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**Datasheet for the decision of 23 January 2024**

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| **Case Number:** | T 0157/22 - 3.3.07 |
| **Application Number:** | 12841616.1 |
| **Publication Number:** | 2768484 |
| **IPC:** | A61K9/127, A61K9/19, A61K31/4745, A61K31/704, A61K47/26, A61K31/7072, A61K31/7068, A61K45/06 |
| **Language of the proceedings:** | EN |

**Title of invention:**
LYOPHILIZED LIPOSOMES

**Patent Proprietor:**
Jazz Pharmaceuticals Research LLC

**Opponents:**
SANDOZ AG
D Young & Co LLP

**Headword:**
Lyophilized liposomes/Jazz Pharmaceuticak Research LLC

**Relevant legal provisions:**
EPC Art. 54, 56

**Keyword:**
Main request - Novelty (Yes)
Main request - Inventive step (No)

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 0157/22 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 23 January 2024

| | |
|---|---|
| **Appellant:** (Opponent 1) | SANDOZ AG<br>Lichtstrasse 35<br>4056 Basel (CH) |
| **Representative:** | Kraus & Lederer PartGmbB<br>Thomas-Wimmer-Ring 15<br>80539 München (DE) |
| **Appellant:** (Opponent 2) | D Young & Co LLP<br>120 Holborn<br>London EC1N 2DY (GB) |
| **Representative:** | D Young & Co LLP<br>120 Holborn<br>London EC1N 2DY (GB) |
| **Respondent:** (Patent Proprietor) | Jazz Pharmaceuticals Research LLC<br>3170 Porter Drive<br>Palo Alto, CA 94304 (US) |
| **Representative:** | Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 November 2021 concerning maintenance of the European Patent No. 2768484 in amended form.** |

**Composition of the Board:**

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|---|---|
| **Chairman** | A. Usuelli |
| **Members:** | D. Boulois |
| | L. Basterreix |

## Summary of Facts and Submissions

I. European Patent 2 768 484 had been opposed under Article 100 (a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

II. The appeal lies from the decision of the opposition division finding that the patent in amended form met the requirements of the EPC. The decision was based on the main request filed on 23 October 2020.

Claim 1 of the main request read:

"1. A lyophilized gel-phase liposomal composition, which composition comprises: (a) gel-phase liposomes that exhibit a melting phase temperature (Tc) of at least 37°C, wherein the liposome membrane of said liposomes is composed of 50-80 mol% distearoylphosphatidylcholine (DSPC), 1-20 mol% distearoylphosphatidylglycerol (DSPG) and 1-20 mol% cholesterol (CHOL), an wherein at least two therapeutic and/or diagnostic agents are antineoplastic agents, wherein said antineoplastic agents are daunorubicin and cytarabine and are encapsulated in said liposomes at a 1:5 molar ratio; and (b) a cryoprotectant external to said liposomes; wherein said liposomes contain substantially no internal cryoprotectant, and wherein, when said gel-phase liposomal composition is reconstituted in a pharmaceutical carrier, the mean diameter of the liposomes is maintained whereby said mean diameter does not increase more than 10% on a volume weighted basis as compared to said composition

prior to lyophilization, and said agents are retained in the liposomes."

III. The documents cited during the opposition proceedings included *inter alia* the following:

D1: WO 03/041681 A2
D1a: US 2011002982
D2: WO 2005/102359 A1
D3: WO 2008/101214 A2
D4: C. Chen et al., J. Control. Rel., 2010, 142, 299
D5: A. Dicko et al., Exp. Opin. Drug Delivery, 2010, 7(12), 1329-1341
D6: A. Dicko et al., Int. J. Pharm., 2010, 391, 248-259
D12: WO 2007/076117
D13: Nounou MM et al., DARU, 2005, 13(4), 133-143
D18: Kim H.P. et al., Exp. Hematol., 2011, 39, 741-750

IV. According to the decision under appeal, the main request met the requirements of Article 123(2) EPC and the claimed invention was sufficiently disclosed.

The claimed subject-matter was novel over D1, D2, D3 and D12.

With regard to inventive step, D3 was the closest prior art. The problem was defined as the provision of an alternative lyophilized gel-phase liposomal composition which synergistically treats cancer even after lyophilization. The claimed solution was not obvious over D3, D12, D13 or D18.

V. Opponent 01 (hereinafter appellant 01) and opponent 02 (hereinafter appellant 02) filed an appeal against said decision.

VI. With its reply to the grounds of appeal dated 5 August 2022, the patent proprietor (hereinafter the respondent), filed a main request and auxiliary requests 1 to 7 corresponding to the requests presented in opposition proceedings and submitted a new evidence:

D38: Raudino et al., Journal of Pharmacy and Bioallied Sciences, 2011, 1, 15-38

VII. A communication from the Board, dated 12 October 2023, was sent to the parties.

VIII. Oral proceedings took place by videoconference on 23 January 2024. During oral proceedings, the respondent withdrew auxiliary requests 1-7.

IX. The arguments of the appellants may be summarised as follows:

Main request - Novelty

Example 2 of D3 was relevant for novelty, since relating to the same liposome composition CPX-351. The liposomes of example 2 were suspended in sucrose, a cryoprotectant located therefore externally to the liposomes and D3 further disclosed in example 2 and in the description that the liposomal composition could be lyophilised (see D3, page 12, lines 11-14). A particular method of preparation was given on page 8, lines 10-23, with reference to D12, and this method involved the presence of sucrose in the external layer of the liposomes. One of the alternative method disclosed in D12 included a process involving the presence of copper gluconate as in example 2 of D3, and this was the process also used in the contested patent. Example 1 of D12 illustrated this particular process.

In addition, D6 showed that the presence of copper gluconate had an effect on the retention of the active substances within the liposome formulation. The functional features of claim 1 were implicit properties of the liposomes and the liposomes of example 2 of D3 would possess such properties.

Main request - Inventive step

According to appellant 01, D3 was the closest prior art and the unique difference was the location of the cryoprotectant sucrose. The absence of sucrose inside the liposomes did not have any effect and the skilled person would have expected that the liposomes in D3 had the same properties. The problem was the provision of an alternative composition. The solution was obvious.

Appellant 02 also considered the location of the cryoprotectant as having no effect. The problem was the provision of an alternative composition. The solution was obvious in view of D3 and D12. In D12, example 1 gave two options with regard to the process of preparation, it was therefore obvious to follow one of the options, which led to the claimed solution. Moreover, D12 pointed to the presence of the cryoprotectant outside the liposomes, as disclosed on paragraph [0028]. The skilled person would have arrived to the solution by simply following the process instructions in D12. The claimed solution was a clear and obvious alternative.

X. The arguments of the respondent may be summarised as follows

Main request - Novelty

Claim 1 of the main request was novel over D3, since D3 did not disclose a lyophilized composition; in particular there was no enabling disclosure of the lyophilization step, since no lyophilization parameters were given in D3, while these parameters were essential. D3 did neither disclose a composition meeting the functional requirements of claim 1 of the main request, even implicitly, and D3 also failed to disclose a liposomal composition having the structural features of claim 1, in particular regarding the external location of the cryoprotectant; when reading D3, it had to be concluded that sucrose was located within and outside the liposomes. It was not possible to conclude that the effects claimed in claim 1 of the main request could be the intrinsic result of the technical features disclosed in D3. Moreover, it was not possible to combine the disclosure of an example with the disclosure of the description, as the appellants did with example 2 and the process described on page 8 of D3. Consequently, the claimed subject-matter differed from the disclosure of D3 in the presence of a lyophilized composition, the presence of the cryoprotectant only externally to the liposome structure and in that the mean diameter of the liposomes was maintained as compared to said composition prior to lyophilization, and active agents were retained in the liposomes.

Main request - Inventive step

There was no information in D3 with regard to the location of sucrose. The distinguishing feature between the claimed subject-matter and D3 was therefore the location of the cryoprotectant, and the technical effects of maintenance of the liposome mean diameter and retention of the drug within the liposomes which were linked with the difference. The problem was the provision of a liposome composition able to treat synergistically cancer even after a long term storage. This effect was shown in the patent, in particular in Tables 1, 4, 5 and example 3. The solution could not be obvious in view of D3, since nothing in D3 would have led the skilled person to modify its product. There was also a possibility that the lyophilization of the product would have led to failure.

XI. Requests

Appellants 01 and 02 (opponents 1 and 2) requested that the decision under appeal be set aside and the patent be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed.

## Reasons for the Decision

1. Main request - Novelty

1.1 Document D3 has been cited by both appellants as relevant for novelty.

1.2 D3 relates to a liposomal composition comprising cytarabine and daunorubicin stably encapsulated in a

liposome delivery vehicle for the treatment of cancer (see D3, page 3, last par. or claim 1). The specific embodiment disclosed in D3 is a composition comprising cytarabine and daunorubicin in a 5:1 mole ratio, wherein the liposome comprises DSPC:DSPG:Chol in a 7:2:1 mole ratio. Said liposomes are provided as a suspension in a sucrose-phosphate buffer at pH 7.4, comprising also sucrose, copper gluconate, and triethanolamine as shown below in Table 3 of example 2 (see D3 claims 1, 9, 10; page 8-10 and example 2, Table 3):

**Table 3 Components of CPX-351 liposomal injection**

| Component | mw | Amount per mL | Amount per unit |
|---|---|---|---|
| Cytarabine, USP | 243 | 5.0 mg | 1.0 mg |
| Daunorubicin USP(reported as the free base) | 528 | 2.2 mg | 0.44 mg |
| Distearoylphosphatidylcholine | 790 | 22.7 mg | 4.5 mg |
| Distearoylphosphatidylglycerol | 801 | 6.6 mg | 1.3 mg |
| Cholesterol, NF | 387 | 1.6 mg | 0.3 mg |
| Copper gluconate, USP | 454 | 4.6 mg | 0.9 mg |
| Triethanolamine, NF | 149 | 0.36 mg | 0.07 mg |
| Sucrose, NF | 342 | 125.5 mg | 25.1 mg |
| Sodium phosphate, monobasic, USP | 120 | 0.5 mg | 0.1 mg |
| Sodium phosphate dibasic, USP | 142 | 4.3 mg | 0.9 mg |
| Water for Injection USP, q.s. | | 1.0 mL | 0.2 mL |

As shown by Table 3, the liposomes are named CPX-351 as in the contested patent. Furthermore, the components of the liposome composition are identical to the components of the liposome composition of claim 1 of the main request or to the components of the liposome used in example 2 of the patent. All the examples of D3 relate to the same liposome composition.

The liposome formulation CPX-351 is provided in example 2 of D3 as a suspension which is stored frozen and thawed at room temperature for 60 minutes prior to dilution and administration. An explicit alternative given in example 2 of D3 is that the liposome formulation CPX-351 may be lyophilized for storage and

resuspended prior to administration. D3 does not provide any details about the lyophilization conditions, however, as noted in paragraph 6.8 of the decision, the lyophilization is a well-known technique thus the Board sees no reason for considering that the skilled person would not be able to lyophilize the liposomes of D3. Accordingly, in the Board's view, example 2 of D3 discloses a lyophilized gel-phase composition. Thus, the lyophilized state of the composition does not constitute a distinguishing feature.

1.3 With regard to the location of a cryoprotectant external to the liposomes with substantially no internal cryoprotectant, the method of preparation of the liposomes and of the liposomal composition appear to be the crucial point.

As discussed in point 1.2 above the liposomes of example 2 of D3 are suspended in a sucrose-phosphate buffer before being sterilized and then stored frozen or lyophilized. Thus, D3 discloses the presence of a cryoprotectant external to the liposomes.

Concerning the preparation of the liposomes, D3 mentions on page 8, lines 8-23, very generally that the liposomes may be prepared by a water-in-oil derived liposome method.

D3 makes in the same passage a direct reference to the process disclosed in WO 07/076117 (D12) as the process to be used for the preparation of the specific liposomes with DSPC, DSPG and Chol in a 7:2:1 mole ratio. It is therefore clear that the process used in example 2 of D3 for the preparation of the liposomes is the one disclosed in D12.

D12 relates to liposomes having the identical lipid composition of the liposomes of the contested patent, i.e a mixture of DSPC:DSPG:Chol in a molar ratio of 7:2:1 (cf. D12, page 6, par. [0025]). Example 1 discloses a method for the preparation of said liposomes. The method involves the dissolution of the lipids in a mixture of chloroform, methanol and water, the evaporation of the solvent and the hydration of the sample with either 100 mM copper gluconate or with a sucrose phosphate buffer to obtain the final liposomes followed by an extrusion step. For the alternative in which copper gluconate is used for the hydration, the external copper gluconate was further exchanged with a 300 mM sucrose/20 mM phosphate/10 mM EDTA by dialysis. Thus, D12 discloses two variants for the preparation of liposomes one of which involves the use of sucrose, i.e. a cryoprotectant, that would remain in the internal part of the liposomes.

In the absence of any information in D3 as to the specific method used for the preparation of the liposomes it is not possible to exclude that precisely the variant involving the use of sucrose in the hydration step was used. Accordingly, it is not possible to conclude that the liposomes of example 2 of D3 do not contain any internal cryoprotectant.

1.4 Consequently, the subject-matter of claim 1 of the main request is novel over D3 already in view of the feature "wherein said liposomes contain substantially no internal cryoprotectant".

2. Main request - Inventive step

2.1 The claimed invention relates to compositions of lyophilised liposomes that contains cytarabine and daunorubicin that can be stored for prolonged periods, containing in an external medium a cryoprotectant having resistance to freeze/thaw and dehydration damage of the liposomes, thus preserving their size and integrity.

2.2 D3 is considered to be the closest prior art. This document discloses the presence of the cryoprotectant sucrose in its example 2, but does not disclose that the cryoprotectant is located only externally to the liposomes. This constitutes a structural distinguishing feature between the claimed subject-matter and the disclosure of D3 (cf. the discussion on novelty in point 1. above). Additionally, D3 does not provide any information with regard to the functional features of claim 1 concerning the diameter of the liposomes and the retention of the drugs in the liposomes.

2.3 The problem was defined by the opposition division as the provision of an alternative gel-phase liposomal composition which synergistically treats cancer even after lyophilization.

The appellants consider the problem as the provision of an alternative composition of cytarabine and daunorubicin.

The respondent defines the problem as the provision of a liposomal formulation encapsulating both daunorubicin and cytarabine, which is able to safely and synergistically treat cancer, in particular myeloid

leukaemia, even after having been stored during a long period.

2.4 The solution to any of these problems is the provision of a liposomal composition characterised by the presence of a cryoprotectant external to said liposomes and wherein said liposomes contain substantially no internal cryoprotectant.

2.5 The respondent relies on Table 1, on paragraph [0092] as well as on example 3 and Tables 4 and 5 of the patent in support of a technical effect.

2.5.1 Table 1 and the paragraph [0092] shows that the size of the liposomes of the claimed invention remains stable after lyophilization and rehydration. Example 3 of the patent shows that the percentage of drug encapsulation over time remains unchanged in lyophilized liposomes, (see Tables 4 and 5).

The cited passages of the description of the patent do however not show any particular effect linked with the exclusive presence of the cryoprotectant outside the liposomes or a comparison with a liposome composition having a cryoprotectant located simultaneously inside and outside the liposome structure. It is therefore not possible to conclude that the requirement that the liposomes do not contain any internal cryoprotectant results in any improvement over the liposomes of D3.

2.5.2 The Board disagrees in particular with the respondent that the presence of the cryoprotectant only externally to the liposomes results in an improved effect in relation to the mean diameter maintenance and the retention of the drug inside the liposomes. This link has not been demonstrated in the contested patent.

There is also no indication in D3 that the mean diameter of the liposomes would increase by more of 10% after reconstitution or that the agents are not retained in the liposomes.

Moreover, the Board does not see any reason to doubt that the liposomes disclosed in D3 can synergistically treats cancer even after lyophilization, since this effect is linked to the presence of cytarabine and daunorubicin in a specific ratio which was not a distinguishing feature between the claimed subject-matter and D3. There is furthermore no evidence of the contrary.

2.5.3 Consequently, it is not possible to establish the existence of an improvement over the prior art.

However, as discussed above, the experimental data disclosed in the patent show that the liposomes of the invention remain stable after lyophilization and rehydration and upon storage.

Thus, the technical problem can be formulated as the provision of a liposomal formulation encapsulating both daunorubicin and cytarabine, which is able to safely and synergistically treat cancer, in particular myeloid leukaemia, even after having been stored during a long period.

2.6 It remains to determine whether the claimed solution would be obvious starting from the disclosure of D3.

2.6.1 In the Board's view, the claimed solution is obvious in view of D3 and D12. Example 2 of D3 indicates that the liposomes are suspended in sucrose-phosphate buffer. The liposomes may then be lyophilised thereby leaving

the sucrose outside the liposomes. Regarding the process for the preparation of the liposomes before the drug encapsulation, as discussed in point 1.3.2 above, the process described in detail in D12 comprises two options. In one of them the sample obtained after evaporating the choloroform/methanol/water solution is hydrated in a solution of copper gluconate (example 1, paragraph [0042]). This option does not lead to the incorporation of a cryoprotectant into the liposomes. Thus, in the step of preparing the liposomes, the skilled person has therefore the choice between two process options, wherein at least one of them would lead to the claimed composition. For this reason alone, the claimed solution is obvious.

2.6.2 The opposition division considered the claimed solution to be not obvious, since there was no hint in D3 to incorporate a cryoprotectant only in the external phase. The opposition division considered that there was no evidence showing that this was part of the common general knowledge. Furthermore, the granted patent states in paragraph [0017] that it has consistently been reported that a cryoprotectant is required both inside and outside of liposomes in order to maintain liposome integrity upon reconstitution after lyophilization, particularly in order to ensure retention of an encapsulated agent.

The Board is not convinced by these conclusions of the opposition division. As discussed above, example 2 of D3 discloses the use of sucrose as an external agent to the liposomes. Although it cannot be ruled out that some sucrose was incorporated inside the liposomes during the process for their preparation (see point 1.3 above), there is no indication in D3 that this would be necessary for the stability of the liposomes.

Similarly to D3, also D2 discloses in example 2 liposomes made of DSPC/DSPG/Chol in a 7:2:1 mole ratio loaded with daunorubicin and cytarabine. The example indicates that the liposomes are buffered exchanged into 300mM sucrose. There is however no indication that a cryoprotectant should be incorporated also into the liposomes in order to preserve their properties.

Furthermore, D12 discusses the content of the intraliposomal phase and the extraliposomal aqueous solution in paragraphs [0027] and [0028]. It indicates that the external aqueous solution can contain components that are cryoprotective. Notably, no mention is made of the presence of such components in the internal phase.

Thus, in the Board's view the skilled person would not regard the presence of an internal cryoprotectant as a mandatory factor for ensuring the liposomes stability and therefore their suitability to synergistically treat cancer.

2.6.3 The further documents cited by the respondent have no incidence on the conclusion on inventive step, as these documents are not relevant or less relevant than the documents cited above.

The respondent relied in particular on the teachings of documents D4 and D5. D4 relates to the impact of lyophilization for the long term stability of liposomes and explains that many factors affecting the lyophilization process need to be optimised to obtain an acceptable product after lyophilization (page 300, left-hand column, 2nd paragraph). On page 306, right-hand column, D4 underlines the importance of having

sugars inside and outside the liposome to provide the most effective protection during lyophilization. However, as remarked by the appellants, D4 also indicates that lyophilization is the main approach used to extend the shelf-life of liposomes. Furthermore, with regard to the possibility of using only a cryoprotectant external to the liposomes, the Board considers that the skilled person would give more weight to the teachings of D3 and D12 which concern the same liposomes as in claim 1 containing two drugs rather than D4 which generically relates to the field of liposome lyophilization.

D5 explains the importance of the 5:1 molar ratio of cytarabine:daunorubicin for obtaining a synergistic effect. However, the liposomes disclosed in example 2 of D3 contains the same molar ratio of cytarabine:daunorubicin. On page 1 of the same document it is explained the importance of maintaining this ratio.

2.7 In view of the above, the Board concludes that the skilled person faced with the technical problem defined in point 2.5.3 above, would obviously consider to provide liposomes as disclosed in example 2 of D3 in which the cryoprotecting agent is only external to the liposomes.

2.8 Concerning the requirements in claim 1 that the mean diameter of the liposomes does not increase more than 10% on a volume weighted basis and that the agents are retained in the liposomes, the Board agrees with the appellants that these features are intrinsic to the composition of the liposomes of claim 1. The respondent did not submit any relevant technical argument against this conclusion.

Thus, the Board concludes that by providing liposomes having the same composition as the liposomes of claim 1 the skilled person would also provide liposomes satisfying the functional features of claim 1.

2.9 It follows that the subject-matter of the main request does not comply with the requirements of Article 56 EPC.

## Order

## For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated