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D E C I S I O N
of 17 May 2001

Case Number: T 1067/96 - 3.3.2
Application Number: 88907808.5
Publication Number: 0331755
IPC: A61K 9/107
Language of the proceedings: EN

Title of invention:

Medicine-containing fat emulsion of the type prepared immediately before use and process for preparing medicine-containing fat elumсион

Patentee:

TEIJIN LIMITED

Opponents:

Hexal-Pharma GmbH & Co. KG
B. Braun Melsungen Aktiengesellschaft
Pharmacia Aktiebolag
Schwarz Pharma AG

Headword:

Extemporaneous Kit/TEIJIN

Relevant legal provisions:

EPC Art. 56, 84, 111(1), 123(2), (3)
EPC R. 57(a)

Keyword:

"Novelty: yes; not contested"
"Main request, auxiliary requests I to V"
"Inventive step: no"
"Auxiliary request VI"
"Sufficiency of disclosure: yes"
"Inventive step: yes"
"Contradiction between the description and the amended claims: remittal to the first instance for further prosecution"
"Examination of compliance with Article 84 EPC"

Decisions cited:

T 0014/83

Catchword:

-



Case Number: T 1067/96

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 May 2001

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 28 October 1996
rejecting the opposition filed against European
patent No. 0 331 755 pursuant to Article 102(2)
EPC.

Composition of the Board:

Chairman: J. Riolo
Members: G. F. E. Rampold
 S. U. Hoffmann

Summary of Facts and Submissions

- I. The respondent is proprietor of European patent No. 0 331 755 which was granted with 9 claims on the basis of European patent application No. 88 907 808.5; claim 1 of the patent as granted reads as follows:

"An extemporaneous kit of pharmaceutical substance-containing fat emulsion which comprises

- (1) a fat emulsion, wherein the fat emulsion is composed of an oil component and an emulsifier, which is at least one selected from phospholipids, lecithin, and hydrogenated lecithin, and
- (2) a pharmaceutical substance composition containing a pharmaceutical substance wherein the pharmaceutical substance is at least one selected from steroids, carcinostatics, prostaglandins, fat-soluble vitamins, anti-inflammatories, cardiotonics, antiarrhythmics, vasodilators, and calcium antagonists and either
 - (a) at least one solvent selected from liquid polyalkylene glycols, liquid alkylethanolamines and liquid polyhydric alcohols, or
 - (b) a saccharide and/or an amino acid as an excipient."

Dependent claims 2 to 8 relate to specific elaborations of the kit according to claim 1.

Claim 9 relates to a method for preparation of pharmaceutical-substance containing fat emulsions by mixing the components (1) and (2) as specified in claim 1.

II. Notices of opposition to the grant of the patent were originally filed by opponent (appellant) 01, opponent (appellant) 02, opponent 03 (party to the appeal proceedings as of right under Article 107 EPC) and opponent (appellant) 04. The opponents requested revocation of the patent in its entirety pursuant to Article 100(a) EPC on the ground of lack of inventive step and pursuant to Article 100(b) EPC on the ground of insufficiency of disclosure. Of the numerous documents cited during the first-instance opposition proceedings, the following remain relevant to the present decision:

- (1) J. P. Davignon *et al*, "Formulation of three nitrosoureas for Intravenous use", published in Cancer Chemotherapy Reports, part 3, Vol. 4, No. 3, 1973, pages 7-11
- (3) K. Thoma *et al*, "Einfluß hydrophiler Lösungsmittel auf die Instabilität von Arzneistoffen", published in Pharm. Ind. 48, No. 2, 1986, pp 179-183
- (5) A. A. El-Sayed *et al*. "Solubilization and stabilization of an investigational antineoplastic drug (NSC No. 27 82 14) in an intravenous formulation using an emulsion vehicle", published in Intern. J. of Pharmaceutics, 13, 1983, pp 303-312
- (6) Rote Liste 1987, Editio Cantor, Aulendorf/Württ., 74. Sera u. Impfstoffe, 74 003 Endobulin®
- (8) EP-A- 0 202 837
- (9) C. L. Fortner *et al*, "Fat emulsion vehicle for intravenous administration of an aqueous insoluble drug", published in Am. J. of Hospital Pharmacy, Vol. 32, June 1975, pp 582-584

(11) L. Rey, "Fundamental aspects of lyophilization", published in *Aspects Théoriques et Industriels de la Lyophilisation*, Ed. by L. Rey, Hermann Paris, 1964 , pages 23-43

III. After considering the grounds for opposition, the opposition division rejected the oppositions under Article 102(2) EPC at the conclusion of the oral proceedings.

In its decision, the opposition held that the facts, evidence and arguments submitted by the opponents in relation to the ground of opposition laid down in Article 100(b) did not justify calling into question the sufficiency of disclosure of the invention as required by Article 83 EPC.

In the opposition division's opinion, the opponents' objections to the patentability were based on *ex post facto* analysis of the cited state of the art and hindsight, since the invention in the sensitive field of pharmacy could not be reduced to a simple matter of trial and error to find solvents suitable for replacing those disclosed in the state of the art so as to provide intravenously injectable fat emulsions free of bubbles and ready for application.

IV. Opponents (appellants) 01, 02 and 04 filed notices of appeal against the decision of the opposition division and requested oral proceedings. On 17 May 2001, oral proceedings took place before the board in the presence of representatives of appellants 01 and 04; duly summoned appellant 02 had informed the board in advance that it did not wish to attend the hearing.

V. During the hearings before the board, the respondent, while maintaining the main request, which was the set of claims 1 to 9 as granted (see paragraph I above), filed auxiliary requests I to VI:

- (A) The set of claims in auxiliary request I corresponds to claims 1 to 9 of the above main request, with the sole exception that the reference under (2)(a) in claims 1 and 9 to **"liquid alkylethanolamines"** as the solvent for the pharmaceutical substance has been amended so as to read **"liquid diethanolamine, liquid triethanolamine"**.
- (B) The set of claims in auxiliary request II corresponds to claims 1 to 9 of the above main request, with the sole exception that **"liquid alkylethanolamines"** have been deleted from the options of the solvents for the pharmaceutical substance specified in claims 1 and 9.
- (C) The set of claims in auxiliary request III corresponds to claims 1 to 9 of the above main request, with the sole exception that the definition of component (1) in claims 1 and 9 has been amended so as to read: "a fat emulsion, wherein the fat emulsion is composed of an oil component, an emulsifier, which is at least one selected from phospholipids, lecithin, and hydrogenated lecithin, and water, and <.....>".
- (D) The set of claims in auxiliary request IV corresponds to claims 1 to 9 of the above main request, with the sole exception that component (2) in claims 1 and 9 has been further specified so as to read: "a pharmaceutical substance

composition containing a *storage instable, shock sensitive or heat sensitive* pharmaceutical substance wherein the pharmaceutical substance is at least one selected from <.....>.

(E) The set of claims in auxiliary request V corresponds to claims 1 to 9 of the above main request, with the sole exception that "*carcinostatics*" have been deleted from the list of pharmaceutical substances referred to under (2) in claims 1 and 9.

(F) Claim 1 of auxiliary request VI reads as follows:

"An extemporaneous kit of pharmaceutical substance-containing fat emulsion which comprises

- (1) a fat emulsion, wherein the fat emulsion is composed of an oil component and an emulsifier, which is at least one selected from phospholipids, lecithin, and hydrogenated lecithin, and
- (2) a pharmaceutical substance composition containing a pharmaceutical substance wherein the pharmaceutical substance is at least one selected from steroids, carcinostatics, prostaglandins, fat-soluble vitamins, anti-inflammatories, cardiotonics, antiarrythmics, vasodilators, and calcium antagonists and a saccharide and/or an amino acid as an excipient, and not at least one solvent selected from liquid polyalkylene glycols, liquid alkylethanolamines and liquid polyhydric alcohols."

Dependent claims 2 to 6 are directed to specific elaborations of the kit according to claim 1.

Claim 7 relates to a method for preparing pharmaceutical-containing fat emulsions by mixing the components (1) and (2) as specified in claim 1.

VI. The appellants criticised in their statements setting out the grounds for appeal and during oral proceedings the interpretation placed by the opposition division on the results of their experimental evidence submitted during the first-instance opposition proceedings, and similarly the results of the experimental counter-evidence submitted by the appellant. Further, the appellants substantially maintained the objections they had already raised before the opposition division that the disclosure of the claimed invention was insufficient and that the claimed subject-matter in the patent in suit did not involve an inventive step in the light of the disclosures of the citations referred to in this decision.

VII. The respondent submitted in essence that the subject-matter of the patent in suit was a two-component kit which enabled in a surprisingly simple and advantageous manner the extemporaneous preparation and immediate administration of a broad variety of pharmaceutical substances. One of the components was a fat emulsion which contained a specified emulsifier; the other component was the pharmaceutical substance together with a particular solvent or excipient specified in the claims of the contested patent. None of the documents cited in the first-instance opposition and the subsequent appeal proceedings disclosed such a two-component kit. According to the respondent, the opposition division was entirely correct in its opinion that the appellants' objections to lack of inventive

step were based on hindsight analysis of the cited state of the art and that none of the cited documents made obvious to a person skilled in the art the two-component kit as claimed in the patent in suit.

VIII. The appellants requested that the decision under appeal be set aside and that the European patent No.0 331 755 be revoked.

The respondent requested that the appeal be dismissed and that the patent be maintained unamended or auxiliarily in amended form on the basis of the first to sixth auxiliary request filed in their numerical order during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.
2. As none of the opponents invoked in its notice of opposition lack of novelty as a ground for opposition under Article 100(a) EPC, novelty was not at issue in the present case. Since, moreover, none of the citations available to the board from the proceedings before the EPO gives cause to call into question the novelty of the claimed subject-matter in the patent in suit, no further discussion of this item appears to be necessary or appropriate.
3. For an objective assessment of inventive step, it is established EPO practice to determine the prior art closest to the invention. In the present case a decision has to be made as to whether the state of the art according to (5) or (9), on the one hand, which has been acknowledged in the introductory part of the

description of the patent in suit, or the prior art of (8), on the other, comes closer to the claimed subject-matter in the main request and any of the auxiliary requests I to V.

- 3.1 El-Sayed et al describe in (5) the use of parenteral fat emulsions for an extemporaneous preparation of an intravenous formulation of the poorly water-soluble and unstable antineoplastic drug NSC No. 27 82 14, ie carbamic acid (1-methylethyl)-[5-(3,4-dichlorophenyl)-2,3-dihydro-1H-pyrrolizine-6,7-diyl] bis(methylene) ester. According to the disclosure in (5), the method for preparing the above-mentioned intravenous formulation involves the steps of first dissolving the active drug in a dimethylacetamide-cremophor® (polyethoxylated castor oil) mixture to provide a solution of the drug, followed by incorporating said solution into a commercial fat emulsion (Intralipid-10%). This results in a suitable parenteral formulation in which the drug was approximately 100-fold more stable than in simple aqueous solution.
- 3.2 Similarly, Fortner et al disclose in (9) a method of preparing an intravenously injectable fat emulsion containing the sparingly water-soluble carcinostatic agent methyl CCNU, ie 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (NSC 95441), as the active agent. The method disclosed in (9) likewise comprises the steps of first dissolving the methyl CCNU in absolute ethanol, followed by mixing the alcoholic solution of methyl CCNU into the fat emulsion used as the vehicle or carrier (Intralipid-10%) to provide the desired parenteral formulation.
- 3.3 In the context of the prior art disclosed in (5) and (9), the description of the patent in suit states at lines 1 to 5 on page 5 that, "when an anhydrous alcohol or a dimethylacetamide-cremophor® mixture is mixed

with a fat emulsion in order to prepare a fat emulsion containing a sufficiently needed amount of a pharmaceutical substance for treatment, bubbles are formed in the emulsion, and the use of such pharmaceutical substance-containing fat emulsion as an injection is not desirable from a safety point of view".

However, contrary to what the respondent apparently sought to suggest by the reference in the patent in suit to the above-mentioned drawbacks allegedly associated with the prior art according to (5) and (9), the state of the art relating to extemporaneous preparations of pharmaceutical substance-containing fat emulsions for intravenous application was, at the priority date of the patent in suit, not limited to the use of either an anhydrous alcohol [see (9)] or a dimethylacetamide-cremophor® mixture [see (5)] as the only practicable solvents for dissolving the respective pharmaceutical substance prior to its incorporation into the fat emulsion. It rather included various other options of suitable solvents for this purpose.

- 3.4 In particular, citation (8) discloses further extemporaneous preparations based on a fat emulsion suitable for safe, parenteral administration of polyene antibiotics, for example, amphotericin B. The preparation of the polyene antibiotic-containing fat emulsion disclosed in (8) involves the steps of dissolving the desired antibiotic in an appropriate solvent to provide a solution of the drug, followed by incorporating the solution thereby obtained into the desired oil-in-water emulsion (see especially page 4, lines 1 to 8). The group of appropriate solvents, which are explicitly disclosed in (8) (see especially page 4, lines 8 to 13) as suitable for dissolving the drug comprises dimethylacetamide (DMA), pyridine,

dimethylformamide (DMF), dimethylsuloxide (DMSO), polyethylene glycol (PEG) and diethylcarbonate. Consequently, the group of solvents in (8) already includes a certain class of solvents, namely polyethylene glycols, which are likewise claimed in the patent in suit as particularly suitable solvents for providing the pharmaceutical substance composition, forming the component (2) of the claimed extemporaneous kit (see especially claim 1; page 7, lines 33 to 35). Similarly, claim 9 refers to liquid polyalkylene glycols as suitable solvents for the preparation of the pharmaceutical substance-containing fat emulsion by mixing the fat emulsion (1) and the solution of the active substance (2).

3.5 The board cannot accept the respondent's submission during the oral proceedings that the state of the art according to (8) did not refer to an extemporaneous kit within the meaning of claim 1 of the patent in suit. Thus, the first alternative [hereinafter referred to as alternative (a)] of the extemporaneous kit of a pharmaceutical substance-containing fat emulsion as defined in claim 1 of the patent in suit merely requires that this kit comprises the following two components:

- (1) a fat emulsion, wherein the fat emulsion is composed of an oil component and an emulsifier, which is at least one selected from phospholipids, lecithin, and hydrogenated lecithin, and
- (2) a pharmaceutical substance composition containing a pharmaceutical substance selected from a broad variety of different groups of pharmacologically active substances and at least one solvent selected from liquid polyalkylene glycols, liquid alkylethanolamines and liquid polyhydric alcohols.

The requirements set forth above are clearly met in the prior art according to (8). Thus, the extemporaneous formulation of the polyene antibiotic-containing fat emulsion disclosed in (8) likewise requires the **separate provision** of the two following components:

- (1) a fat emulsion, for example, Intralipid-20% which is a publicly available parenteral soybean oil-in-water emulsion containing egg lecithin as the emulsifier (see especially page 3, lines 28 to 35) and
- (2) a pharmaceutical substance composition containing a polyene antibiotic as the pharmaceutical substance dissolved in an appropriate solvent, eg a liquid polyethylene glycol (see especially page 4, lines 1 to 15).

The polyene antibiotic-containing fat emulsion is prepared in (8) by mixing the fat emulsion (1) and the solution of the drug (2), as is the case with the preparation of the pharmaceutical substance-containing fat emulsion according to the claimed invention (see claim 9).

- 3.6 From the foregoing observations it is clear that the only difference between the claimed alternative (a) in the patent in suit and the prior art of (8) resides in the selection of the group of pharmaceutical substances used for incorporation into the fat emulsion. These are extremely broadly defined in claim 1 as granted and include any drug, irrespective of its particular chemical structure, selected from steroids, carcinostatics, prostaglandins, fat-soluble vitamins,

anti-inflammatories, cardiotonics, antiarrythmics, vasodilators, and calcium antagonists (see especially patent specification page 7, line 44, to page 8, line 22), but do not include antibiotics.

3.7 According to the established jurisprudence of the Boards of Appeal (see "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition 1998, D. 3.1, pages 111 ff), the closest prior art for the purpose of objectively assessing inventive step is generally that which corresponds to the same or a similar use as the claimed invention and, at the same time, requires the minimum of structural and functional modifications to arrive at the claimed subject-matter. On the basis of the criteria set forth above, the state of the art according to citation (8) comes, in the board's judgment, closer to the extemporaneous kit according to claim 1 than that of citations (5) or (9), because (8) teaches not only the use of **the same fat emulsion**, forming component (1) of the claimed kit, but also the use of partially **the same solvents** as the patent in suit for providing the solution of the active drug, ie component (2) of the kit, to be incorporated into the fat emulsion (1) by mixing components (1) and (2).

It is clearly derivable from the disclosure in the contested patent and the respondent's submissions that the essence of the claimed invention lies in the choice of the particular solvents specified in claim 1 rather than in the selection of particular pharmaceutical substances used for the claimed extemporaneous preparation. In this context, it seems worthwhile to note that in the application as filed and published

antibiotics are explicitly included in the list of pharmaceutical substances suitable for incorporation into the fat emulsion of the extemporaneous kit according to the claimed invention (see eg claim 6).

4. Thus, given the disclosure of (8) as representing the closest state of the art, the technical problem which the claimed invention in the main request and any of the auxiliary requests I to V sets out to solve may therefore be seen as that of providing extemporaneous formulations, using a fat emulsion as a vehicle or carrier, for the safe, parenteral administration of a variety of different classes of pharmaceutical substances insoluble or only poorly soluble in water, other than antibiotics. The patent in suit suggests solving this problem by substituting, for the antibiotics used in citation (8), various other classes of pharmaceutical substances specified in more detail in claim 1 of the patent in suit.

4.1 The appellants [see the experimental report filed on 21 August 1995 by opponent 01 with letter dated 17 August 1995 and the experimental reports of Prof. Wagner filed by opponent 01 on 9 August 1996 with faxed letter of the same date and on 30 September 1996 with letter dated 19 September 1996, respectively] provided in the course of the first-instance opposition proceedings experimental evidence suggesting that a fat emulsion prepared by mixing the components (1) and (2) of an extemporaneous kit in accordance with the claimed invention (active substance: prostaglandin E1; solvent: triethanolamine) was unsuitable for injection purposes due to formation of foam and bubbles in the emulsion. This was contradicted by the results in the Takahashi declaration filed on 6 September 1996 with the respondent's faxed letter of the same date. In the said

declaration it is reported that repetition of Example 3 of the patent in suit led to a bubble-free emulsion suitable in clinical use for safe parenteral administration of the medicament.

- 4.2 As is discussed in more detail below (see especially points 7 and 13), the solvent triethanolamine, which was used by the parties for carrying out the experiments referred to in point 4.1 above, falls outside the ambit of the claims of the patent as granted and the application as filed. Consequently, the contradicting experimental results reported by the parties in their experimental reports can have no further significance to the question as to whether or not the technical problem posed has been solved.

The appellants failed to submit evidence substantiating the allegation that the problem defined in point 4 above could not successfully be solved by using any of the solvents covered by the claims. On the basis of the results reported in the patent in suit (see especially Examples 1, 2, 7 and 8), the disclosure in the state of the art according to citation (8), and in the absence of any evidence to the contrary, the board is satisfied that the problem is plausibly solved.

5. It still remains to be determined whether the requirement of inventive step is met by the claimed subject-matter in the patent in suit.

Main request

- 5.1 Persons skilled in the art would have been aware from the state of the art according to citation (8) that polyethylene glycols are appropriate, non-toxic solvents, which enable the poorly water-soluble and unstable antibiotics used in (8) to become incorporated into an oil-in-water emulsion as a stable microemulsion

and which are, accordingly, suitable for creating the desired pharmaceutical substance-containing fat emulsions. They would, moreover, have learned from (3) that polyethylene glycols are a particularly suitable, conventionally used class of solvents with a stabilizing effect for a broad variety of strikingly different classes of pharmaceutical substances, such as analgesics and anti-inflammatories, eg acetyl salicylic acid, indomethacin; antihypertensives (steroids), eg reserpine; cardiotonics or antiarrhythmics, eg nifedipine, nitroglycerin; hypnotics and sedatives, eg amobarbital, phenobarbital, pentobarbital, pentobarbital; tranquillizers, eg chlorodiazepoxide, diazepam, nitrazepam; vitamins; antimykotika, eg cyclopirox; or antihistamines, eg antazoline (see (3) especially Tables 1 to 4).

5.2 Consequently, in the present case the notional skilled person was provided with a clear hint from the prior art pointing him in the direction of the claimed solution. Once it became obvious from the cited state of the art that polyethylene glycols are suitable solvents for the incorporation of the desired pharmaceutical substance into a parenteral fat emulsion of an extemporaneous kit, comprising said fat emulsion as the carrier or vehicle and said substance as the active drug, determination of other classes of pharmaceutical substances, which are likewise suitable for use as the active drugs in an extemporaneous kit of this type, and their substitution for the antibiotics used in (8) was then merely a matter of routine operation for the skilled practitioner. In the light of the disclosure in (8) and (3) the person skilled in the art had plausible reasons to expect the problem posed to be successfully solvable by using polyethylene glycols as the solvents for the desired pharmaceutical substance. It was then only necessary to confirm experimentally that the highly probable result was in

fact obtained. The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious.

5.3 For all these reasons, the board concludes that both independent claims 1 and 9 include subject-matter which is obviously derivable from a combination of the teachings of citations (8) and (3) and that both claims are therefore devoid of inventive step. The main request is accordingly not acceptable under the terms of Article 52(1) in conjunction with Article 56 EPC.

5.4 In point 3.7 above the board has given detailed reasons why it considers citation (8) to represent the closest state of the art. However, even if the prior art of either (5) or (9) was taken as starting point for the assessment of the inventive step and the problem to be solved was accordingly determined as that of overcoming the disadvantages allegedly associated with the solvents used in (5) or (9) for the incorporation of the active drug into the fat emulsion vehicle of the claimed extemporaneous kit (see for more details point 3.3 above), the outcome of the decision would be the same for the following reasons. Citation (8) contains no indication whatever that, when using any of the solvents disclosed in (8), the disadvantages allegedly encountered in prior art according to (5) or (9) might also occur.

Consequently, for a skilled person, knowing from (8) the usefulness of polyethylene glycols for incorporating the desired antibiotic substance into the fat emulsion and from (3) the broad applicability of polyethylene glycols as stabilizing solvents for a great variety of pharmaceutically active substances, it would thus have been similarly obvious to try combining the teaching of (8) with that of (3) to solve the particular problem defined in the foregoing paragraph.

6. In these circumstances, there is no need for the board to decide whether or not insufficiency of disclosure, which was invoked in the notice of opposition as a second ground for opposition under Article 100(b) EPC, would prejudice the maintenance of the opposed patent.

Auxiliary request I

7. The groups of solvents specified under 2(a) in claims 1 and 9 as granted include polyalkylene glycols, liquid alkylethanolamines and liquid polyhydric alcohols, but do not cover liquid diethanolamine and liquid triethanolamine which have been introduced into claims 1 and 9 of auxiliary request I to replace alkylethanolamines as possible solvents (see paragraph V(A) above). From a chemical and structural point of view both solvents diethanolamine and triethanolamine clearly do not fall under the generically defined group of liquid alkylethanolamines in claims 1 and 9 as granted. Consequently, the board concurs with the appellants' objection that the proposed amendment to claims 1 and 9 of auxiliary request I extends the scope of protection beyond that conferred by the claims as granted and is therefore not acceptable under the terms of Article 123(3) EPC.

- 7.1 However, irrespective of the decision on the issue of the scope of protection conferred by the amended claims, the objections in points 5.1 to 5.4 to the patentability of the claims in the main request apply equally to the claims in the first auxiliary request, because the amended claims still include polyethylene glycols.

Auxiliary requests II to V

8. These requests are, as regards inventive step, no more allowable than the main request, for the same reason.

- 8.1 The amendments in claims 1 and 9 of auxiliary requests II (see paragraph V(B) above) and III (see paragraph V(C) above) have been introduced to deal with the appellants' objections to sufficiency of disclosure. Since both requests are not acceptable on the ground of lack of inventive step, insufficiency of disclosure is not at issue in both these requests.
- 8.2 Citation (5) suggests clearly to a person skilled in the art that the extemporaneous preparation disclosed in the cited document is particularly suitable for storage-unstable pharmaceutical substances to provide a parenteral fat emulsion in which the active drug is approximately 100-fold more stable than in a simple aqueous solution. The further specification of the pharmaceutical substance in auxiliary request IV (see paragraph V(C) above) is thus clearly obvious in the light of the cited state of the art and, therefore, cannot contribute to the acknowledgment of an inventive step either.
- 8.3 According to auxiliary request V (see paragraph V(D) above) it is suggested that carcinostatics be deleted from the list of pharmaceutical substances to be incorporated into the fat emulsion. Since the arguments and conclusion in points 5.1 to 5.4 above, which led to the decision that the claimed invention is devoid of inventive step, do not focus on the particular pharmaceutical substance or class of pharmaceutical substances used for incorporation into the fat emulsion, the proposed amendment is unable to change the adverse decision.

Auxiliary request VI

9. As is apparent from paragraph V(F) above, claims 1 to 7 of auxiliary request VI have been limited to that particular embodiment of the claimed invention wherein

the pharmaceutical substance composition, which forms component (2) of the claimed extemporaneous kit, contains the desired pharmaceutical substance in combination with a saccharide and/or an amino acid as an excipient for the substance.

9.1 This limitation has already been proposed as auxiliary request IV in the proceedings before the opposition division. It is to be seen as a *bona fide* attempt by the respondent to overcome the appellants' objections to the patentability of the claimed subject-matter in the patent in suit on the ground of lack of inventive step and to proceed with an amended version of the claims which possibly complies with the requirements of the Convention. The proposed amendment can thus fairly be said to be occasioned by a ground for opposition specified in Article 100(a) EPC and is accordingly admissible under the terms of Rule 57a EPC.

9.2 The wording, which was proposed during the oral proceedings before the board for the definition of component (2) of the kit in independent claims 1 and 7 ["a pharmaceutical substance composition containing a pharmaceutical substance wherein the pharmaceutical substance is at least one selected from <.....> and a saccharide and/or an amino acid as an excipient, and not at least one solvent selected from liquid polyalkylene glycols, liquid alkylethanolamines and liquid polyhydric alcohols"], makes it unequivocally clear that all claims in auxiliary request VI have been strictly limited to the particular alternative (b) only of the two alternatives (a) or (b), which were originally available for component (2), ie the pharmaceutical composition, of the extemporaneous kit in the application as filed and the patent as granted. The amended claims accordingly comply with the provisions of Article 123(2) and (3) EPC.

10. Apart from the fact that, in the board's opinion, the person skilled in the art would understand the technical term "fat emulsion" in the present claims as necessarily including water as the aqueous phase of such an emulsion, it has been consistent case law of the boards of appeal since at least decision T 14/83 (OJ EPO 1984, 105) that sufficiency of disclosure within the meaning of Article 83 EPC must be assessed on the basis of the application as a whole, including the description and the claims, and not of the claims alone. The description discloses repeatedly in a clear and unequivocal manner that the term "fat emulsion" in the claims stands for an emulsion having very fine particles of fat homogeneously dispersed in water (see eg page 5, lines 32 to 35; page 6, lines 16 to 18; Examples 1 to 8).
- 10.1 Consequently, the appellants' objection under Article 83 EPC cannot be accepted that, in the absence of an explicit reference in the claims to water being present as the aqueous phase in the fat emulsion, the disclosure of the invention is insufficient. This objection certainly provides no basis for an opposition under Article 100(b) EPC.
- 10.2 Other objections, which were the raised under Articles 100(b) and 83 EPC in the course of the first-instance opposition proceedings and which were maintained in the subsequent appeal proceedings, related only to that embodiment of the claimed invention, wherein the pharmaceutical substance composition forming component (2) of the claimed extemporaneous kit contains the desired pharmaceutical substance dissolved in least one solvent selected from those specified in claim 1, ie alternative (a). In view of the limitation of the claims, these objections no longer apply to the claimed subject-matter in auxiliary request VI.

11. The alternatives (a) and (b) relate to different realisations of the claimed invention which are, in the board's judgment, technically quite unrelated with respect to each other. The limitation of the scope of the claims to the subject-matter of auxiliary request VI and, more specifically, the exclusion of the alternative (a), has therefore drastically changed the essence of the claimed invention. For this reason, the board considers that the inventive step of the claimed subject-matter is now to be assessed in the light of citation (9) as representing the closest state of the art (see for more details 9.2 above), because carcinostatics are likewise mentioned in present claims 1 and 9 as suitable pharmaceutical substances for the claimed extemporaneous kit in the patent in suit.

11.1 Starting from the disclosure of (9) as the closest state of the art, the technical problem the invention sets out to solve may be seen as that of providing a suitable alternative to the extemporaneous preparation disclosed in (9). According to claim 1 it is suggested that this problem be solved by providing component (2) of the kit for incorporation into the fat emulsion (component 1) in the form of a combination of the desired pharmaceutical substance with a saccharide and/or an amino acid as an excipient for the substance.

On the basis of the results reported in Examples 5 and 6 of the contested patent and in the absence of any evidence to the contrary, the board is satisfied that the stated technical problem has been plausibly solved. This was anyway not contested by the appellants for alternative (b).

12. The appellants failed to provide any evidence in the state of the art which would have promised or suggested to a person skilled in the art that the pharmaceutical substance could appropriately be incorporated into the fat emulsion of an extemporaneous kit by using a saccharide and/or an amino acid as an excipient for the substance. In the extemporaneous kits described in Examples 5 and 6 the pharmaceutical substance is provided in combination with the excipient, ie glycine (Example 5) or mannitol (Example 6), in the form of a lyophilized, powdery composition. The person skilled in the art, in order to arrive at the present invention, had therefore to depart from the conventional way of using a solution of the pharmaceutical substance in an appropriate solvent for mixing with the fat emulsion of the extemporaneous kit [see eg citations (9), (5), (8)] and to go in the completely different direction of using a dry powdery composition.

12.1 In the context of alternative (b) of the claimed extemporaneous kit, the appellants essentially referred to the prior art of citations (1), (11) and (6). However none of these citations provided the skilled person with a technical teaching pointing him in the direction of the proposed solution to the present technical problem.

Citation (1) refers, *inter alia*, to a product which was supplied in the form of the following components: (a) BCNU, 100 mg and mannitol, 400 mg/vial (b) absolute ethanol 3 ml/vial. This shows at least two clear differences from the claimed invention, namely no fat emulsion is present as the vehicle and the active drug is dissolved in ethanol.

Citation (11) suggests, *inter alia*, the addition of inert excipients such as saccharides or amino acids to preparations in order to obtain a homogeneous stiff cake after lyophilization, especially when the drug is a highly active, potentially unstable substance that cannot be pre-concentrated, such as hormones, vitamins and antibiotics.

Citation (6) refers to a final parenteral formulation containing in 1 ml solution 50 mg minimum of human immunoglobulin, 50 mg glucose and 5 mg PEG 4000.

However, as is clear from the foregoing, the teaching of all three citations, taken either individually or in combination, fails to provide the skilled person with any suggestion or hint that he should use saccharides or amino acids as an excipient for the pharmaceutical substance of an extemporaneous kit of a parenteral, pharmaceutical-substance-containing fat emulsion to facilitate incorporation of the substance into the fat emulsion. Certainly, there is absolutely no suggestion or hint whatsoever in the cited documents leading him to the idea of departing from the conventional way of using the pharmaceutical substance dissolved in an appropriate solvent for mixing with the fat emulsion and going in the direction of the claimed solution to the problem posed.

- 12.2 In view of the foregoing observations, the board is satisfied that the subject-matter of claims 1 to 7 of auxiliary request VI involves an inventive step within the meaning of Article 56 EPC.
13. The appellants objected during the oral proceedings under Article 84 EPC to the clarity of the term "liquid alkylethanolamines" used in claims 1 and 7 in the light of certain statements in the description. In the board's opinion there can be no reasonable doubt that

the term "liquid alkylethanolamines" defines a definite class of chemical compounds using correct chemical (IUPAC) nomenclature, and that consequently the claims as such define clearly the object of the claimed invention in auxiliary request VI.

13.1 Nevertheless, there exists not only in present auxiliary request VI but also in the application as filed and the patent as granted a severe contradiction between the actual chemical structure and nature of compounds which are correctly defined in the claims as "liquid alkylethanolamines", on the one hand, and the objectively wrong and misleading statement in the description that "an example of the liquid alkylethanolamines is diethanolamine or triethanolamine", on the other. Certain contradictions and discrepancies between the claims and the description have already been noticed by the opposition division in the impugned decision. This was, however, a matter of clarity under Article 84 EPC and was therefore no ground in itself for amending the patent as granted during the first-instance opposition proceedings, because Article 84 EPC is no ground for opposition under Article 100 EPC (see page 6, paragraph c) of the decision of the opposition division).

13.2 Since, however, the provisions of Article 84 EPC become now relevant to the proper examination of the allowability of the amended claims contemplated after grant and, moreover, in view of the ~~flagrant~~ deficiencies and inconsistencies mentioned in point 13.1 above, the board considers it necessary to remit the case to the first instance for further prosecution as provided for in Article 111(1) EPC. It has still to be examined whether, in the course of the necessary adaptation of the description to the claims

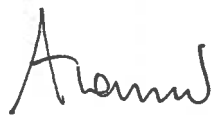
in auxiliary request VI, any existing contradiction or discrepancy between the claims and the description and, accordingly, any cause of non-compliance with Article 84 EPC will be adequately and finally removed.

Order

For these reasons it is decided that:

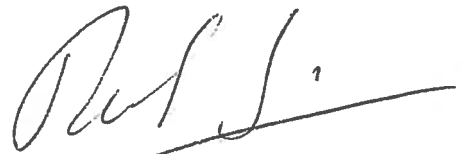
1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution.

The Registrar:



A. Townend

The Chairman:



J. Riolo

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