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Datasheet for the decision of 7 September 2021

Case Number: T 1302/19 - 3.3.07

Application Number: 05745505.7

Publication Number: 1746976

IPC: A61K9/127, A61K31/4745

Language of the proceedings: EN

Title of invention:
LIPOSOMES USEFUL FOR DRUG DELIVERY

Patent Proprietor:
Ipsen Biopharm Ltd.

Opponent:
Teva Pharmaceuticals Industries Ltd

Headword:
Liposomes /IPSEN

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 100(c), 100(a), 56

Keyword:
Late-filed evidence
Amendments - intermediate generalisation - allowable (yes)
Inventive step - (yes)

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Case Number: T 1302/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 September 2021

Appellant: (Opponent)	Teva Pharmaceuticals Industries Ltd 5 Basel St. 49131 Petach Tikva (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Patent Proprietor)	Ipsen Biopharm Ltd. Ash Road Wrexham Industrial Estate Wrexham LL13 9UF (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 March 2019 rejecting the opposition filed against European patent No. 1746976 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 1 746 976 (hereinafter "the patent") was granted on the basis of 6 claims. Claim 1 of the patent read as follows:

"A composition comprising a liposome in a medium, wherein the liposome comprises 1,2-distearoyl-SN-phosphatidylcholine, cholesterol and N-(omega-methoxy-poly(ethylene glycol)oxycarbonyl)-1,2-distearoylphosphatidyl ethanolamine in the molar ratio 3:2:0.015, and entrapped inside the liposome are irinotecan and sucrose octasulfate."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked an inventive step and it extended beyond the content of the application as filed.

III. The opposition division took the decision to reject the opposition.

The decision cited among others the following document:

D1: Chou et al., "Effect of composition on the stability of liposomal irinotecan prepared by a pH gradient method", J. Bioscience and Bioengineering, vol. 95(4), pp. 405-408, 2003

IV. In particular, the opposition division decided that:

(a) The technical features extracted from example 11 and incorporated into claim 1 were not so closely associated with other features of the examples as to determine the effect of the claimed invention.

Thus the ground of Article 100(c) EPC did not prejudice the maintenance of the patent as granted.

(b) D1 represented the closest prior art. The distinguishing feature of the claimed invention was the presence of sucrose octasulfate entrapped inside the liposome. The objective technical problem was the provision of liposomes with improved retention of irinotecan. The claimed solution was not obvious in light of the prior art. Hence the ground of lack of inventive step under Article 100(a) EPC did not prejudice the maintenance of the patent as granted.

V. The opponent (appellant) lodged an appeal against the decision of the opposition division.

With its statement setting out the grounds of appeal, the appellant submitted the following documents:

D7: Sharma, A. et al., International Journal of Pharmaceutics 154 (1997) pp.123-140
D8: Lasic, D. and Papahadjopoulos,D., eds. Medical Applications of Liposomes, Elsevier, Amsterdam, 1998
D9: Drummond, D.C. et al., Clin Cancer Res 2005; 11(9), 2005

VI. With its reply to the appeal, the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1-3 filed on 27 March 2018.

VII. The Board set out its preliminary opinion in an communication under Article 15(1) RPBA dated 14 May 2021.

VIII. The respondent filed further submissions by letters dated 30 July 2021, 16 August 2021 and 5 September 2021.

IX. On 7 September 2021, oral proceedings were held before the Board by videoconference. The appellant did not attend the oral proceedings, as announced in its letter dated 6 August 2021.

X. The appellant requests that the decision under appeal be set aside and that the patent be revoked in its entirety.

XI. The respondent requests that the appeal be dismissed, or, alternatively, that the case be remitted to the opposition division and maintained on the basis of one of auxiliary requests 1-3 filed on 27 March 2018.

The respondent also requests that documents D7-D9 not be admitted into the proceedings.

XII. The appellant's arguments can be summarised as follows:

(a) Added subject-matter

A basis for claim 1 of the main request could not be found in paragraph [0116] and in example 11 of the application as filed. Firstly, claim 1 only recited the structural features of the liposomes described in paragraph [0116], and not the corresponding functional features such as prolonged drug release or toxicity. Secondly, there was no support for the feature in claim 1 that the sucrose octasulfate (SOS) was "entrapped inside the liposome". Thirdly, claim 1 failed to recite the molecular weight of the N-(omega-methoxy-poly(ethylene glycol) oxycarbonyl)-1,2-

distearoylphosphatidyl ethanolamine (PEG-DSPE) used in Example 11.

Furthermore, claim 1 resulted from the extraction of one feature (the composition of the lipid matrix) from the combination of features of example 11 (including liposome size, drug loading, further compositional features such as the presence of triethylammonium (TEA), or the manufacturing method). This intermediate generalisation was not permissible, because all the structural and functional features of the liposomes of example 11 (including the composition of the lipid matrix) were inextricably linked with one another and together defined the properties of the liposome (see D7, section 3, and D8).

Lastly, there was no disclosure of the claim feature that the composition comprised a "medium" in either paragraph [0116] or example 11.

(b) Inventive step

D1 could be considered as the closest prior art document. The distinguishing feature was the presence of SOS entrapped inside the liposome. There was no demonstration that this difference resulted in any improved effects over the disclosure of D1. The technical problem was the provision of an alternative liposomal irinotecan formulation.

D1 motivated the skilled person to include sulfated oligosaccharides in the liposomal formulations with the aim of reducing leakage. Whilst D1 exemplified dextran sulfate as the sulfated oligosaccharide, it would be a routine matter to replace dextran sulfate with other known sulfated oligosaccharides such as SOS in the

reasonable expectation of solving the above identified technical problem. Thus the subject-matter of claim 1 of the main request lacked an inventive step.

Furthermore, the patent was not entitled to benefit from the priority date, and the subject-matter of claim 1 of the main request also lacked an inventive step over D9.

XIII. The respondent's arguments can be summarised as follows:

(a) Admittance of D7-D9 into the proceedings

D7-D9, filed by the appellant with its statement of grounds of appeal, should not be admitted into the proceedings for the following reasons. These documents had not been filed in response to any change in the subject-matter of the proceedings. The appellant has provided no explanation or justification for their late filing. In addition, D9 was filed to support a totally new inventive step attack, and was published after the patent’s priority date. If D9 were admitted, the validity of the priority claim would have to be examined for the first time on appeal.

(b) Added subject-matter

Claim 1 of the main request found basis in the application as filed according to either Derivation A or Derivation B.

According to Derivation A, claim 1 resulted from the allowable combination of the features:
- "A composition comprising a liposome in a medium", based on paragraphs [0003], [0009],

- "the liposome comprises 1,2-distearoyl-SN-phosphatidylcholine" [DSPC], "cholesterol, and N-(omega-methoxy-poly(ethylene glycol)oxycarbonyl)-1,2-distearoylphosphatidylethanolamine" [PEG-DSPE] "in the molar ratio 3:2:0.015", based on paragraph [0099] and [0101] together with the examples, the majority of which used the above specific lipid blend and molar ratio, and
- "entrapped inside the liposomes are irinotecan and sucrose octasulfate", based on paragraphs [0009], [0010] and [0074], and particularly disclosed in combination in the final sentence of paragraph [0116].

Following Derivation B, claim 1 found basis in example 11, considered together with the other examples, and the remainder of the application as filed taken as a whole. No unallowable intermediate generalisation was involved. In particular, in view of paragraphs [0099], [0100] and [0102] or claims 94-97, 99 and 100 of the application as filed, the molecular weight of the PEG-DSPE used in example 11 was not an essential feature and was not inextricably linked with the other features of Example 11 recited in claim 1. Furthermore, example 11 disclosed a process leading to liposomes having various different particular sizes, and drug/lipid ratios. In light of paragraph [0113], the liposomes produced in example 11 did not inevitably contain triethylammonium (TEA). Lastly, the presence of entrapped aqueous material in the liposomes was as implicit in example 11 as it was in claim 1 of the main request.

Hence the main request did not contain any added subject-matter.

(c) Inventive step

D1 could not constitute the most promising and appropriate starting point for the assessment of inventive step, because D1 omitted important technical information which was essential for its disclosure to be complete.

Even if D1 was taken as closest prior art, the subject-matter of claim 1 differed therefrom in that it required the liposomes to contain SOS, and in that it required the presence of the lipids DSPC, cholesterol, and PEG-DSPE in a 3:2:0.015 molar ratio.

The objective technical problem was the provision of an improved liposomal composition of irinotecan which showed improved stability with respect to drug retention, longer half-life of drug release, improved therapeutic efficacy, and reduced toxicity.

SOS was not an obvious alternative to the dextran sulfate of D1. None of the prior art documents cited by the appellant disclosed SOS. The sweeping statement of D1 that compounds of the broad class "sulphated oligosaccharides" could form insoluble complexes with irinotecan was not supported by any data. In addition, SOS, a sulfated disaccharide, was not a "sulphated oligosaccharide" within the meaning of D1, which focused on dextran sulfate, a branched species having many more than two sugar units.

Accordingly, the criteria of inventive step were met.

Reasons for the Decision

1. Admittance of D7-D9 into the proceedings

1.1 The appellant filed D7-D9 together with its statement setting out the grounds of appeal. The respondent contests the admittance of these documents.

1.2 Since the statement setting out the grounds of appeal was filed before 1 January 2020, the question whether D7-D9 should be admitted must be decided on the basis of Article 12(4) RPBA 2007 (see Article 25(2) RPBA 2020).

1.3 In the Board's opinion, the filing of the review article D7 and the textbook extract D8 represents an appropriate reaction to developments in the previous proceedings and as an attempt by the appellant to fill in the gaps in its arguments presented in the first instance regarding added subject-matter.

1.4 In contrast, D9 is not to be admitted into the proceedings. The appellant relies on D9 to raise a completely new objection of lack of inventive step. In addition, this objection based on D9 would require that the validity of the priority be assessed for the first time, since D9 was published during the priority interval. Thus the filing of D9 constitutes an attempt to bring about a fresh case in the appeal proceedings.

1.5 Accordingly, D7 and D8 are admitted into the proceedings, whereas D9 is not admitted into the proceedings.

2. Main request (patent as granted)

2.1 Article 100(c) EPC, added subject-matter

Claim 1 of the main request pertains to
- a composition comprising a liposome in a medium,
- wherein the liposome comprises
  - 1,2-distearoyl-SN-phosphatidylcholine (DSPC),
  - cholesterol and
  - N-(omega-methoxy-poly(ethylene glycol)oxycarbonyl)-1,2-distearoylphosphatidyl ethanolamine (PEG-DSPE)
  - in the molar ratio 3:2:0.015, and
- entrapped inside the liposome are irinotecan and sucrose octasulfate (SOS).

2.2 The Board agrees with the respondent that the application as filed generally discloses a composition comprising a liposome in a medium (see paragraph [0009]). Within its inner space, or, in other words, entrapped inside, the liposome comprises a polyanionized sugar (see paragraph [0009]) and an entity such as irinotecan (i.e. CPT-11, see the "second" paragraph [0010] on page 4). As polyanionized sugar, SOS is not only mentioned in a list in paragraph [0079] (see page 20 line 3) but is also disclosed as preferred in combination with irinotecan in paragraph [0116] (see last sentence), independently of any drug lipid mass ratio, drug release or toxicity properties.

2.3 As to the remaining features of claim 1 regarding the lipid matrix, i.e the combination of DSPC, cholesterol and PEG-DSPE in the molar ratio 3:2:0.015, the following is noted.

Paragraph [0101] discloses that the liposome may include lecithin such as 1,2-distearoyl-lecithin (i.e. DSPC) and cholesterol in a molar ratio of 3:2, and an amphipathic polymer in a amount of 0.1-1 mole%, such as a polyethylene glycol-lipid derivative. However, this passage does not specifically disclose the combination of DSPC and cholesterol with PEG-DSPE in the claimed molar ratio 3:2:0.015. These features are found in a number of examples, in particular example 11. In this, the Board agrees with the appellant that the amendment represents an "intermediate generalisation", in the sense that it amounts to a generalisation of a particular embodiment (here e.g. example 11) but the subject-matter resulting from said amendment is still more specific than the original definition of the invention in general terms (found in e.g. paragraph [0101]).

2.3.1 The relevant question regarding added subject-matter is whether this intermediate generalisation is allowable, i.e. whether these lipid matrix features can be extracted from the examples, in particular example 11.

According to established case law (see Case Law of the Boards of Appeal, 9th edition 2019, II.E.1.9), it will normally not be allowable to base an amended claim on the extraction of isolated features from a set of features originally disclosed only in combination, e.g. a specific embodiment in the description. An intermediate generalisation is justified only in the absence of any clearly recognisable functional or structural relationship among the features of the specific combination, or if the extracted feature is not inextricably linked with those features.

2.3.2 The appellant submits that, starting from example 11, the features of the lipid matrix of claim 1 have been isolated from the PEG-DSPE molecular weight of 2787, the liposome size of paragraph [0162], the factors controlling the drug load ratio (see paragraphs [0107]-[0108] and [0164]), the presence of triethylammonium (TEA) and further aqueous material and the features resulting from the specified manufacturing method. The appellant further argues that, considering the skilled person's common general knowledge (as reflected in D7 and D8), these features together determine the properties of the liposomes and thus cannot be isolated from one another.

2.3.3 The Board does not share the appellant's opinion.

Regarding the isolation of PEG-DSPE from its molecular weight specified in example 11 (see paragraph [0159]), the Board concurs with the respondent that the more general disclosure of the application as filed teaches that a polymer-conjugated lipid such as PEG-DSPE can be used in the liposomes irrespective of its molecular weight (see paragraphs [0099], [0100] and [0102], and claims 94-97, 99 and 100 of the application as filed). No functional or structural relationship can be recognised between this molecular weight and the nature of the amphipathic polymer (PGE-DSPE) or it molar amount (0.015). Thus the absence of limitation regarding molecular weight in claim 1 of the main request does not introduce added subject-matter.

As to the liposome size, example 11 (see paragraph [0162]) considers the use of filters of various pore sizes and different numbers of extrusions to achieve different liposome sizes, without establishing any inextricable link between the extracted lipid matrix

features and these chosen liposome sizes. As explained by the respondent, example 11 is not limited to any particular liposome size.

The drug load ratio in paragraph [0164] results from the parameters of the production process which the skilled person is at liberty to chose, such as the drug/lipid ratios. Likewise, the appellant did not specify which process steps or resulting features should be regarded as inextricably linked to the lipid matrix features. The Board also shares the respondent's position that the presence of aqueous material in the liposomes of claim 1 is implicit, such that no generalisation is introduced by claim 1 of the main request in this respect.

Finally, as pointed out by the appellant, in the process of example 11, SOS is added to the liposomes as a solution of TEA-SOS (see [0160]-[0161]). This however does not necessarily lead to the presence of TEA in the final liposomes, as explained by the patentee with reference to paragraph [0113] of the application as filed. This passage makes clear that, generally, the ammonium may be completely replaced by the irinotecan active ingredient during incubation. This is consistent with paragraph [0066] of the application as filed, mentioning the presence of ammonium (here TEA) *and/or* polyanion (SOS), i.e. the presence of both is not required in liposomes. There is accordingly no reason to consider the presence of TEA as inextricably linked to the features of the lipid matrix.

The appellant cited D7 and D8 to show that all the structural and functional features of the liposomes of example 11 (including the composition of the lipid matrix) defined together the properties of the liposome

(see D7, section 3, and D8, pages 1, 575 and 580). In the Board's opinion, the fact that the behavior or properties of liposomes are influenced by several factors does not necessarily mean that these factors cannot be chosen independently from one another. As explained above, the Board holds that the application as filed teaches that the features pertaining to the lipid matrix are not closely associated with the other features of example 11. Additionally, the respondent pointed out that a large majority of the examples relating to liposomes and lipid blends in the application as filed use the specific lipid blend and molar ratio specified in claim 1. In the Board's opinion, this confirms that the use of this lipid matrix applies, beyond example 11, to the more general context.

Accordingly, the ground for opposition under Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

2.4 Article 100(a) EPC, inventive step

2.4.1 The appellant considers D1, in particular figures 1 and 4, to represent the closest prior art.

The respondent disagrees and submits that the information provided in D1 would not be sufficient to allow its teaching to be reproduced. Considering the Board's conclusion regarding inventive step, this point need not be decided.

2.4.2 D1 discloses irinotecan containing liposomal formulations comprising DSPC:cholesterol:DSPE-PEG_{2000} in the ratio 100:30:5 (see Fig. 1), or

EPC:cholesterol:DSPE-PEG_{2000} in the ratio 100:30:5 and dextran sulfate (see Fig. 4).

2.4.3 The subject-matter of claim 1 of the main request differs from the liposomes of D1 (in particular those of Fig. 1) in that the claimed liposomes contain SOS, and further in that the DSPC:cholesterol:DSPE-PEG molar ratio is 3:2:0.015.

2.4.4 The respondent relies on the achievement of the following technical effects:
- improved drug retention and half-life of drug release, and
- improved therapeutic efficacy and reduced toxicity.
The question as to whether the above differentiating features convincingly lead to these improved technical effects is however not decisive in the present case.

2.4.5 The objective technical problem can accordingly be formulated, in the appellant's favour, as the provision of an alternative liposomal irinotecan formulation.

2.4.6 The appellant did not convincingly show that the skilled person would consider the use of SOS in irinotecan liposome formulations. The only document on which the appellant relies in this respect is D1, which states that "it was also found that sulfated oligosaccharides can form an insoluble complex with irinotecan (data not shown). Consequently, the leakage of the drug was reduced by the generation of such a complex within the liposomal aqueous compartment" (see page 408, left column, lines 23-28). However, this assertion in D1 is to a large extent unsubstantiated, the only actual sulfated oligosaccharide used in D1 being dextran sulfate, a branched species comprising a large number of sugar units. D1 neither mentions SOS

nor offers any hint that SOS, a sulfated disaccharide, could be used as an alternative to dextran sulfate or be suitable for use in irinotecan liposome formulations, irrespective of any associated improvement.

Accordingly, the subject-matter of claim 1 of the main request involves an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated