue the proceedings in writing before the first instance.

Accordingly, the Board has decided to invoke its powers under Article 111(1) EPC and to remit the case to the Opposition Division with the order to prosecute the proceedings further.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The main request and the auxiliary requests 1 to 4 of the appellant are rejected.

3. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon