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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0004/98 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 October 2001 correcting the
Decision of 9 August 2001

Appellant: (Opponent)
Inex Pharmaceuticals Corporation
1779 West 75th Avenue
Vancouver
B.C. V6P 6P2 (CA)

Representative:
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Respondent: (Proprietor of the patent)
SEQUUS PHARMACEUTICALS, INC.
(a Delaware Corporation)
960 Hamilton Court
Menlo Park
CA 94025 (US)

Representative:
Hallybone, Huw George
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43 Bloomsbury Square
London, WC1A 2RA (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 14 October 1997 concerning maintenance of European patent No. 0 496 813 in amended form.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. F. E. Rampold
C. Rennie-Smith

In application of Rule 89 EPC the decision of 9 August 2001 is hereby corrected as follows:

In point 13.1 of the Reasons, the second and third sentences of the second paragraph are deleted.

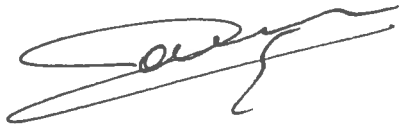
Reason:

The said sentences were erroneously transcribed from a draft to the final text of the decision as sent to the parties. An error of transcription has thus occurred within Rule 89 EPC requiring this correcting decision.

The Registrar:

A. Townend

The Chairman:



P. A. M. Lançon

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D E C I S I O N
of 9 August 2001

Case Number: T 0004/98 - 3.3.2

Application Number: 90916409.7

Publication Number: 0496813

IPC: A61K 9/127

Language of the proceedings: EN

Title of invention:
LIPOSOME MICRORESERVOIR COMPOSITION AND METHOD

Patentee:
SEQUUS PHARMACEUTICALS, INC. (a Delaware Corporation)

Opponent:
Inex Pharmaceuticals Corporation

Headword:
Liposome Compositions/SEQUUS

Relevant legal provisions:
EPC Art. 52(4), 54, 56, 83, 84, 106, 114(2), 123(2),(3)
EPC R. 57a, 58(4), 67, 71a

Keyword:
"Second medical use (no): no indication of a therapeutic application within the meaning of Article 52(4)"
"Non-therapeutic process for the preparation of a liposome-based formulation"
"Novelty (yes): process features not disclosed in the state of the art"
"Inventive step (no): alternative process for preparing liposome compositions obviously derivable from the state of the art"
"Procedural violations (no): no reimbursement of appeal fee"

Decisions cited:
G 0005/83, G 0002/88, T 0075/91

Headnote:

1. In accordance with the principles in G 5/83 and subsequent case law, the concept of second or further medical use can only be applied to claims to the use of substances or compositions (here, liposome compositions) for the preparation of a medicament intended for use in a method referred to in Article 52(4) EPC. (See Reasons, paragraph 8.1)

2. The concept of "therapy" or "therapeutic application" includes treatment of a particular illness or disease with a specified chemical substance or composition in a specified human or animal subject in need of such treatment. In the absence of the identification of at least (i) the illness or disease to be treated or the ailment to be cured or (ii) the nature of the therapeutic compound used for treating or curing the disease or (iii) the subject to be treated, a mere process feature cannot be construed as specifying a particular method of treatment or therapeutic application within the meaning of Article 52 (4) EPC. (See Reasons, paragraphs 8.1 and 8.2)

3. Unless a proven substantial Procedural violation relating to one or more issues in the first instance proceedings (here, violations alleged in relation to two issues, neither established) is so serious that the case must be remitted to the first instance with the effect that the whole decision under appeal is overruled, reimbursement of the appeal fee would not be equitable under rule 67 EPC if the appellant had no choice but tu appeal on other issues unaffected by an procedural irregularity (here, seven such issues). thus giving the appellant a "fee-free" appeal on such issues.(See Reasons, paragraph 13.3)

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Case Number: T 0004/98 - 3.3.2

D E C I S I O N
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 14 October 1997 concerning maintenance of European patent No. 0 496 813 in amended form.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. F. E. Rampold
C. Rennie-Smith

Summary of Facts and Submissions

I. The respondent is proprietor of European patent No. 0 496 813 which was granted with 25 claims on the basis of European patent application No. 90 916 409.7 which claimed priority from US application No. 425 224 dated 20 October 1989.

II. The appellant filed notice of opposition requesting revocation in full of the European patent pursuant to Article 100(a) EPC on the grounds of lack of novelty and inventive step and pursuant to Article 100(b) EPC on the ground of insufficiency of disclosure. Of the numerous documents cited during the first-instance opposition and subsequent appeal proceedings against the patentability of the claimed subject-matter in the patent in suit, the following remain relevant to the present decision:

(1): EP-A-0 354 85

(2): WO-A-88 049 24

(3): WO-A-90 043 84

(10): Ostro *et al*, Am. J. Hosp. Pharm. (1989),46, 1576

(11): Lopez-Bernstein *et al*, J. Infect. Dis. (1983), 147(5), 939

(12): Mayer *et al*, Cancer Research, (1989),49,5922

(13): Klibanov *et al*, FEBS, (1990), 268(1), 235

III. During prosecution of the case before the opposition division, amended sets of claims were filed by the proprietor, by way of first and second auxiliary

requests. In an interlocutory decision posted on 14 October 1997, the opposition division refused both the proprietor's main request that the opposition be rejected and its first auxiliary request that the patent be maintained on the basis of amended claims filed during the oral proceedings before it, but decided to maintain the patent in amended form on the basis of the claims in the secondary auxiliary request filed on 18 August 1997 with claim 20 further amended at the oral proceedings. Claim 1 is worded as follows:

"Use of a liposome composition effective to extend to at least 24 hours, the period of effective activity of a therapeutic compound which can be administered intravenously in a therapeutically effective amount and which is cleared in free form in the blood stream with a half-life of less than about 4 hours, comprising liposomes (I) composed of vesicle-forming lipids and between 1-20 mole percent of a vesicle-forming lipid derivatised with a polyethyleneglycol, and (ii) having a selected mean particle diameter in the size range between about 0.1 to 0.4 μm (microns), and the compound in liposome-entrapped form, for the preparation of a composition ***for intravenous administration at a dose of the composition which contains an amount of the liposome-entrapped compound which is at least three times such therapeutically effective amount.***"

The last feature in claim 1, which is highlighted in bold italic letters, is also present in independent claims 4 and 10. Hereinafter, for the purpose of discussion, this feature is simply referred to as the "three times dosage" feature; independent claims 17 and 20 recite a corresponding feature where "intravenous" is replaced by "subcutaneous" and "three times" by "ten times", hereinafter referred to as the "ten times dosage" feature.

IV. In its reasons for the decision the opposition division, in exercising its discretion according to Rule 71a and Article 114(2) EPC, concluded that the amended claims were filed in time. It found that the change of category from the original "composition" claims to claims in the "second or further medical use format" was also admissible pursuant to Rule 57a EPC and considered the amended claims to be acceptable under the terms of Article 123(2) and (3) EPC. Similarly, it did not accept the opponent's submissions as to insufficiency of disclosure of the invention under Article 100(b) EPC.

As to novelty, the opposition division considered that the "three times dosage" feature and as regards subcutaneous administration, the "ten times dosage" feature constituted specified new therapeutic applications for the liposome compositions defined in the claims. Concerning inventive step, the opposition division determined the problem as that of providing a drug formulation for administering a therapeutic compound for an extended period in the bloodstream. Although the opposition division concluded that the claim to priority was not valid, it found that the proposed solution to the problem, ie the use of liposomes with the claimed composition and size, was not obvious to a skilled person in the light of the state of the art cited in the opposition proceedings (documents 1 to 9).

V. An appeal against the decision of the opposition division was lodged by the opponent (appellant). The statement of grounds of appeal was accompanied, *inter alia*, by documents (10) to (18). Further submissions were filed by the appellant on 18 May 2001 enclosing documents (19) to (27). The respondent filed observations in reply and submitted amended sets of claims by way of third and fourth auxiliary requests.

VI. In its introductory remarks at the oral proceedings, held on 9 August 2001, the board expressed its opinion that the claims in the second auxiliary request upheld by the opposition division (see paragraph III above) differed only linguistically from those in the third and fourth auxiliary requests and that in this respect the wording of the claims in the fourth auxiliary request appeared to be preferable. The respondent then withdrew all but the fourth auxiliary request. Claim 1 of this request corresponds to claim 1 in the second auxiliary request (see paragraph III above), the end portion of the claim differing as follows:

"Use of a liposome composition <.....> in liposome-entrapped form, ***directly*** for the preparation of a ***medicament*** for intravenous administration at a dose of the said liposome composition which contains an amount of the liposome-entrapped compound which is at least three times such therapeutically effective amount."

Independent claims 4, 10, 17 and 20 in the fourth auxiliary request were similarly amended.

VII. The principal grounds relied on by the appellant in its written submissions and during the hearing before the board were the following:

In the circumstances of the present case, the change of category from "composition claims" to claims in the "second or further medical use format" was inappropriate, since it was inherently incapable of solving the patentability problems faced by the respondent. The second auxiliary request which was filed only one month in advance of the oral proceedings

and further amended during the oral proceedings should therefore have been rejected by the opposition division as inadmissible and out of time in view of the provisions of Article 114(2) and Rules 71a and 57a EPC.

The opposition division was in error in its finding that the amended claims met the requirements of Article 123(2) and (3) EPC. The mere fact that the amended claims were drafted in the "second or further medical use format" in accordance with decision G 5/83 did not, contrary to the opposition division's opinion, *eo ipso* allow the conclusion to be drawn that such claims would not contravene Article 123(2) and (3) EPC. The opposition division was likewise wrong to conclude that the requirement of sufficient disclosure was met. On the contrary, the disclosure in the specification was insufficient to enable the skilled person to perform the claimed invention over the whole area claimed without the burden of an undue amount of experimentation and without needing inventive skill, since the examples in the patent in suit related only to release of one single class of therapeutic compounds, ie peptides or proteins, from the particular liposome compositions specified in the claims. Moreover, the "three (or ten) times dosage" feature lacked clarity contrary to Article 84 EPC and introduced obscurity into the claims which lead to further objections of insufficiency of disclosure under Article 83 EPC.

The last part of claim 1, ie the "three times dosage" feature, had the sole effect of adjectively qualifying the composition which is being prepared, merely meaning that the composition must be suitable for intravenous administration in the stated way. Since the opposition division held in its decision that such a feature would be inappropriate to distinguish the claimed composition of claim 1 as granted from the disclosure of citation

(1), there was no reason to conclude that present claim 1 should be any different in this regard. Apart from the fact that citation (1) already described the making of relevant compositions, the feature in question did not relate to a specified new therapeutic application and could therefore not be regarded as a distinguishing feature over (1) such as to confer novelty upon claim 1.

PEGylated liposomes (ie liposomes derivatised with a polyethylene glycol) of the type used in the patent in suit were described in (1). The advantages provided by PEGylated liposomes disclosed in (13) with their enhanced stability and longevity in the circulation would make them wholly obvious candidates to try in sustained drug release compositions for *in vivo* use. In the alternative, the claimed subject matter was the obvious result of replacing the particular liposomes with enhanced circulation time used in (2) by PEGylated liposomes having similar properties, as disclosed in (3) and (13).

In view of the alleged "abuses of procedure" by the opposition division not to give reasons in its written decision as to the objections to the second auxiliary request under Article 84 EPC and not to give the appellant sufficient time to consider the amended description submitted by the respondent, the request for reimbursement of the appeal fee in accordance with Rule 67 EPC was justified.

VIII. The respondent's arguments submitted in reply to the appeal statement and during the oral proceedings before the board, can be summarised as follows:

The independent claims maintained by the opposition division were claims of the second (further) medical indication type permitted in decision G 5/83. In the

present case the second medical indication was the novel mode of administration at an increased dosage level of the liposome-entrapped compound. Since this mode of administration of much larger, but less frequent doses of liposome-encapsulated drug was a further medical indication and had important practical and psychological advantages in therapy, the opposition division was correct to accept the claims of the second auxiliary request as admissible and filed in time in accordance with Rule 57a and Article 114(2) and Rule 71a EPC.

The only difference between the change of category considered as acceptable in decision G 2/88 (OJ EPO 1990, 93) and the present case was that the amended claims were drafted in the conventional "second or further medical use" format. There was, however, no reason to make a difference, in view of the provisions of Article 123(2) and (3) EPC, between this type of claims and claims directed to the second non-medical use. Moreover, the wording "use of a composition <.....> for the preparation of a medicament" in the context of a second medical use type claim would always be understood by a person skilled in the art as meaning "use directly for the preparation of the medicament", ie use in the medicament. It followed that the principles of decisions G 5/83 and G 2/88 were directly applicable to the amended claims.

The characterising features of the present "second medical use claims" were the mode of administration, namely the three-times dosage feature, on the one hand, and the use of PEGylated liposomes, on the other. Since none of the citations available in the proceedings disclosed the combination of these two characterising features, novelty of the claimed subject-matter in the patent in suit was beyond doubt.

The technical problem to be solved was the provision of improved sustained release intravenous and subcutaneous compositions that enable a larger systemic dose to be administered and be effective over an extended period without unacceptable toxicity. The proposed solution to this problem was not obviously derivable from any of the documents cited in the proceedings taken either in isolation or in combination with each other.

IX. The appellant requested that the decision under appeal be set aside and the patent be revoked and that the appeal fee be reimbursed.

The respondent requested that the appeal be dismissed and that the patent be maintained in amended form on the basis of the fourth auxiliary request filed on 25 November 1998 (now its only request).

Reasons for the Decision

1. The appeal is admissible.

2. The board considers the opposition division exercised its discretion under Article 114(2) and Rule 71a EPC correctly in allowing the respondent to file the second auxiliary request which subsequently formed the basis of its decision to maintain the patent in amended form. Although this request was filed late in the opposition proceedings - by a faxed letter on 18 August 1997, one month before the oral proceedings - it was a response to the objections raised during the written first instance opposition proceedings. The board also agrees with the opposition division that the amendment made to

claim 20 of that request at the oral proceedings was merely the correction of an obvious error - the other claims had been amended to a form directed to a second medical indication and, by an oversight on the part of the respondent, claim 20 had not been so amended.

3. The amendments to the claims effected during the opposition and subsequent opposition appeal proceedings can fairly be said to be occasioned by grounds for opposition specified in Article 100(a) EPC and to constitute a *bona fide* attempt on the part of the respondent to overcome the appellant's objections to lack of novelty and inventive step in the opposition and appeal statements. The proposed amendments to the granted patent are thus admissible under the terms of Rule 57a EPC.

4. The board also considers that documents (10) to (18) filed with the statement of the grounds of appeal and the documents (19) to (27) filed with the appellant's letter of 16 May 2001 should be admitted as evidence. As regards the earlier set of documents, these included some of clear relevance to both the issues as developed during the first instance oral proceedings and the reasons given for the decision under appeal. As regards the second set of documents, the appellant's assertion that these formed a response to the respondent's written arguments in the appeal appears *prima facie* correct. That said, those arguments were filed over two years previously, on 25 November 1998, and the board does not condone such lateness *per se*. However, in the circumstances of this case the respondent had nearly three months in which to consider and prepare arguments in reply to the late evidence. Coupled with the fact that the respondent to a large extent prompted such evidence by its own arguments, the board exercises its discretion in favour of the appellant.

5. In the board's judgment, all the features of claim 1 of the respondent's only request before the board can be found in the application for the patent as filed; and the scope of the claims has not been extended by the amendments made to the claims as granted. The change of category of the independent claims from product to use claims, ie from claims directed to a liposome composition *per se* to claims directed to the use of that liposome composition in the form typically intended to claim a second medical indication, represents a major limitation of the scope and is not *per se* contrary to Article 123 EPC. Accordingly the claims now under consideration meet the requirements of Article 123(2) and (3) EPC.

6. Although an objection under Article 84 EPC cannot in itself be a ground of opposition under Article 100 EPC, the Board accepts that such an objection can be raised during opposition or opposition appeal proceedings if amendments made in those proceedings emphasise a problem of clarity. In this case, as the respondent conceded during the oral proceedings, claim 1 was not well drafted (and the other independent claims shared the difficulties this caused). However, the claim was sufficiently clear that this issue was not crucial to an understanding of the other issues and, in view of the board's decision on the further matters referred to below, no final decision on this issue is necessary in this case.

7. While Article 83 EPC can form a ground of opposition (Article 100(b) EPC) and arguments were raised by the appellant as to the insufficiency of disclosure, these were closely related to the understanding of the exact meaning of the independent claims and thus to the question of clarity. Accordingly, for the reasons in the previous paragraph, the board also considers it unnecessary to give a final decision on this issue.

8. Independent claims 1, 4, 10, 17 and 20 are all drawn up in the conventional "second (further) medical use format". In spite of that particular form of the claims ("Swiss type claims"), the board has difficulties in accepting the opposition division's opinion and the respondent's written and oral assertions that these claims reflect in fact a second (further) medical use and that the "three times dosage" feature at the end of claims 1, 4 and 10, or the corresponding "ten times dosage" feature at the end of claims 17 and 20, constitutes a specified therapeutic application from which novelty for the claims can be derived in accordance with the principles of decision G 5/83 (OJ EPO, 1985, 64).

8.1 As generally understood, the concept of "therapy" or "therapeutic application" includes treatment of a particular illness or disease with a specified chemical substance or composition in a specified human or animal subject in need of such treatment. By comparison, the "three (or ten) times dosage" feature fails to provide any indication of at least (i) the illness or disease to be treated or the ailment to be cured, (ii) the nature of the therapeutic compound used for treating or curing the disease and (iii) the subject to be treated. In the absence of the identification of any of these parameters (i) to (iii), the "three times (or ten times) dosage" feature actually relates to the intravenous (or subcutaneous) administration of an unspecified therapeutic compound in liposome-entrapped form in an amount, which is at least three (or ten) times the therapeutically effective amount of said unspecified therapeutic compound, for the treatment of an unspecified illness or disease in an unidentified patient or other human or animal subject. This being the case, the board fails to see how this feature could be construed as specifying a particular method of treatment or a therapeutic application within the

meaning of Article 52(4) EPC. In accordance with the principles set out in decision G 5/83 (see especially Reasons, end of point 21) and the substantial body of case law which has been developed by the boards of appeal in this respect (see eg "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition, 1998, I. C. 6.2, pp 98-103), the concept of "second (further) medical use" can only be applied to claims to the use of substances or compositions (here the liposome compositions defined in the claims) for the preparation of a medicament intended for use in a method referred to in Article 52(4) EPC. For the reasons given above, this is clearly not the case here.

8.2 In view of the foregoing observations, the subject-matter of the above-mentioned independent claims is accordingly to be understood as relating to a non-therapeutic technical activity (process). The "three times (or ten times) dosage" feature" can then only be construed as one of the process features characterising the claimed process.

8.3 More specifically, the subject-matter of claim 1 essentially relates to a process for the preparation of a liposome-based formulation suitable for intravenous administration of a therapeutic compound, which is cleared in free form from the bloodstream with a half-life of less than 4 hours, so as to provide controlled sustained release of the liposome-entrapped drug in a therapeutically effective amount over an extended period of time in the bloodstream, ie at least 24 hours. This process involves the steps of (i) loading (encapsulating) the desired drug in an amount, which is at least three times its therapeutically effective amount, into liposomes composed of vesicle-forming lipids and between 1-20 mole percent of a vesicle-forming lipid derivatised with a polyethyleneglycol (hereinafter referred to as "PEG-liposomes" or

"PEGylated liposomes"), and having a selected mean particle diameter in the size range between about 0.1 to 0.4 μm (microns), followed by (ii) converting the liposome composition thereby obtained into a galenic formulation suitable for intravenous administration.

Novelty and inventive step have therefore to be assessed on the basis of the interpretation of the claims described above.

9. The patent in suit claims priority from a national application of 20 October 1989 in the United States (Serial No. 42 52 24) and has an accorded filing date of 19 October 1990. In the board's judgment, the opposition division was correct in its finding in the impugned decision that the respondent's claim to priority is invalid. Since the respondent did not appeal against the refusal of the claimed priority date by the opposition division, the board sees no reason to depart from it. The effective date for the assessment of novelty and inventive step is therefore the European filing date.

10. The only prior art cited by the appellant against the novelty of the claimed subject-matter in the patent in suit is the disclosure of citation (1). Although the only therapeutic compound in liposome-entrapped form which is specifically disclosed in (1), *viz.* haemoglobin, is neither explicitly nor implicitly described in the cited document as being cleared in free form from the blood stream with a half-life of less than 4 hours, on page 11 of the impugned decision reference is made to the short clearance period of haemoglobin of less than 4 hours being confirmed by the experts present for both parties at the oral proceedings before the opposition division. This confirmation in first-instance proceedings was contested by the respondent during oral proceedings

before the board. The board considers it nevertheless unnecessary to go into further detail on this issue for the purpose of assessing novelty, since novelty can in any event be derived from other features of the claims.

10.1 Thus, neither is the functional feature in present claim 1 requiring that the liposome composition be "effective to extend to at least 24 hours the period of effective activity of the therapeutic compound" directly and unambiguously derivable from the disclosure in (1), nor is the feature requiring that the liposome composition "contain an amount of the liposome-entrapped therapeutic compound which is at least three times the therapeutically effective amount", even when account is taken of matter which is implicit to a person skilled in the art in addition to what has been expressly mentioned in (1).

10.2 Since each of the other independent claims 4 (see "effective at least 48 hours", "at least three times the therapeutically effective amount"), 10 (see "at least three times the therapeutically effective amount"), 17 (see "effective at least one week", "at least ten times the therapeutically effective amount"), and 20 (see "at least ten times the therapeutically effective amount") contains at least one feature corresponding to those mentioned above for claim 1 and, moreover, use claims 17 and 20 refer to a medicament suitable for subcutaneous administration, as opposed to the liposome composition suitable for intravenous administration disclosed in citation (1), the novelty of all further independent claims 4, 10, 17 and 20 can likewise be acknowledged.

10.3 The novelty of the "composition claims" 23 to 25 was never attacked in the opposition and subsequent appeal proceedings. Since none of the citations available to the board from the proceedings before the EPO calls

into question the novelty of claims 23 to 25, even if they are extremely broad, no further consideration of this appears to be necessary or appropriate.

11. The closest state of the art, which is citation (2), discloses liposome compositions with enhanced circulation time in the bloodstream for the preparation of a liposome-based formulation suitable for intravenous administration of a variety of drugs and other pharmacologically active agents so as to provide controlled sustained release of the liposome-entrapped drug at physiologically effective levels for up to 1 day (24 hours) or more (see (2), page 22, lines 25 to 27) and up to 48 hours (see (2), page 23, lines 17 to 20). The therapeutic compounds used in (2)(see especially page 23, line 21, to page 25, line 4) are to a large extent the same as those referred to in the patent specification (see especially page 9, lines 21 to 34, and the paragraph bridging pages 9 and 10) as having in free form a blood half-life of 4 hours or less.

The process for the preparation of the liposome-based formulation in (2) involves similarly the steps of

(i) loading (encapsulating) the desired drug, in an amount which provides a suitable drug dosage over the expected delivery time, into liposomes composed of conventional vesicle-forming lipids and between 5-20 mole percent of a vesicle-forming lipid derivatised with a glycolipid component selected from ganglioside GM_1 (hereinafter referred to as GM_1-liposomes), hydrogenated phosphatidylinositol, and sulfatide, ie sulfate esters of lactocerebrocidesmonogalactosyl, and having a selected mean particle diameter in the size range between about 0.07 and 0.4 μm (see (2),see page 25, lines 5 to 8 and the paragraph bridging pages 8 and 9), followed by

(ii) converting the liposome composition thereby obtained into a galenic formulation (eg a suspension) suitable for intravenous administration.

11.1 Consequently, starting from the above disclosure of citation (2) as representing the closest state of the art, the problem to which the invention set out in claim 1 seeks a solution may be seen as that of providing an alternative process for the preparation of a liposome-based formulation suitable for the intravenous administration of a therapeutic agent.

11.2 Comparison of the process according to claim 1, as outlined in point 8.3 *supra*, with the process disclosed in (2) and referred to in point 11 above establishes that both processes are substantially identical with the sole exception that in the claimed process "PEG-liposomes" are substituted for "GM_1-liposomes" used in (2) for encapsulating the therapeutic compound. On the basis of the disclosure of the invention, the results given in Examples 6 to 16 and in the corresponding Figures 7 to 18 of the patent specification and, moreover, in the absence of any evidence to the contrary, the board is satisfied that the proposed substitution of "PEG-liposomes" for "GM_1-liposomes" plausibly solves the problem. This much was not contested by the appellant.

12. At the filing date of the contested patent it was already known that the properties of "GM_1-liposomes" on the one hand, and "PEG-liposomes", on the other, are substantially identical in that both types of liposomes show a very low rate of uptake by the reticuloendothelial system (RES). As a consequence of this, both types of liposomes have two important benefits, as compared to conventional liposomes, when used as drug delivery systems. One is a significant prolongation in the blood circulation half-life of

"GM_1-liposomes" and "PEG-liposomes", which increases the pharmacokinetic benefits of controlled slow sustained release of the drug from the liposomes into the bloodstream over an extended period of time, and also provides greater opportunity for tissue targeting where the liver, spleen, and lungs are not involved. The second benefit is the decreased liposome loading of the RES (see (2): page 8, lines 10 to 18; page 11, lines 3 to 24; page 22, line 17, to page 25, line 11; *versus* (3): page, 2, lines 9 to 12; page 4, line 13 from the end, to page 5, end of the first full paragraph; and (13): abstract at the beginning of page 235; page 235, Introduction; pages 236 to 237, Results and Discussion.)

12.1 The skilled person seeking in the state of the art a solution to the problem posed would have carefully studied the disclosure of citation (13). In doing so, he would certainly have learned with great interest that the circulation time of "PEG-liposomes" in the bloodstream is even greater than that of "GM_1-liposomes" and that "PEG-liposomes" are *expressis verbis* suggested in (13) as a particularly favourable alternative to "GM_1-liposomes" for the sustained drug release and the targeted drug delivery by liposomes (see page 235, abstract, lines 4 to 6 and Figure 2).

12.2 From the disclosure in the penultimate paragraph in the left-hand column on page 236 and the data set forth in Figure 1 of (13) it is moreover readily apparent that "PEGylation" of liposomes does not increase the leakage rate of the liposomes' contents, eg the encapsulated drugs, and that, with respect to the release of their contents due to mechanical instability, "PEG-liposomes" behave in a manner similar to conventional "non-PEGylated" liposomes and "GM_1-liposomes". Thus, the skilled person would have learned from this teaching in

(13) that "PEG-liposomes" do not have any different or disadvantageous properties that distinguish them from conventional liposomes or "GM_1-liposomes" as being unsuitable for sustained drug release.

12.3 In the absence of the identification of at least the kind of drug or pharmacologically active agent used and the disease to be treated, the insertion in claim 1 of the feature requiring at least three times the therapeutically effective amount of the therapeutic compound to be present in the liposome formulation appears to be a limitation to a more or less arbitrarily chosen amount of the therapeutic compound encapsulated in the liposome composition, which has no particularly recognisable technical significance or relevance.

The teaching of citation (2) clearly expresses what appears to be self-evident to a person skilled in the art namely that, for appropriate and useful sustained drug-release via the bloodstream, the liposome composition must be administered intravenously in an amount sufficient to provide a suitable drug dosage over the expected delivery time (see page 25, lines 5 to 8). Thereafter, determination of the amount required for a particular drug encapsulated in a liposome composition according to the claimed invention so as to avoid release of toxic or intolerable doses and to ensure a suitable even therapeutic dosage level over the expected or desired delivery period would be a matter of mere routine experimentation for the skilled practitioner and a typical activity for a pharmacologist exercising his professional skills in drug design.

12.4 In case there was nevertheless any question regarding the basic capability and usefulness of liposomes for encapsulating therapeutic compounds at much higher

doses than the therapeutically effective amount, this was likewise already known in the state of the art. Thus, as examples only, citation (10) discloses in the paragraph bridging pages 1583 and 1584 the administration of a dose of amphotericin B in liposome-encapsulated form seven times the maximum tolerated dose for the free drug. Other similar references include citation (11) which states half-way down in the left-hand column on page 944 that the maximal tolerated dose for liposomal amphotericin B was not achieved even if 12 times the maximal tolerated dose of the free drug was encapsulated in the liposomes. Furthermore citation (12) shows in Table 3 on page 5925 that, when a seven fold increased amount of the anticancer drug doxorubicin was encapsulated in liposomes, the toxicity was not greater than that of the free drug. As has already been mentioned in point 12.2 above, "PEG-liposomes" do not differ from conventional liposomes or "GM_1-liposomes", as far as their capability of drug encapsulation, their leakage rate and mechanical stability are concerned.

12.5 To summarise, the skilled person, knowing from (13) the substantially extended lifetime of "PEG-liposomes" in the bloodstream, their low leakage rate and their mechanical stability and from (2) the direct relationship between the lifetime of liposomes in the bloodstream and the sustained release of the liposome-entrapped drug at physiologically effective levels, would reasonably expect the problem posed to be soluble by simply substituting "PEG-liposomes" for "GM_1-liposomes" in the known liposome compositions, without changing any of the other parameters such as, for example, the selected mean particle diameter of the

liposomes. It was then only necessary to confirm experimentally that the highly probable result was in fact obtained. The necessity of experimentally confirming a reasonably expected result does not render an invention non-obvious.

12.6 It follows from the foregoing that the subject-matter of claim 1 does not involve an inventive step contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC. Since a decision can only be taken on each request as a whole, there is no need to look into the patentability of the other claims.

13. The appellant sought reimbursement of the appeal fee on the basis of either or both of two alleged substantial procedural violations (referred to in the grounds of appeal as "abuses of procedure").

13.1 First, the appellant claimed it was not given time to consider the amended description submitted by the respondent at the end of the first instance oral proceedings. It says, as appears to be common ground, that those oral proceedings continued late into the evening, although the written decision records that both parties wished to finish the case at those oral proceedings (page 20, paragraph 11), and that the opposition division was wrong to say "... the opponent is neither obliged to comment nor is he obliged to agree or disagree with the description". The appellant observes that this comment conceals the fact that the description may affect subsequent interpretation of the claims by the board or a national court.

However, these arguments overlook the procedure which in practice means that the appellant was not disadvantaged. When the opposition division, as in this case, maintains a patent in amended form, it waits until the interlocutory decision becomes final before

writing to the patent proprietor seeking his formal approval to the amendments (Rule 58(4) EPC) for the simple reason that during the period referred to in Article 108 EPC the proprietor or opponent may appeal (Article 106(3)EPC). Such an interlocutory decision is delivered in all cases where a European patent is maintained in amended form, even if the opponent has approved the text communicated by the opposition division or has not commented on it (see Part D, Chapter VI, 6.2.2 of the Guidelines for Examination in the European Patent Office). If the opponent appeals, his disapproval of the first instance decision is self-evident and any comments from him on the amended description would be academic. Further, an appeal by either party has the effect of suspending the decision under appeal (Article 106(1) EPC). Moreover, for the very reason advanced by the appellant, an opponent is unlikely to indicate his agreement to an amended description since this could be held against him in subsequent proceedings. Accordingly, the board cannot see that any procedural violation took place in this respect.

13.2 Second, the appellant claims it was an "abuse of procedure" for the opposition division not to give reasons in its written decision on the objections to the second auxiliary request under Article 84 raised by the appellant during the oral proceedings. That such objections were argued is clear from paragraphs 14 and 15 of the minutes of the oral proceedings which also record that the opposition division did not accept them. The board, as appears from paragraph 6 above, does not necessarily share that view. However, since Article 84 EPC cannot itself be a ground for opposition, the opposition division may well have considered such reference in the minutes to the fact Article 84 EPC was mentioned and a reasoned treatment in its written decision of each ground of opposition

argued before it sufficient. The board is also satisfied that the decision and minutes give an adequate account of both the arguments raised by the parties and the line of reasoning adopted by the opposition division in arriving at its decision. Whether those reasons were convincing - and, as to the Article 84 EPC arguments, no reasons would have been likely to convince the appellant - is another matter which has nothing to do with a substantial procedural violation (see T 75/91 of 11 January 1993, not published in OJ EPO, Reasons, paragraph 7).

13.3 Accordingly, the board finds neither of the alleged substantial procedural violations to be established. Further, even if either or both such violations were proven to the board's satisfaction, reimbursement of the appeal fee would not appear to be equitable (as Rule 67 EPC requires) since the appellant would in any event have had to appeal in order to obtain a reversal of the first instance decision on the other issues, no fewer than seven in number, the subject of this appeal (see the Notice of Appeal and the Grounds of Appeal, pages 2 to 4, paragraphs D.1 to D.7), none of which is alleged to be the subject of any procedural irregularity. While cases could be imagined in which a procedural violation in relation to just one issue was so serious that reimbursement would be appropriate, in such cases the board would usually remit the case to the first instance with the effect that the whole decision under appeal would be overruled. In cases such as the present it would not be equitable for the appellant to have a "fee-free" appeal on issues dealt with quite properly at first instance and on which the appellant had no choice but to appeal.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The European patent No. 0 496 813 is revoked.

3. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

U. Bultmann P. A. M. Lançon