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D E C I S I O N
of 7 May 1998

Case Number: T 0673/94 - 3.3.2

Application Number: 88904135.6

Publication Number: 0313617

IPC: A61K 31/22

Language of the proceedings: EN

Title of invention:
Lipid emulsion and method for intravenous infusion

Patentee:
Baxter International Inc. (a Delaware corporation)

Opponent:
Pharmacia & Upjohn AB

Headword:
Lipid emulsion/BAXTER INTERNATIONAL INC

Relevant legal provisions:
EPC Art. 123(2), (3), 54, 56

Keyword:
"Main request - product claims - novelty - no - prior art range comprised within claimed range"
"Auxiliary request - use claims - novelty - yes"
"Inventive step - no - clear pointer towards the claimed solution"

Decisions cited:
-

Catchword:
-

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Case Number: T 0673/94 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 May 1998

Appellant: (Proprietor of the patent)
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Respondent: (Opponent)
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Representative:
-

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 27 June 1994 revoking European patent No. 0 313 617 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. 0 313 617 was granted on the basis of sixteen claims contained in European patent application No. 88 904 135.6 corresponding to International application No. PCT/US88/01278 with International publication No. WO88/08301. Claims 1 and 15 as granted read as follows:

"1. A lipid emulsion for intravenous administration whilst avoiding hyperlipidaemia comprising an emulsifier, a glyceride oil and water, characterised in that the weight ratio of emulsifier to glyceride oil is less than 0.04, and in that a composition consisting of soy bean oil, egg phosphatides, and glycerol and water having said weight ratio of 0.01 is disclaimed.

"15. The use of a lipid emulsion comprising an emulsifier, a glyceride oil and water, the weight ratio of emulsifier to glyceride oil being less than or equal to 0.04, in the manufacture of a medicament for the intravenous infusion of lipids into a patient whilst avoiding hyperlipidaemia."

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

(1) US-A-3169094,

(3) J. Of Parenteral and Enteral Nutrition, vol. 10, no. 6, 1986, pages 662 to 626, Tashiro et al,

(4) Clinical Nutrition, 5(suppl.), page 43, 1986, Carpentier et al,

(5) 8th Congress of the European Society of Parenteral and Enteral Nutrition, Paris 14 to 17 September 1986, O12, Haumont et al,

III. By a decision delivered orally on 9 June 1994 with the written reasons posted on 27 June 1994, the patent was revoked under Article 102(1) EPC.

With reference to document (1) disclosing a ratio of egg phospholipid to fat of 0.001 (0.05w%/50w%), the Opposition Division pointed out that the subject-matter of claim 1 lacked novelty within the meaning of Article 54 EPC, but chose to revoke the patent on the grounds of lack of inventive step since the patentee had not had the opportunity to consider the said novelty objection, which was discussed for the first time at the oral proceedings.

For the assessment of inventive step, the Opposition Division considered that the problem to be solved was to find fat emulsions for intravenous administration which, contrary to known emulsions, did not cause hyperlipidaemia when used over a long period of time.

The skilled person faced with this problem would inter alia combine the prior art known from documents (1), (3), (4) and (5).

These documents taught that by using lower ratios of emulsifier to fat, fewer problems with hyperlipidaemia occurred and that emulsions having low ratios such as 0.01, 0.04 and 0.06 were stable. Since furthermore the

mechanism of hyperlipidaemia was known in the art, it was at least obvious to try whether emulsions with even lower emulsifier to fat ratios would induce even less hyperlipidaemia.

The Opposition Division furthermore concluded that the values for a ratio of 0.04 according to Figure 1 of the patent in suit were based on a linear extrapolation from the values of the ratios 0.12 and 0.07, and consequently this figure did not show an unexpected effect for the lower values of emulsifier to fat ratios. Moreover, in the light of the disclosure of document (4), the skilled person would expect an increase in short term clearance depending on decreased emulsifier fat ratios. Finally, it was pointed out that the fact that even years after the priority date of the patent in suit there was a lack of availability of a product on the market having emulsifier to fat ratios below 0.04 could not support an inventive step.

IV. The Appellant lodged an appeal against the said decision. With the grounds for appeal, the Appellant submitted a new main request, with claims 1 to 10 relating to the use of a lipid emulsion in the manufacture of a medicament for the intravenous infusion of lipids into a patient, claim 11 relating to a lipid emulsion for intravenous administration, and claims 12 to 14 relating to a process for preparing a composition for intravenous infusion, together with one auxiliary request including only claims 1 to 10 of the main request. New claim 1 corresponds to claim 15 as granted and new claim 11 corresponds to claim 1 as granted, with the claims being restricted to the use of phospholipid emulsifiers.

Oral proceedings took place on 7 May 1998.

The arguments of the Appellant both during the written procedure and at the oral proceedings may be summarised as follows:

The Opposition Division wrongly interpreted the disclosure of document (1) since "a typical fat emulsion" according to this prior art was prepared by using a ratio of phospholipid emulsifier to fat of 0.12. The ratio of 0.001 referred to by the Opposition Division was not within the teaching of document (1). Furthermore, this prior art clearly taught if there are problems with physical properties of the emulsion, by using lower amounts of egg phosphatide, to add other synthetic emulsifiers. However, in order to avoid further discussions about novelty, a disclaimer relating to a ratio of 0.01 representing the lower limit of the weight range of egg phosphatides used in Example 2, the most relevant one, was introduced into product claim 11 of the main request. Moreover, it was necessary to take into account that said claim 11 was restricted to a lipid emulsion for intravenous administration whilst avoiding hyperlipidaemia.

For the assessment of inventive step it was emphasised that the inventors in the patent in suit found for the first time that lowering the phospholipid content of the emulsion to a 0.04 ratio of phospholipid/lipids caused a dramatic reduction in the rate of increase of triglyceride levels in the plasma during administration, as well as much lower maximum levels. This was a surprising effect, since it would have been expected that a reduction in phospholipids would provide only a proportional reduction in triglyceride metabolism. In particular, Figure 1 of the patent in suit showed that, contrary to the Opposition Division's conclusion, it was clear that the steady state levels are not proportional to phospholipid content. The fact that for the product according to the new request a

ratio of 0.04 had been disclaimed in order to provide novelty over the prior art did not preclude Figure 1 and the related description from serving as an illustration of the invention.

The Appellant agreed that document (3) represented the closest prior art, but took the view that this prior art merely could serve as confirmation of what the skilled person would have expected on the priority date of the patent in suit, namely that the rise of phospholipid and cholesterol, but not triglyceride, contributed to the hyperlipidaemia during intravenous administration of Intralipid 10%. Moreover, document (3) gave confirmation that a phospholipid/fat ratio of 0.06 permitted formation of a satisfactory emulsion and that there was no incentive for the skilled person to solve remaining problems by trying lower phospholipid/fat ratios. It was pointed out in particular that the whole prior art when referring to the possible use of phospholipid/fat ratios of 0.06 was totally silent as to the criticality of high levels of triglycerides during administration, and that the person skilled in the art did not recognize that the rapid increase of lipids in plasma during infusion to high levels was in itself a problem.

Inventive step was furthermore supported by the fact that before the priority date of the patent in suit in addition to document (3) also documents (4) and (5) related to studies indicating that hyperlipidaemia was due to the administration of high levels of phospholipids. Two possible solutions to this problem were proposed, one of which was to carefully control dosages to try to ensure that phospholipid concentrations in plasma were not in excess, so that "lipoprotein X", which was slow to clear from plasma, was avoided. The other solution was to reduce the phospholipid/fat ratio to 0.06. An emulsion with the

said ratio of 0.06 allowed rapid clearance of lipids from plasma. Although this emulsion became clinically accepted and was marketed in the mid 1980's as a "20%" solution, and the "lipoprotein X" problem appeared to have been solved, hyperlipidaemia remained with some patient groups, such as low birth-weight infants.

Since tests with the 20% solution indicated that the clearance of lipids was not the problem and since lower levels of phospholipids in the emulsion could cause instability problems, there was no good reason to try ratios below the clinically accepted 0.06 value.

The experts in the 1980's were so cautious in reducing from a 0.12 ratio, and regarded 0.06 as the lowest limit to aim for, since the formation of "lipoprotein X" was avoided at that ratio.

Document (4) provided no lead to a skilled person to try any other phospholipid/triglyceride ratios than 0.12 and 0.06. It merely taught to keep to lower infusion rates with a 0.12 ratio, but that high rates can be used with a 0.06 ratio emulsion.

Accordingly, starting from document (3) and taking into account the disclosure of any of the other cited documents, it was more than speculative for a person skilled in the art to think about phospholipid/triglyceride ratios below 0.06 when faced with remaining hyperlipidaemia problems.

Finally, it was emphasised that it was not until 1993 that a 0.04 ratio phospholipid/lipid emulsion, the 30% emulsion, was first put on the market.

The Appellant's argumentation was supported by expert opinions, including references to several further prior art documents.

In the Appellant's view, none of the additional documents filed by the Respondent should be admitted into the proceedings because they were submitted very late and were no more relevant than the other documents already considered by the Board.

V. The Respondent contested the above arguments.

As regards the question of novelty, it was pointed out that document (1) clearly exemplified intravenously injectable fat emulsions ready for clinical use and compositions which fell within the scope of the alleged invention according to the patent in suit. Regarding Example 2 being an extension of Example 1c, it was clear that auxiliary emulsifiers did not represent an obligatory component of the intravenously injectable fat emulsions ready for clinical use.

As regards a starting point for discussing inventive step the Respondent agreed that document (3) represented the closest prior art.

Document (3) also confirmed that it is the liposomes (bilayered particles formed from the excessive phospholipids in "0.12" emulsions) that produce the hyperlipidaemia. Since it was furthermore known in the art that bilayered particles disappeared if the amount of phospholipids was reduced in an emulsion and that the disappearance did not follow a linear relationship, a skilled person would expect what was demonstrated in Figure 1 of the patent in suit when going from ratios from 0.12 to 0.07 and 0.04. Accordingly, it was not surprising to experience drastic improvements in certain parameters dependent on the phospholipid level (or the number of liposome-like particles present, originating from the phospholipid excess).

A person skilled in the art knowing the closest prior art as well as documents (4) and (5) would without the exercise of inventive skill arrive at the finding that phospholipids were a factor in causing the high levels of lipids in plasma during administration which then caused hyperlipidaemia. In particular, document (5) made reference to premature infants as a specific group of patients receiving the lipid emulsions. The existence of such patients as low birth-weight infants were in itself a motivation for the skilled person to consider a further reduction of the phospholipid to triglyceride ratio.

It was also stated that there were other reasons, such as meeting high energy demand or demand of restricted fluid intake for selecting emulsions having a lipid level (ratios of 0.12, 0.06 or 0.04), than any concern about hyperlipidaemia. Accordingly, the long time span between the marketing of Intralipid® 10%, 20% or 30% was not due exclusively to a lack of ability to solve the hyperlipidaemia problem.

The Respondent filed supplementary documentation which should clarify the physical characteristics of lipid emulsions and their clinical relevance for parenteral use. Reference was made in particular to document

(33) Gastroenterology, Vol. 91 1986, No. 4, pages 919 to 925,

in order to file evidence that before the priority date of the patent in suit Intralipid emulsions with a phosphatide/fat ratio of 0.04 were clinically used for parenteral nutrition.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request filed on 28 October 1994.

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Except for the documents not published before the priority date of the patent in suit, the Board regards each item of the new evidence filed by the parties at the appeal stage, including the two affidavits, as a logically consistent response to the Opposition Division's decision and technical background and support for arguments on file.

3. The Board notes that a weight ratio of emulsifier/glyceride oil of 0.01 corresponding to the disclaimer of claim 11 finds support on page 2, lines 28 to 33, of the original disclosure of the description. The Respondent made no objection under Article 100(c) EPC and the Board considers that for the claims according to the main and auxiliary requests the requirements of Article 123(2) and (3) EPC are satisfied.

3.1 The Board wishes to point out that it appears highly questionable whether document (1), as suggested by the Appellant, represents a so-called accidental disclosure, which is one of the requirements for the introduction of a disclaimer only based on an anticipation. However, having regard to the fact that the said ratio of 0.01 excluded in claim 11 finds a

basis in the original disclosure of the patent in suit, there is, in the present case, no need to go into detail about the meaning of the wording "a composition consisting of ... is disclaimed".

4. Having regard to the objection under Article 54 EPC pointed out by the Opposition Division and the fact that the Appellant as well as the Respondent in the appeal proceedings filed detailed technical argumentation regarding this objection, the novelty of the product of claim 11 of the main request must be considered vis-à-vis the disclosure of document (1) and, at the oral proceedings the Appellant did not object to discussing the question of the novelty of the claimed subject matter.

4.2 Document (1) describes in column 4, Example 2 a specific soy bean emulsion containing 0.2 kg to 2.4 kg of egg phosphatides and 20 kg soy bean oil corresponding to the ratios of 0.01 and 0.12. It is, however, also necessary to take into account that more specifically, document (1) discloses in column 2, lines 50 to 55 **one** preferred **range** of the concentration of the fat between 5 and 50 percent by weight and **one** preferred **range** of 0.05 or 3 percent by weight of egg phosphatides suitable for emulsifying the fat in the aqueous phase.

Thus, by combination of the four values, this prior art disclosure unambiguously discloses specific ranges of ratios of percent by weight of emulsifier to fat, among which a range between 0.001 and 0.01, which is clearly comprised within the claimed range of less than 0.04 and takes away the novelty of claim 1. It is particularly to be noted that the teaching of the patent in suit also covers compositions where the fat comprises by weight 50 percent of the emulsion and that by the wording of claim 1 "the weight ratio ... is less

than ...." protection is sought for a so-called open-ended claim intended not to exclude the lower values of weight ratios.

4.3 Since the claim of the main request for which the broadest protection is sought fails to meet at least one of the requirements for patentability under the European Patent Convention, the Appellant's main request has to be rejected.

5. The auxiliary request comprises only claims relating to the use of a lipid emulsion in the manufacture of a medicament for the intravenous infusion of lipids into a patient. These claims include the functional feature that the use of the emulsion avoids hyperlipidaemia.

5.1 It was undisputed by the parties at the oral proceedings that document (3) relating to "alteration of lipoprotein profile during total parenteral nutrition with Intralipid 10%" and discussing the problem of hyperlipidaemia represents the closest prior art.

The document is based on studies of lipid profiles of a plurality of patients in a stable condition, none of which had diabetes, hepatitic or renal disorders, or hyperlipidaemia. The subjects consisted of eight patients between the age of 48 and 78 suffering from pancreatic head cancer, colon cancer, esophageal cancer, gastric cancer, rectal cancer and gastric ulcer. Total cholesterol, triglyceride and phospholipid content in low density lipoprotein (LDL), high density lipoprotein (HDL), and very low density lipoprotein (VLDL) were determined enzymatically after density gradient ultracentrifugation. As one of the results it is indicated that the rise of phospholipid and cholesterol, but not triglyceride, contributed to the hyperlipidaemia during intravenous administration of

Intralipid 10% (see page 622, "*Materials and Methods*" and "*Results*", third paragraph). Under the point "*Discussion*" starting on page 624, reference is made to several other studies. It is inter alia indicated on page 625, right-hand column, that the phospholipids of Intralipid formed a single-bilayer vesicle, which rapidly extracted free cholesterol from tissues and developed abnormal LDL, lipoprotein-X. The authors of document (3) then confirm that increased LDL with intravenous fat emulsion appears to be identical to lipoprotein-X. Having regard to the fact that the Intralipid 10% fat emulsion has a ratio of phospholipids to fat of 12:100 (0.12), they then suggest that in order to avoid pronounced increases in the levels of LDL, phospholipid and cholesterol in serum, the ratio between phospholipids and fat should be reduced from 12:100. Subsequently reference is made to pending studies on lipid metabolism during administration of Intralipid 20%, which has a ratio of phospholipids to fat of 6:100 (0.06). It is furthermore indicated that hyperlipidaemia is generally assumed to have harmful features. According to a final statement, further investigations are necessary to clarify the role of hyperlipidaemia with intravenous fat emulsions and the extent of deleterious effects related thereto.

5.2 In the light of the said prior art, the problem underlying the patent in suit can be seen in further reducing the risk of hyperlipidaemia in patients when using lipid emulsion systems in the production of a medicament for intravenous infusion.

The problem is solved by the use of a lipid emulsion set out in claim 1. Having regard to the worked examples of the patent in suit, which illustrate on the basis of the evaluation of a number of kinetic parameters indicative of metabolism of lipid emulsions

as used in the patent in suit an enhanced metabolism when lowering the phospholipid to oil ratio to 0.04, the Board is satisfied that the problem has indeed been solved.

6. After examining the cited prior art, the Board has reached the conclusion that the use of the emulsion according to claim 1 is not disclosed therein and that the claimed subject-matter of the auxiliary request is therefore novel. This was not disputed by the Respondent.

7. It therefore remains for the Board to decide whether or not the said solution would, in view of the citations, have been obvious to a person skilled in the art faced with the problem defined above.

7.1 In order to demonstrate that there was no pointer to the claimed solution, the Appellant has sought to construe a substantial difference between the findings of the authors of document (3) and the inventors of the patent in suit as regards the mechanism of hyperlipidaemia induced by the administration of lipid emulsions.

7.2 Although it appears credible that in the skilled person's mind the so-called lipoprotein-X problem no longer existed when using the emulsion with a phospholipid to fat/ratio of 0.06, the 20% Intralipid solution referred to in document (3), and that this emulsion became clinically accepted, the Board cannot follow the Appellant's argumentation that there was no motivation in continuing to search for better tolerance of lipid emulsions to be administered to patients. In this respect, it is clearly necessary to take into account that according to clinical practice not only elder patients suffering for example from certain types of cancer of the digestive system as mentioned in

document (3) are treated with lipid emulsion systems for parenteral nutrition, but, depending on the circumstances each group of patients in need, including neonates, will receive intravenous fat infusions for nutritional support.

7.3 Document (5), cited in the form of an abstract, relates to studies on the tolerance of premature infants to 10% and 20% LCT (long chain triglyceride) fat emulsions having a phospholipid(PL)/triglyceride(TG) ratio of 0.12 and 0.06 respectively. The whole content of this prior art provides evidence that even by switching from the 10% solution with the 0.12 PL/TG ratio to the 20% solution with the 0.06 PL/TG ratio, the skilled person does not regard the fat infusion as being absolute satisfactory and completely harmless for premature infants in need. Document (5) clearly indicates that excellent tolerance was shown by premature infants only in the case of slow infusion rates, but it is proposed that more concern should be given to the amount of PL concomitantly infused and that emulsions with low PL/TG seem preferable. Moreover, document (5) as well as document (4) (see tables of enzymatically determined triglyceride "TG" levels in both abstracts) provide evidence that before the priority date of the patent in suit a person skilled in the art was aware of the fact that levels of the triglycerides in plasma are proportional to the phospholipid content of the emulsion to be infused. Both tables show lower TG levels when infusing the "20% solution" with a PL/TG ratio of 0.06 instead of the "10% solution" with a PL/TG ratio of 0.12. Accordingly, the prior art shows the same trend of triglyceride levels as Figure 1 of the patent in suit.

7.4 Once the skilled person's attention has been drawn to the possibility of influencing fat emulsion tolerance problems by lowering phospholipid/triglyceride ratios, and there is a motivation to further reduce the hyperlipidaemia risk for premature infants, a particular group of patients in need, in the present case the only question remains whether, in accordance with the Appellant's argumentation, there are strong technical reasons not to try in clinical practice to infuse lipid emulsions having a lower phospholipid/triglyceride ratio of 0.06. Document (33), however, provides proof that an Intralipid emulsion containing essentially 30% (wt/wt) of soybean oil emulsified in 1.2% (wt/wt) egg lecithin has been clinically used for parenteral nutrition (see *Lipids* page 920, under **Materials and Methods**). In these circumstances, the Appellant's argumentation that the experts in the 1980's were so cautious in reducing from a 0.12 ratio and did regard 0.06 as the lowest limit to aim for must fail.

7.5 From the preceding paragraphs it follows that on the priority date of the patent in suit a person skilled in the art knowing the disclosures in documents (3) to (5) would have tried to use lipid emulsions having a weight ratio of emulsifier to glyceride oil equal to 0.04 as known from document (33) in the manufacture of a medicament for intravenous infusion to avoid hyperlipidaemia in premature infants and would thus have tried to further reduce the risk of hyperlipidaemia described in document (3).

7.6 Since the prior art clearly shows a pointer towards using the low PL/TG ratios according to the claimed solution, and since the prior art also shows at least the trend that the triglyceride level decreases when lowering the said PL/TG ratio, the Appellant's finding

that a reduction in phospholipid levels from a 0.07 ratio to a 0.04 ratio provides much more than the expected proportional effect on triglyceride metabolism as compared with a reduction from 0.12 to 0.07, and thus, even by regarding the said effect as a surprising one, can only be regarded as a quantitative bonus effect, which itself cannot establish inventiveness of an obvious solution to the problem defined above.

7.7 In these circumstances, it is therefore also not decisive whether hyperlipidaemia caused by infusion of lipid emulsions on the one hand in adults and on the other in neonates follows the same or a different mechanism. Taking into account the first situation, the skilled person only had to go further in line with the teaching of document (3), and in the second situation the skilled person additionally found the explanation of an effect by using the known compound in an obvious way. The mere explanation of such an effect, even if it turns out, as already set out above, to be an unexpected and surprising effect, cannot confer the required inventive step on an obvious solution.

The subject-matter of claim 1 of the auxiliary request accordingly lacks inventive step.

Dependent claims 2 to 10, which relate to preferred embodiments, must fall with claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P.Martorana P. A. M. Lançon