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D E C I S I O N
of 19 February 1998

Case Number: T 0574/93 - 3.3.2

Application Number: 84902489.8

Publication Number: 0153926

IPC: A61K 9/22

Language of the proceedings: EN

Title of invention:
Microdroplets of water-insoluble drugs

Patentee:
Pharma-Logic, Inc.

Opponent:
B. Braun Melsungen Aktiengesellschaft

Headword:
Microdroplets/PHARMA-LOGIC, INC.

Relevant legal provisions:
EPC Art. 123(2), (3), 84, 56, 54(5), 52(4)

Keyword:
"Main request and first auxiliary request - clarity - no"
"Second auxiliary request - clarity - yes - first medical indication - novel and inventive"

Decisions cited:
-

Catchword:
-

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Case Number: T 0574/93 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 19 February 1998

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 28 April 1993 revoking European patent No. 0 153 926 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
J. H. van Moer

Summary of Facts and Submissions

I. European patent No. 0 153 926 was granted on the basis of 22 claims contained in European patent application No. 84 902 489.8 (International publication No. WO 85/00011 -henceforth termed the originally filed document - corresponding to International application No. PCT/US84/00906).

II. Opposition was filed against the granted patent. According to the grounds for opposition the patent was opposed for lack of novelty and lack of inventive step under Article 100(a) EPC. Of the numerous documents cited during the opposition only the following remain relevant to the present decision:

(1) DE-A-2513797
(8) US-A-4073943

III. By a decision posted on 28 April 1993 the Opposition Division revoked the patent under Article 102(1) EPC.

The Opposition Division took the view that the subject-matter of claims 12 and 13 relating to a microdroplet; claim 14 relating to an injectable pharmaceutical composition; claim 15 relating to a timed release drug delivery vehicle and claim 18 relating to a process for producing microdroplets, lacked novelty over either document (1) or document (8). It was pointed out in particular that the said claims did not contain a feature distinguishing the microdroplet particles according to the patent in suit from the emulsion particles disclosed in the prior art. Reference was made inter alia to example 6 of document (1) and example 19 of document (8).

IV. The Appellant lodged an appeal against the said decision.

With the letter dated 10 May 1994, the Respondent withdrew the Opposition.

Oral proceedings took place on 19 February 1998 during which the Appellant filed a main request and four auxiliary requests. For the wording of claim 1 of the main request and that of the first auxiliary request see point 2 for the reasons for the decision. Claim 1 of the second auxiliary request reads as follows:

"1. An aqueous suspension of microdroplets of from 20 nm to 10 µ in diameter consisting essentially of a sphere of:

(i) a substantially water-insoluble general or inhalation anaesthetic in liquid form; and

(ii) a phospholipid monolayer surrounding the anaesthetic;

the suspension being free of a fat or oil of vegetable or animal origin;

for use in a method of inducing anaesthesia at the site at which anaesthesia is desired in human or animal body."

V. The arguments of the Appellant, both in the written procedure and at the oral proceedings may be summarised as follows:

Claim 1 of the main request as well as that of the first and second auxiliary requests was in the first medical use format and thus these product claims were clearly and unambiguously limited to an aqueous

suspension of microdroplets in a method of treatment in accordance with Articles 52(4) and 54 (5) EPC. The claims were furthermore limited to an aqueous suspension free of a fat or oil of vegetable or animal origin. This disclaimer would clearly establish novelty over the prior art according to documents (1) and (8).

In fact, document (1) and document (8) suggested the simple mixing of components in order to provide emulsions. Having regard to the overall disclosure of document (1) a person skilled in the art was not taught by example 6 of that document to provide a mixture of propofol and a phosphatide alone. The microemulsion according to this prior art required a high amount of 10% Tween 40 surfactant for solubilisation of 2% propofol. Even if the Tween 40 or one of the other surfactants proposed in document (1) was replaced with a phospholipid, repetition of the same methodology would result in an unstable product consisting mostly of large liposomes. This was proven by comparative tests relating to formulations with different ratios of the surfactant to drug and lecithin to drug. There was not the slightest hint in document (1) or any other cited prior art how to adjust the ratio of drug substance to phospholipid and to provide sufficient input of shear energy necessary in order to form microdroplets with a phospholipid monolayer surrounding the drug. For the preparation of microdroplets it was necessary, contrary to what a skilled person would expect for the preparation of oil in water emulsions, to decrease the amount for surfactants proposed in document (1) and drastically to increase the energy far above values not normally contemplated in the preparation of oil in water emulsions. It was furthermore pointed out that the surfactants of document (1) such as Tween 40 show some disadvantages since they could cause gross cellular disruption after injection. Since document (8) also taught the use of

surfactants such as Span 80 and Myrj 52, the formulations described therein involved the same disadvantages as those known from document (1). An additional disadvantage of the formulations of document (8) was that of the risk of bacterial contamination and induction of hyperlipidaemia. It was furthermore important to note that example 19 of document (8) did not contain specific details about the composition and its preparation method.

The Appellant emphasised that in the field of anaesthesia there was a strong need for further injectable local anaesthetics.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or the first, second, third or fourth auxiliary request filed at the oral proceedings of 19 February 1998.

Reasons for the Decision

1. The appeal is admissible.

Main request and first auxiliary request

2. The Appellant has based his argumentation on the assumption that the subject matter of claim 1 of the main request and that of claim 1 of the first auxiliary request would relate to a product within the meaning of a so-called first medical indication. However, having regard to the wording of those claims:

"1. An aqueous suspension of microdroplets of from 20 nm to 10 µ in diameter consisting essentially of a sphere of:

(i) a substantially water-insoluble **drug substance in liquid form (main request);** *[anaesthetic in liquid form (first auxiliary request)]*; and

(ii) a phospholipid monolayer surrounding the anaesthetic;

the suspension being free of a fat or oil of vegetable or animal origin (emphasis added)",

it is not clear whether protection is sought for an aqueous suspension of microdroplets including beside other components a drug (anaesthetic) component and thus the subject-matter of the claim would relate to a product without any restrictions as to its use, or would relate to an aqueous suspension representing as such a pharmaceutical preparation for use in a method mentioned under Articles 52(4) and 54(5) EPC. These articles only permit a purpose-limited substance claim **clearly stating a specific or general therapeutic purpose**.

Since claim 1 of the main request and claim 1 of the first auxiliary request do not clearly and unambiguously define the matter for which protection is sought, the main request and first auxiliary request do not fulfil the requirements of Article 84 EPC.

Accordingly, the Appellant's main request and first auxiliary request have to be rejected.

Second auxiliary request

3. The Board sees no objection under Article 84 EPC to claim 1 of the second auxiliary request since this claim clearly relates to an aqueous suspension of microdroplets for use in a method of inducing anaesthesia at the site at which anaesthesia is desired

in the human or animal body. Since the description as originally filed and that as granted indicates that "one of the unique features of the invention lies in the use of volatile liquid general anesthetics to produce local anesthesia" (see in particular page 6, lines 24 to 26 as originally filed), the wording of claim 1 clearly exemplifies local anaesthesia in the human or animal body in the form of a first medical use of the claimed aqueous suspension of microdroplets.

4. Claim 1 is based on claims 1, 7, 8 and 10 as originally filed (claims 12, 17 and 19 as granted) in combination with the description on page 2, lines 31 to 33, page 3, lines 1 to 4 and page 4, lines 15 to 17 as originally filed (column 5, lines 16 to 25 of the description as granted).

4.1 The description as originally filed and that according to the specification as granted leave no doubt that aqueous suspensions are contemplated. In fact, each of the worked examples results in the preparation of aqueous suspensions of microdroplets. The wording of claim 1 "for use in a method of inducing anaesthesia at the site at which anaesthesia is desired **in a human or animal body**" is based on claim 8 as originally filed relating to a "method of inducing local anaesthesia **in a subject in need** of same" in combination with the worked examples originally filed showing the in vivo efficacy of anaesthesia achievable by the pharmaceutical preparation claimed (claim 1 and the worked examples as granted).

The feature that "the suspension being free of a fat or oil of vegetable or animal origin" is based on the disclosure of document (8), example 19 in combination with column 4, lines 65 to 68, and provides a disclaimer with respect to this prior art which otherwise would represent - even taking into account

the fact that example 19 is a comparative example outside the general teaching of document (8) - an accidental novelty destroying disclosure for the subject matter of claim 1.

4.2 Claim 2 is based on claim 4 as originally filed (claim 14 as granted); claim 3 can be derived from claims 7 and 8 as originally filed (claims 1 and 17 as granted); claims 4 to 6 are based on page 9, lines 22 to 24 (claims 2 to 4 as granted); claims 7 and 8 are based on examples 1 and 6 for intradermal injection and example 4 for intramuscular injection. Claim 9 is based on claims 7 and 8 as originally filed (claim 17 as granted).

4.3 The scope of the claims according to the second auxiliary request is narrower than that of the claims as granted. The requirements of Articles 123(2) and (3) EPC are accordingly satisfied.

5. Each of the nine claims according to the second auxiliary request includes the aqueous suspension of microdroplets as defined in claim 1.

5.1 In fact, example 19 of document (8) which represents the only disclosure of this prior art relevant to the question of novelty relates to an emulsion composition containing 5 per cent of methoxyflurane in a carrier system of **soybean oil** emulsified in water with the help of egg phosphatides.

5.2 None of the other documents cited in the course of either the examination or opposition procedure discloses an aqueous suspension of microdroplets as defined in claim 1 for use in a method within the

meaning of Article 54(5) EPC. Having regard to the inclusion of the disclaimer in claim 1 as discussed under point 4 above, the Board is thus satisfied that the second auxiliary request relates to novel subject-matter.

6. The Board considers document (1) to be the closest state of the art.

6.1 This prior art relates to a pharmaceutical composition which may be administered parenterally to a warm-blooded animal for the production of general anaesthesia. The composition is preferably an aqueous composition which comprises the compound 2,6-diisopropylphenol in sterile admixture with water and a surfactant or other solubilising agent and may optionally contain one or more additional solvents. Reference is made to a long list of suitable non-ionic surfactants, particularly preferred are inter alia those sold under the trade mark "Tween", "Myrj", "Brij", "Pluronic", "Emulphor", "Texophor", "Cremophor" or "Micelliphor". It is then indicated that other surfactants which may be used in the composition, especially if the composition is of an emulsion type, are phosphatides such as lecithin, or esters of a hexitol anhydride and a fatty acid known under the trade mark "Span" (see page 1, first paragraph; page 1, last paragraph up to page 2, first paragraph; page 3, second paragraph up to page 4, second paragraph).

According to example 6 on pages 10 and 11, distilled water (90 ml) is added to a solution of 2,6-diisopropylphenol (2g) in polyoxyethylene-(20)-sorbitan monopalmitate ("Tween" 40, 10 g). The emulsion thus obtained is repeatedly passed through a homogeniser until the particle size of the emulsion is reduced to an average of 5 µ and the resulting micro-emulsion is sterilised. There is thus obtained a sterile

composition suitable for parenteral administration to a warm-blooded animal. According to further experiments the process described above is repeated by using inter alia other non-ionic surfactants of the "Tween" and "Myrj" type.

None of the worked examples in document (1) relates to the use of a phosphatide surfactant.

6.2 According to the Appellant's submissions Tween surfactants can disrupt cell membranes and when products as described in document (1) were introduced onto the market, they met with disastrous results due to the surfactants' proclivity for haemolysing red cells and attacking the vasculature. The Appellant argued furthermore that in the field of anaesthesia there was a considerable need for further local anaesthetics since up to the priority date of the patent in suit local anaesthesia could only be accomplished without any risk of toxic side effects by injection of water-soluble compounds into the site to be anaesthetised.

6.3 On the basis of the comparative tests submitted at the oral proceedings, the Appellant provided convincing evidence that a simple replacement of the surfactants used in the worked examples according to document (1), particularly a replacement of the surfactant used in example 6 which describes a particle size of 5 µ of a microemulsion containing a Tween surfactant, by phospholipids would result in an unstable product consisting mostly of large liposomes. In contrast to the phospholipid monolayer structure defined under point (ii) of claim 1, liposomes have a bi-layer shell consisting of two layers of the surfactant. Accordingly, taking into account these comparative tests, the problem to be solved can be seen in the provision of a non-toxic and stable local anaesthetic.

6.4 The problem is solved by the aqueous suspension of claim 1 consisting essentially of spheres of a general or inhalation anaesthetic in liquid form surrounded by a phospholipid monolayer. In the absence of any counter evidence and having regard to the experimental evidence in the patent in suit, the Board finds it plausible that the problem has been solved.

6.5 The whole thrust of document (1) is the finding that the known compound 2,6-diisopropyl phenol (propofol) has activity as a general anaesthetic and that pharmaceutical compositions comprising the same can be administered parenterally to warm blooded animals for the production of general anaesthesia. There is nothing in this document itself to suggest that the skilled person, in order to provide a pharmaceutical composition suitable for local anaesthesia, should investigate the large number of surfactants mentioned therein only as an equivalent to emulsifying propofol, and should drastically decrease the high amount of surfactant proposed in (1) only in order to dissolve propofol to give an aqueous solution. In the absence of any hint as to a preference or an advantageous use of phosphatides in the preparation method as described in document (1), there is also no straightforward or one way street situation for a person skilled in the art to replace the Tween surfactant or one of the others used in example 6 by a phosphatide such as lecithin.

6.6 Document (8) describes pharmacologically active water in oil emulsion systems containing phospholipids respectively phosphatides as a stabilizer. This prior art refers generally to enhancing the administration of water insoluble pharmacologically active agents, and inter alia refers to internal local administration of a drug directly in an operation wound. Anaesthetics are mentioned in a group of other centrally and peripherally acting agents such as depressants,

analgetics, stimulants, spasmolytics, muscle relaxants, vasodepressants and X-ray contrast agents (see column 2, lines 25 to 40; column 3, lines 21 up to column 4, line 23; column 4, line 62 up to column 5, line 9 and the examples). However, each of the emulsion systems exemplifying the use of phosphatides or phospholipids **within the scope of the invention as set out in document (8)**, contains a further surfactant or detergent in combination with soybean oil as the pharmacologically acceptable lipoid phase for dissolving the pharmacologically active agent. Example 1 contains beside egg phosphatides additionally a "Myrj 52" surfactant and phenyramidol as pharmacologically active agent; Example 2 also contains beside egg phosphatides additionally a "Myrj 52" surfactant and hexobarbital as pharmacologically active agent; Example 5 contains beside phospholipids "Span 80" and "Tween 80" as additional surfactants and hexobarbital as pharmacologically active agent; Example 7 contains beside phospholipids "Span 80" and "Tween 80" as additional surfactants and tribromoethanol as pharmacologically active agent; Example 10 contains beside phosphatides "Pluronic F-86" as additional surfactant and Cyclandelate as pharmacologically active agent and Example 17 contains beside egg yolk phosphatides acetylated monoglycerides as additional surfactant and diazepam as pharmacologically active agent. It is indicated that the dispersion of the lipoids is stabilized in the form of particles substantially less than 4 µ. Each of these examples comprises the clear teaching of document (8) that for an enhanced diagnostic or therapeutic effect to be achieved, it is necessary to dissolve the drug into a lipoid and to stabilize the drug containing lipoid particles in an oil in water emulsion by the use of surfactants. Therefore, document (8), which follows abandoned continuation in part applications back to 1968, and which has a more recent filing date than

document (1), does not contain, even in combination with the closest prior art document, a pointer in the direction of stabilising spheres of the drug itself by a monolayer of phosphatides in order to solve the problem as defined above.

6.7 Example 19 of document (8) has been singled out in these proceedings as it refers to the anaesthetic methoxyflurane and it describes the use of egg phosphatides without an additional surfactant.

However, even by taking the view that example 19 represents a separate teaching not related to the rest of the disclosure of document (8), in the light of the fact that the emulsion composition prepared according to this example contains "5 per cent of methoxyflurane...in a carrier system of soybean oil emulsified in water with the help of egg phosphatides" there is neither explicitly nor implicitly an incentive for a skilled person to deviate from the general teaching that it is necessary to dissolve the drug into a lipoid and to stabilize the drug containing lipoid particles in an oil in water emulsion by the use of surfactant.

Moreover, as a result of the administration of the formulation according to example 19 to mice, it is indicated that "it was not possible to establish a relation between sleeping time and the administered dose". Since methoxyflurane belongs to the class of general anaesthetics, and since the formulation was administered to mice by unspecified means there is no reason to assume that another type of anaesthetic was induced as general anaesthetic.

6.8 Furthermore, since document (8) as well as document (1) relate to oil in water emulsions neither being identical with the **structure of the phase system** according to claim 1 nor rendering it obvious, it is irrelevant for the question of inventive step that both documents describe a particle size of the emulsified hydrophobe phase falling within the range of particle size as required by claim 1.

6.9 In these circumstances the Board concludes that only by way of hindsight would it have been foreseeable to attain a non-toxic and stable local anaesthesia on the basis of the experimental work in documents (1) and (8) relating inter alia to emulsified general anaesthetics and their application exclusively in inducing general anaesthesia.

6.10 In the absence of any counter evidence, the Board agrees with the Opposition Division's point of view that the other documents cited in the course of the proceedings only contain background information.

Thus, there is no basis for the Board to conclude that the required inventive step is lacking. Claim 1 as well as claims 2 to 9, including the aqueous suspension as defined in claim 1 in the form of a pharmaceutical preparation satisfy the requirements of Article 56 EPC.

7. Since the Board has decided to allow the Appellant's second auxiliary request, it is no longer necessary to consider the third and fourth auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent with the following claims and a description to be adapted:

   Claims 1 to 9 (second auxiliary request) filed at the oral proceedings of 19 February 1998.

The Registrar:

P. Martorana

The Chairman:

P. A. M. Lançon