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D E C I S I O N
of 14 December 1999

Case Number: T 0596/96 - 3.3.2

Application Number: 85301602.0

Publication Number: 0158441

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:

Liposome-forming composition

Patentee:

Phares Pharmaceutical Holland B.V.

Opponent:

Rhône-Poulenc Rorer GmbH

Headword:

Pro-liposome/PHARES PHARMACEUTICAL

Relevant legal provisions:

EPC Art. 123(2)(3), 111(1)

Keyword:

"Main request (no): Disclaimer neither supported by the application as filed nor justified by an accidental anticipation"

"Auxiliary request (yes): Broad interpretation of non-precisely defined feature"

Decisions cited:

T 0079/96, T 0863/96

Catchword:

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Boards of Appeal

Chambres de recours

Case Number: T 0596/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 14 December 1999

Appellant: Phares Pharmaceutical Holland B.V.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 9 May 1996 revoking
European patent No. 0 158 441 pursuant to
Article 102(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
C. Rennie-Smith

Summary of Facts and Submissions

- I. European patent No. 0 158 441 was granted in response to European patent application No. 85 301 602.0 on the basis of two sets of 25 and 23 claims, the former for the designated Contracting States DE, FR, GB and IT and the latter for AT, BE, NL, SE and CH.

The granted claims were directed to pro-liposome compositions, to aerosol compositions and to a method of making an aqueous dispersion of liposomes.

- II. Notice of opposition was filed by the respondent, requesting revocation of the patent in its entirety pursuant to Article 100 EPC within the terms of Articles 52 to 57 EPC.

On 23 March 1995 an amended main request and two auxiliary requests were filed, the first auxiliary request being further amended on 9 January 1996. Each request consisted of two sets of claims for the two groups of designated Contracting States mentioned above.

The text of claim 1 of the first set of claims according to the main request considered by the opposition division read as follows:

"Process for making an aqueous dispersion of liposomes by mixing a pro-liposome composition with an excess of water, said pro-liposome composition comprising a uniform mixture of:

(a) at least one membrane lipid,

(b) at least one water miscible organic solvent selected from ethanol, isopropyl alcohol, methanol and butanol, and optionally
(c) an amount of water,
the proportion by weight of (a) to (b) being from 40:1 to 1:20, such that, on addition of excess water, the composition spontaneously forms vesicles or liposomes."

Claims 24 to 41 of the same set of claims were directed to aerosol compositions or pro-liposome compositions.

During the proceedings the respondent, while maintaining its original objections raised additional objections as to compliance of the amended claims with the requirements of Articles 83 and 123(2) EPC.

III. Without further consideration of the original aspects of the opposition, the opposition division revoked the patent on the ground that the granted claims did not meet the requirements of Article 123(2) EPC. It was argued that all the requests included claims for compositions and processes in which the presence of the water was an optional feature, despite the fact that there was no disclosure in the application as filed of processes carried out by using anhydrous pro-liposome compositions. In fact, in the view of the opposition division, the expressions "up to 20% of water" or "up to 40% of water", which were used in several passages of the application as filed and which, as the appellant contended, implicitly covered anhydrous pro-liposome compositions, did not disclose the figure 0% of water.

IV. The appellant (patentee) lodged an appeal against this

decision.

In response to three communications issued by the Board dealing in detail with the admissibility under Article 123(2) EPC of the amended claims, the appellant submitted a new main request and an auxiliary request, both including two sets of 24 and 22 claims, on 2 July 1999 and 27 September 1999 respectively. All the preceding requests were abandoned.

Claim 1 of the first set of claims according to the main request (DE, FR, GB and IT) reads as follows:

"A method which is suitable for making large volumes of liposomes in aqueous dispersion, said method comprising mixing with excess of water a pro-liposome composition and optionally agitating the mixture, said pro-liposome composition comprising a uniform mixture of:

- (a) at least one membrane lipid,*
- (b) at least one water-miscible organic liquid which is a solvent for the lipid and is selected from ethanol, isopropyl alcohol, methanol and butanol, and optionally*
- (c) an amount of water,*

such that, on addition of excess water the composition spontaneously forms vesicles or liposomes, the proportion by weight of a) to b) being from 40:1 to 1:20, said method not involving the injection of a dilute ethanolic solution of lipids through a fine hypodermic needle into an aqueous phase and not involving sonication."

Independent claim 2 is directed to a corresponding method in which, however, the presence of water is not

optional.

Independent claim 21 reads as follows:

"An aerosol composition comprising in a volatile liquid propellant:

(a) at least one membrane lipid,

(b) at least one water-miscible organic liquid which is a solvent for the lipid, and optionally

(c) up to 40%, by weight on the combined weight of a), b) and c) of water,

such that, on coming into contact with excess water, the composition spontaneously forms vesicles or liposomes,

the proportion by weight of a) to b) being from 40:1 to 1:20."

Claim 1 of the second set of claims, for AT, BE, NL, SE and CH, differs from the corresponding claim 1 of the first set in that the "organic liquid" is not further defined.

The auxiliary request differs from the main request only in that the disclaimer "*said method not involving the injection of a dilute ethanolic solution of lipids through a fine hypodermic needle into an aqueous phase and not involving sonication*" is deleted from all the claims concerned.

V. During the appeal proceedings, the respondent withdrew the opposition.

VI. The appellant requested that the decision of the

opposition division be set aside and the patent be maintained in the form of the main or auxiliary requests.

Reasons for the Decision

1. The appeal is admissible.

2 *Main request*

Article 123(2) EPC

2.1 All the independent claims directed to the method for making liposomes include a disclaimer, which provides that the claimed method does not involve the injection of a diluted ethanolic solution of lipids through a fine hypodermic needle into an aqueous phase and does not involve sonication.

In support of this limiting feature, the appellant relied on passages in the application as filed in which the relevant prior art was generally acknowledged, although without any reference to specific prior documents. It also relied on the Batzri and Korn reference "The Journal of Cell Biology, 66, (1975), pp. 621-634", (document 2) describing a method for the preparation of liposomes, in which an ethanolic solution of lipid was injected into an aqueous solution through a fine hypodermic needle, as well as the Konihiko Goto reference "Tohoku J. Exp. Med., 131, (1980) pp. 399-407" (document 3) describing sonication.

The Board wishes to emphasize that the part of the application as filed relied on by the appellant does not form part of the description of the invention, but simply the description of the prior art. From the language of this part of the application, seen in relation to the actual description of the invention, the skilled reader could not deduce directly and unambiguously that the invention as filed was intended to exclude the methods which are now the object of the disclaimer. The main problem left unsolved by the known methods of preparing liposomes, a problem intended to be solved by the invention of the opposed patent, was that of the low ratio of drug entrapment. Yet, it is evident from the description that this problem occurred with all the known types of liposomes and was therefore independent from the use of the specific sonication or injection techniques. Thus the skilled reader could not have deduced from the application as filed that two such known methods, that is sonication and injection of an ethanolic solution of lipid into an aqueous phase, were excluded from the original teaching.

For these reasons, the disclaimer cannot be regarded as supported by the filed application.

- 2.2 The Board concedes that, in particular circumstances such as in the case of an **accidental anticipation** of the invention, a disclaimer may be based on a well-defined novelty-destroying prior document. However, the conditions which would justify this possibility deserve special consideration.

The first condition is that the prior art document must be indisputably novelty-destroying. However, in the

present case, no novelty objection had been raised on the basis of documents (2) or (3) above, cited by the appellant in support of the disclaimer. Owing to the objections under Article 123(2), the examination for novelty was not taken further by the opposition division. Therefore, the introduction of the disclaimer cannot be considered as a reply to a substantiated objection of lack of novelty raised during the opposition proceedings. Moreover, it should be stressed that no disclaimer of this type can be allowed as a simple precautionary or auxiliary measure for the purpose of "**further clarifying** the distinction" between the claimed subject-matter and the prior art, as stated in the appellant's contentions. Indeed, if a "distinction" between the claimed subject-matter and a prior document exists, such a document does not represent a novelty-destroying anticipation.

