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D E C I S I O N
of 28 June 2001

Case Number: T 0602/96 - 3.3.2

Application Number: 88903062.3

Publication Number: 0352282

IPC: A61K 9/127

Language of the proceedings: EN

Title of invention:
Paucilamellar lipid vesicles

Patentee:
Micro Vesicular Systems, Inc.

Opponent:
L'Oreal

Headword:
Paucilamellar lipid vesicles/MICRO VESICULAR SYSTEMS

Relevant legal provisions:
EPC Art. 83, 100(b)

Keyword:
"Sufficient disclosure of the invention - no - skilled person entirely confused"

Decisions cited:
T 0094/82

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0602/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 28 June 2001

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 27 June 1996 concerning maintenance of European patent No. 0 352 282 in amended form.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
S. U. Hoffmann

Summary of Facts and Submissions

I. European patent No. 0 352 282 was granted on the basis of 14 claims contained in European patent application No. 88903062.3 (international publication No. WO 88/06883 corresponding to international application No. PCT/US 88/00723).

The only independent product claim of the granted patent is claim 4 which reads as follows:

"Paucilamellar lipid-vesicles consisting of 2-8 lipid bilayers in the form of substantially spherical shells separated by aqueous layers, said lipid bilayers and said aqueous layers forming an onion-like structure surrounding a large, substantially amorphous central cavity which is free of lipid bilayers, said lipid layers comprising
a surfactant selected from a group consisting of
fatty acid esters having the formula,

$$R_1\text{-}COO(C_2H_40)_nH$$

where R_1 is lauric, myristic, cetyl, stearic, or oleic acid, or their derivatives and n = 2-10;
polyoxyethylene fatty acid ethers, having the formula

$$R_2\text{-}CO(C_2H_4O)_mH$$

where R_2 is lauric, myristic, or cetyl acids or their derivatives, single or double unsaturated octadecyl acids or their derivatives, or double unsaturated eicodienoic acids or their derivatives and m ranges from 2-4; diethanolamines, having the formula

$$(HOCH_2\text{-}CH_2)_2NCO\text{-}R_3$$

where R_3 is caprylic, lauric, myristic or linoleic acids or their derivatives;

long chain alkyl hexosamides having the formula

$$R_4\text{-}NHCO\text{-}(CH_2)_b\text{-}CH_3$$

where b ranges from 10-18 and R_4 is a sugar molecule selected from a group consisting of glucosamine, galactosamine, and N-methylglucamine;

long chain acyl amino acid amides having the formula

$$R_5\text{-}CH(COOH)\text{-}NHCO\text{-}(CH_2)_cCH_3$$

where c ranges from 10-18 and R_5 is an amino acid side chain; long chain alkyl amides having the formula

$$HOOC\text{-}(CH_2)_d\text{-}N(CH_3)\text{-}(CH_2)_3\text{-}NHCO\text{-}R_6$$

where R_6 is an alkyl chain having 12-20 carbons and not more than two unsaturations, and d ranges from 1-3; polyoxyethylene (20) sorbitan mono- or trioleate; polyoxyethylene glyceryl monostearate with 1-10 polyoxyethylene groups; and glycerol monostearate."

II. Opposition was filed against the granted patent by the Appellant requesting revocation as a whole. 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 opposition was based, *inter alia*, on the following document:

(4) EP-A-0349593 (earliest priority 13.3.87 US 25525)

III. By a decision delivered orally on 10 June 1996 with the written reasons posted on 27 June 1996, the Opposition Division maintained the patent in amended form under Article 102(3) EPC.

Since the patent in suit disclosed 16 examples illustrating the formation of paucilamellar lipid vesicles having 2-8 lipid bilayers and since the parties agreed that it was possible to detect the number of bilayers of a vesicle by applying means of electron microscopy known from the prior art, in the absence of counter-evidence, the Opposition Division concluded that the requirements of Article 83 EPC are met.

In the Opposition Division's view in the light of the disclosure of the most relevant documents the paucilamellar vesicles of independent claim 4 of the patent in suit also met the requirements of novelty and inventive step.

IV. The Appellant (Opponent) lodged an appeal against the said decision and oral proceedings took place on 28 June 2001.

The Appellant directed its appeal to claims 4 to 6 as granted with the view that any request containing claims 4 to 6 as granted should be refused.

The statement of grounds of appeal contained

substantive arguments under Article 100(a) in relation with claims 4 to 6 and under 100(b) EPC in relation with the description.

During the written proceedings the Appellant filed *inter alia* the document:

(23) Repetition of examples 1, and 12 (partially) of the patent in suit filed on 18 February 1998 with letter dated 16 February 1998.

In the Appellant's view the patent in suit lacked any technical information about the thickness of the bilayers, the size of the vesicles or the meaning of the relative term "large...central cavity" of the vesicles particularly since according to the description the dimension of the cavity of the vesicles was a critical element of the invention.

Regarding insufficiency of disclosure the Appellant put emphasis on the fact that according to the patent in suit paucilamellar vesicles having 2 to 8 bilayers were described as a sub group of multilamellar vesicles but that document (4) filed by the same applicant, claiming the same priority date as the patent in suit and containing most of the examples of the patent in suit, related to multilamellar vesicles instead of paucilamellar vesicles. Accordingly, the Appellant concluded that it was impossible for a person skilled in the art to determine whether one and the same example led to the production of vesicles having 2 to 8 bilayers or more than 8 bilayers and consequently that it was impossible for a skilled person to know whether he produced vesicles within or outside the scope of claim 4 of the patent in suit.

In the Appellant's view the lack of insufficiency of disclosure was clearly proven by worked examples and optical as well as electron microscope photos, particularly the electron microscope photos A to C of document (23).

More particularly, it was pointed out that photos "A" and "B" of document (23) showed the presence of paucilamellar vesicles contrary to what was disclosed on table 11, page 13 of the patent specification for the use of the surfactants sorbitan monopalmitate and sorbitan monostearate. Photo "C" of document (23) showed that example 1 of the patent in suit only led to the production of unilamellar vesicles. Furthermore, it was noted that not only the electron microscope photos of document (23) proved insufficiency of disclosure of the invention but also the optical microscope photos. The latter showed birefringence of the vesicles of example 2 of the patent in suit and must relate to multilamellar vesicles having many more than 8 bilayers since for physical reasons it was not possible to detect by optical methods birefringence of vesicles with 8 or fewer bilayers. Even accepting that the examples of the patent led to a mixture of vesicles there was a lack of disclosure regarding means to sort out vesicles having 2 to 8 bilayers.

Regarding the question of costs of comparative tests, it was stated that the electron microscopic photos filed by the Appellant were taken by a foreign institute for a price of around 3000 [Swiss] francs per photo.

Finally, it was noted that the definition of some of the groups of surfactants as set out in claim 4 by

general formulas led to confusion about the chemical structure of the individual components to be selected.

V. During the appeal proceedings the Respondent filed on 23 April 1997 document:

(20) "Declaration of Norman Weiner" attached to the letter dated 23 April 1997.

When contesting the Appellant's arguments the Respondent (Patentee) emphasized that the issues raised under Article 100(b) related solely to the clarity of claim 4, which was not amended during the opposition proceedings.

It was important to recognize that all paucilamellar lipid vesicles are multilamellar lipid vesicles but not all multilamellar lipid vesicles are paucilamellar and thus the fact that document (4) shared certain examples with the description of the patent in suit was not relevant to the interpretation of the term paucilamellar. Beside other differences it was clear from the description of the patent in suit that in contrast to multilamellar lipid vesicles paucilamellar lipid vesicles showed a large amorphous central cavity. Accordingly, the fact that certain examples in the patent in suit and in document (4) were identical in no way implied that multilamellar and paucilamellar vesicles were not distinct and that the skilled person was misled by the examples. Moreover, document (4) did not form part of the state of the art.

Each of the Appellant's arguments based on the presence of birefringence shown on optical microscope photos must be refused since on the basis of such photos it

was only possible to distinguish between unilamellar and multilamellar vesicles.

By reference to document (20) the Respondent further contested the validity of the microscope photos of document (23) as regards their meaningfulness and significance for the number of lipid bilayers forming a vesicle. It was inter alia necessary to base test results on a distribution curve of the number of bilayers by analysing a large number of microscope photos of the same example. Apart from the fact that good experimental work did not rely on a single vesicle in order to determine its classification there were suspicions that the individual photos of document (23) were a negative selection out of a large group of other photos. In this respect it was particularly noted that the outer shell of the vesicle of photo "A" of document (23) clearly represented an artefact of electron microscopy.

Having regard to the risk that one might obtain spurious and even meaningless results from electron microscope photos and having regard to the bad quality of the photos under discussion, there was no shift of the burden of proof.

Moreover, the feature relating to 2 to 8 lipid bilayers of the vesicles was only essential for defining the scope of claim 4 and there was no evidence that the core of the invention could not be carried out without undue burden.

It was emphasized that a fair degree of generalization of an invention must be allowed.

Finally, it was pointed out that comparative tests involving electron microscopy were cost-intensive and the owner of the patent in suit was not a big company and had no access to an electron microscope at any time.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed and that the patent be maintained as maintained by the Opposition Division (main request) or on the basis of the auxiliary request as filed during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The Appellant did not oppose under Article 100(c) EPC, and during the oral proceedings before the Board of Appeal waived former objections under Article 123(2) EPC against the patent in suit as maintained in amended form by the Opposition Division. Having regard to the outcome of the present decision, the Board also sees no reason to discuss this matter further.