The second condition to be met is that the allegedly novelty-destroying prior document must be an **accidental** anticipation. It is clear from the case law of the Boards of Appeal dealing with this exceptional means of re-establishing novelty that such a disclaimer is only allowable if the prior document containing the excluded disclosure has no relevance for any further examination aspect of the claimed invention and that, upon introduction of the disclaimer, this prior document must disappear from the prior art field to be taken into consideration (see T 863/96 of 4 February 1999, not published in the OJ EPO).

In the present case, documents (2) "The Journal of Cell Biology (1975)" and (3) "Tohoku J. Exp. Med. (1980)", allegedly justifying the introduction of the

disclaimer, indisputably relate to the same field as the claimed invention: ie production of liposomes using membrane-lipids. Moreover, a preliminary examination of all the cited prior documents revealed that document (2) may even be a candidate to represent the closest prior art. Therefore these documents remain highly relevant to the further examination aspects of the invention with or without a disclaimer in the amended claims. In such circumstances, it is evident that if documents (2) and (3) represent anticipations of the invention, they definitely cannot be considered to be "accidental" anticipations. The conditions for allowing the use of the proposed disclaimer are therefore not met.

For these reasons, the Board considers the main request to be in breach of the requirements of Article 123(2) EPC.

3. *Auxiliary request*

Article 123(2) EPC

3.1 The independent claims of the two sets in the auxiliary request do not include the disclaimer discussed above, however, they still include the feature whereby water is absent or is an optional component in the pro-liposome composition, and hence the feature which caused the revocation of the patent (see claims 1, 5, 6 and 21 of the first set and claims 1, 5 and 19 of the second set).

The Board wishes to stress that, in addition to this feature, the granted claims also differ from the claims

as filed in many respects. However, during the opposition proceedings neither the opponent nor the opposition division objected to the admissibility of these further amendments, implicitly recognising that they complied with the requirements of Article 123(2) EPC. The Board shares this opinion, and therefore will only consider in the present decision the admissibility of the feature which was the object of the decision under appeal (ie optional presence of water in the pro-liposome composition) and the other amendments introduced during the appeal proceedings.

These amendments are the change of category of most of the product-claims into method claims for making liposome suspensions (claims 1 to 20 and 23 and the corresponding claims in the second set); the introduction in the text of at least claim 1 of both sets of claims of the expressions: "which is suitable for making large volumes of liposomes" and "optionally agitating the mixture", and finally the replacement of the word "solvent" by "liquid which is a solvent for lipid" in the definition of component (b).

All these amendments are disclosed in the application as filed. Specifically, the change of category is justified by the paragraph on page 4, lines 11 to 15, in combination with the originally filed claims; the feature "*which is suitable for making large volumes of liposomes*" is disclosed in the passage bridging pages 18 and 19; the step "*optionally agitating the mixture*" is disclosed on page 10, lines 32 to 34; the new definition of component (b), ie the solvent, corresponds to the original definition used in the application as filed.

3.2 As to the optional presence of water in the pro-liposome composition, the Board has considered first of all the expression "up to 40% by weight of water" included in the text of claim 1 as filed.

This expression, being open-ended, does not precisely identify the range of water, and for this reason it is open to interpretation. It is a well-established principle laid down by the case law of the boards of appeal that a non-specific definition in a claim should be given its broadest technically sensible meaning. This applies not only when assessing the allowability under Article 123(2) of an amendment but also when assessing novelty, inventive step and any other requirement of the EPC (see eg T 79/96, 20 October 1998, not published in the EPO OJ).

In keeping with this principle and in absence of any evidence to the contrary, the Board holds that the meaning of "up to 40%..." also includes the figure 0%, which means anhydrous composition. This conclusion is fully confirmed by the disclosure in the application as filed.

Many passages in the original application indicate that the presence of water in the claimed compositions is only a preferred form, and not an essential feature. This is evident from eg lines 34 to 36 on page 6, or lines 19 to 23 on page 7 or from Example 5, which relates to a pro-liposome composition in anhydrous form to be used in a sprayable composition.

It is important to note that the two types of composition employed in the claimed methods, namely the

pro-liposome and the aerosol compositions, are not independent embodiments of the invention, but that the "aerosol composition" is indeed the pro-liposome composition added to a **liquid propellant** to enable spraying. This is evident from the dependence of original claim 14 (composition in the form of aerosol) on original claims 1 or 2 (pro-liposome compositions). This is also made plain by the table on page 19 reporting Examples 2 to 6 and illustrating different pro-liposome compositions which, after preparation, are then mixed with the suitable propellant (Arcton) in order to produce a sprayable composition. Among these preparations, four comprise water and one is in anhydrous form. The Board is therefore of the opinion that, on the one hand, the anhydrous character is not a feature closely associated with the aerosol composition and, on the other, that all the pro-liposome mixtures of Examples 2 to 6, including that of Example 5, represent embodiments of the claims protecting the pro-liposome compositions as such, regardless of whether they are later converted to sprayable compositions suitable for aerosol use. Under these circumstances an anhydrous pro-liposome composition and methods using the same for making liposome dispersions are to be considered as a general embodiment disclosed by the application as filed.

3.3 In view of the foregoing, the Board considers that the two sets of claims of the auxiliary request fulfil the requirements of Article 123(2) EPC.

4. *Article 123(3) EPC*

With the exception of claims 21, 22 and 24 (first set

of claims) and claims 19, 20 and 22 (second set), which are the sole product-claims maintained in the auxiliary request, the remaining claims are now directed to a method suitable for making liposomes in aqueous dispersion. Apart from the fact that the granted patent already comprised claims directed to a method for making an aqueous dispersion of liposomes (claims 15 to 23 and 13 to 23 respectively), the replacement of product-claims with method-claims is not in breach of Article 123(3) EPC since the protection conferred by a product claim cover any process for the preparation of this product.

Moreover, the valid method claims comprise additional features, not cited in the granted claims, which more specifically define the claimed subject-matter, so making the conferred protection narrower. These features are that the method *"is suitable for making large volumes of liposomes"* and that the component (b) is an *"organic liquid which is a solvent for the lipid"*. The Board therefore holds that the amended claims comply with the requirements of Article 123(3) EPC.

5. *Articles 83 and 84 EPC*

5.1 In the present case, Articles 100(b) and 83 EPC were not cited as a ground of opposition. The repeatability of the invention is therefore not a point at issue in the appeal proceedings. In any case, the Board notes that the amendments introduced into the claims under consideration have not altered the definition of the invention in such a way as to justify any consideration under Article 83 EPC.

- 5.2 No objection under Article 84 EPC was raised during the proceedings before the opposition division in relation to the amended claims. The Board considers that the amendments introduced into the text of the valid claims during the appeal do not give rise to any question regarding their clarity.
6. Although the opposition division anticipated in writing its preliminary opinion as to the novelty and inventive step involved in some of the claims, then under consideration, those claims have subsequently either been abandoned or so modified that a complete examination appears to be necessary.

The Board wishes to point out that on 12 November 1999 the appellant requested that all stages of the opposition-appeal be expedited and that a request for accelerated proceedings had already been filed as reported in point 4 of the opposition division's decision. Nonetheless, after the decision revoking the patent was issued, three further communications from the Board proved to be necessary in order to arrive at a set of claims which could be considered at least admissible under Article 123(2) EPC.

Even when an opposition has been withdrawn at the appeal stage, the primary function of appeal proceedings is to decide on the correctness of a first instance decision and not to carry out a first-instance substantive examination of the novelty and inventive step of the amended claims in the light of the entire cited prior art.

For these reasons, although Article 111(1) EPC gives

the Board discretion to exercise any power within the competence of the department responsible for the attacked decision, the specific circumstances make it necessary to remit the case to that department and to give to the case special priority justified by the delay already caused.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the Opposition Division for further prosecution.

The Registrar:

The Chairman:

M. Dainese

P. A. M. Lançon