3. The Board agrees with the Respondent's arguments

(i) that the requirements of Article 84 EPC that the claims be clear and concise and be supported by the description are not the subject of opposition and appeal proceedings for claims 4 to 6 maintained in unamended form as granted;

(ii) that there is no requirement under the EPC that a test method must always be disclosed in the patent in suit for each of the features defining the scope of a claim;

3.1 Notwithstanding the situation under point 3 above, and the fact that it is not mandatory to give instructions in the claim itself as to how the product is to be obtained, when deciding on the question of sufficiency of disclosure of the invention under Article 83 (100(b)) EPC, in general one of the essential points to be taken into account is that the description of a patent in suit must fulfil these requirements to the extent that the person skilled in the art is enabled to obtain a product as defined in the claim (see T 94/82, OJ EPO 84, page 75 ff, in particular point 2.5 of the Reasons for the Decision and Head note 2).

Accordingly, in the present case the description of the patent in suit including the worked examples 1 to 16 must disclose the invention in a manner sufficiently **clear and complete** to enable a skilled person to decide whether or not a product according to the invention falls within the scope of the claims and in particular claim 4.

3.2 In these circumstances it is necessary to consider first the content of claim 4 regarding the subject matter for which protection is sought.

In accordance with the Appellant's submissions, the Board considers it appropriate to subdivide the features of claim 4 into two categories, the first one defining alternatives for the chemical constitution of surfactants forming the lipid bilayers of the vesicles,

and the second one relating mainly to the physical structure of the vesicles, i.e. to the number of bilayers and arrangement thereof.

3.2.1 Since during the oral proceedings the Respondent agreed to the Appellant's interpretation of the meaning of the general formulas for the alternative surfactant groups polyoxyethylene fatty acid esters as well as the polyoxyethylene fatty acid ethers, which groups the Board considers technically meaningful as specified in the relevant worked examples of the patent in suit, there is no need for the purpose of the present decision to discuss the disclosure of each of the surfactant alternatives encompassed by claim 4 and thus no need to go into detail with the rest of the features relating to the first category.

3.2.2 Having regard to the second category of features of claim 4 the Board cannot agree with the Appellant's argument that lack of definition of the size of the vesicles or parts of them such as the bilayers or central cavity is in itself a ground for considering the patent in suit as not complying with the requirements for sufficiency of disclosure. In this respect the objections put forward by the Appellant, particularly those relating to the number of bilayers, indeed do not give rise *a priori* to doubts as to the structure of paucilamellar lipid vesicles.

3.3 Starting from the description of the patent in suit on page 3, lines 22 to 24, which reads:

"The methods and materials disclosed herein for producing the paucilamellar lipid vesicles all yield vesicles with a high aqueous or oil volume. Electron

micrographs confirm that the paucilamellar lipid vesicles are distinct from the LUV's and the classic MLV's.",

the skilled person would expect a differentiation of classic multilamillar vesicles (MLV's) from the paucilamellar vesicles (PLV's) according to the invention to be disclosed either on the basis of technical information derivable from the content of the description, e.g. examples of the patent in suit or by presentation of electron microscope photos as means which then may serve to confirm sufficiency of disclosure of the invention.

Since apart from the above mentioned statement on page 3, lines 22 to 24, neither the rest of the description, nor the examples, nor the claims of the patent in suit show any proof whether the invention actually allows the production of paucilamellar vesicles and more particularly those with 2 to 8 bilayers, the skilled person is left alone with its own skill and inevitably will turn to additional technical information and known test methods in order to sort out PLV's from MLV's and ULV's.

3.4 The Appellant has presented the arguments that on the one hand document (4) would raise doubts as to the class of vesicles the skilled person would expect to be produced from the worked examples of the patent in suit and on the other hand that electron microscope photos of particles obtained according to specific examples of the patent in suit would not help the skilled person to clarify the situation.

3.5 The Board accepts the Appellant's view that

document (4) can be taken as a declaration by the inventor, since this document in fact does not represent prior art under Article 54(2) and (3) EPC but was undisputedly filed by the same applicant (change of name of the company) and goes back to the same inventor, claiming the same earliest priority date as the patent in suit. In these circumstances, the Board sees no reason to reject the electron microscope photos of document (23), although filed for the first time during the appeal proceedings, since they represent a meaningful supplement to a repetition of examples of the patent in suit.

The Proprietor of a patent in suit here the Respondent can be expected to have been in a position to comment on a repetition of examples of his own patent when this repetition has been filed three years before the oral proceedings.

3.5.1 Document (4) contains eleven examples eight of which being undisputedly the same as those of the patent in suit. Thus, the impression is given that the same examples may serve to illustrate different inventions, namely on the one hand an invention dealing with MLV's (see document (4), page 3, lines 35 to 38) having, as argued by the Respondent, a smaller central cavity in comparison with PLV's, and on the other hand an invention relating to PLV's with an alleged large central cavity of PLV's. In this context the Board notes that document (4) on page 3, line 38 also refers to a "high captured volume". Document (4), however, neither contains technical information about the number of bilayers nor the dimension of the central cavity of the vesicles. Confronted with these contradictions, the skilled person remains confused.

The Respondent's argument that PLV's represent a subgroup of MLV's (*"all PLV's are MLV's but not all MLV's are PLV's"*) cannot help to solve the question which type of vesicles are actually produced by applying the invention of the patent in suit, and the Board can only conclude that the term paucilamellar itself is not sufficient to support a **clear and complete** disclosure of the alleged invention of the patent in suit.

3.5.2 The question arises whether the further characterisation of the vesicles by reference to the alleged constitution of 2 to 8 lipid bilayers is sufficient to complete the disclosure of the invention.

Assuming, as argued by the Respondent that by means of optic microscopy it is not possible to distinguish between PLV's and MLV's but only to sort out ULV's (unilamellar vesicles) from the PLV/MLV-mixture and assuming in favour to the Respondent that the patent in suit by reference to electron micrographs discloses means which make it possible to plausibly confirm that PLV's having 2 to 8 lipid bilayers can be produced according to the method as set out in the description and according to the worked examples, the only available technical information which would provide proof on this are the electron microscope photos of document (23). Denying in general the validity of electron micrographs in the present case would immediately result in a failure of the patent in suit under Article 83 EPC (100(b)).

3.6 Photos A and B of document (23) show vesicles produced by a repetition of example 12 of the patent in suit. Instead of helping to solve the above mentioned

contradiction, these photos cause further confusion since in contrast to what is indicated in table 11 of example 12, particularly on page 13, line 32 and line 35, paucilamellar vesicles are produced by using surfactants which are described as not working in accordance with the invention.

The Respondent's argumentation that example 12 of the patent in suit should be only regarded as a basis for experiments which are not intended to allow a final conclusion as to whether or not the invention as such is reproducible cannot remove the confusion the skilled person is confronted with when repeating this example.

3.7 Moreover, photo C of document (23) shows that a repetition of example 1 of the patent in suit only results in the production of unilamellar vesicles. Thus apart from lack of proof of the presence of 2 to 8 bilayers as required by the invention and claimed in claim 4, on the basis of this evidence it is clear that the invention in general regarding the product to be obtained, and not only the necessary distinction between multilamellar and paucilamellar vesicles, is insufficiently disclosed for a person skilled in the art.

3.8 The Board notes that the Respondent did not contest the individual test reports regarding the experimental work carried out by the Appellant in order to repeat example 12 (partially) and example 1 of the patent in suit, but only criticised in sweeping statements the quality and relevance of the electron microscope photos with reference to the Weinert declaration of document (20).

3.8.1 In the absence of any substantial counter-evidence, particularly in the absence of electron microscope photos allowing the conclusion that the technical information derived from the photos of document (23) are based on artefacts and an unfair selection of photos or that the photos of document (23) from a statistical point of view are unacceptable and of bad quality, there is no room for the Respondent's argument that the burden of proof for further experimental work refuting the criticism of document (23) rests on the Appellant.

The declaration of the Respondent's expert in document (20) does not change this situation since it clearly says: *"While it is possible to determine the number of lipid bilayers in a particular liposome using electron microscopy, unless the proper techniques are followed one may obtain spurious and even meaningless results"* but also does not contain any specific evidence against the experimental work on which document (23) is based.

3.9 Finally, it is to be noted that, even accepting the situation that the Respondent as proprietor of the patent in suit is a small company in comparison with the Appellant's so-called big company supported by a large research department, the Board is not convinced

that the Respondent in any case was unable to have electron microscope photos made by a foreign institute as done by the Appellant for allegedly 3000 [Swiss] francs per photo.

3.10 Taking into account all the facts and evidence discussed above, the Board is convinced that the alleged invention regarding paucilamellar lipid vesicles consisting of 2-8 lipid bilayers as set out in the description of the patent in suit and reflected by the corresponding features of claim 4 cannot be reproduced by the skilled person, and therefore the Board can only conclude that the arguments put forward by the Appellant under Article 100(b) EPC convincingly demonstrate that the patent in suit does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

3.11 Since the patent in suit as a whole by failure to disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art does not meet the requirements of one of the Articles of the EPC, relating to patentability there is no need to discuss the Respondents auxiliary request also based on the alleged invention.

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 P. A. M. Lançon