BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File No.: T 0434/91 - 3.3.2

Application No.: 83 303 427.5

Publication No.: 0 097 481

Classification: A61K 31/557

Title of invention: Emulsion containing prostaglandin E_1 and method for production thereof

D E C I S I O N
of 4 March 1993

Applicant: -

Proprietor of the patent: Taisho Pharmaceutical Co. Ltd.,
The Green Cross Corporation

Opponent: 1) Schwarz Pharma AG
2) Kabi Pharmacia AB

Headword: Prostaglandin E_1 emulsion/TAISHO PHARMACEUTICAL

EPC: Art. 56

Keyword: "Inventive step (no)"

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0434/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 4 March 1993

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 12 March 1991, posted on 2 April 1991 concerning maintenance of European patent No. 0 097 481.**

Composition of the Board:

Chairman: P.A.M. Lançon
Members: D. Holzner
E.M.C. Holtz

Summary of Facts and Submissions

I. European patent No. 97 481 was granted with 12 claims in response to European patent application No. 83 303 427.5. Claim 1 reads as follows:

> "1. An emulsion which comprises 5-50% (W/V) of soybean oil containing an effective amount of prostaglandin E_1, 1-50 parts by weight of a phospholipid per 100 parts by weight of the soybean oil, and a suitable amount of water."

II. Notices of opposition were filed against the European patent by two parties. Revocation of the patent was requested on the grounds of Articles 100(a), 52(1), 54 and 56 EPC.

During the procedure before the Opposition Division the following documents, inter alia, were cited:

(1) EP-A-0 041 772
(2) US-A-4 073 943.

III. The Opposition Division maintained the patent unamended.

Adopting the technical problem as defined in the patent in suit, the Opposition Division considered that its object was to protect PGE_1 from inactivation in the body by vehicle means which would prevent it from being present to a degree in the water phase where it would be attacked, and to provide a vehicle which allows intravenous administration to be effective in a desired area.

After consideration of the above documents and comparison of the respective technical problems and

solutions, the Opposition Division concluded that a solution to a problem which apparently only exists for a small number of prostaglandins would not suggest itself to the expert. It further concluded that the main request satisfied Article 56 EPC.

IV. The Appellant (Opponent 1) filed an appeal against the decision and at the same time paid the corresponding fee.

V. In the proceedings and at the oral hearing on 4 March 1993 the Appellant argued essentially as follows: The novelty of the subject-matter of the claims of the patent in suit was not contested.

The appeal only contested the inventive step of the subject-matter of Claim 1.

The emulsion system to which prostaglandin E_1 (hereinafter PGE_1) was added was known from documents (1) and (2). So it was not just a single document suggesting application of pharmacologically active compounds in a carrier emulsion, but two documents, which means that the carrier system was well known in the prior art.

It was true that PGE_1 was not mentioned in one of these documents, but it was to be questioned whether the substitution of one active agent by another, i.e. PGE_1 in the case of the patent in suit, can account for inventive step. Such substitution had to be supplemented by something special to account for inventive step, as impediments to such substitution were not discernible.

In this connection those parts of document (2) were cited which refer to preferably intravenous administration, in order to obtain a longer duration of

the effect in those cases in which the agent is normally attacked rapidly by enzymes in metabolic processes,and finally to an active agent which is not completely dissolved in the hydrophobic phase so that both the phases may contain the active agent. Itwas concluded along these lines that the skilled person would have tried to incorporate PGE_1 into a carrier system as known from document (2).

VI. The Respondent (Proprietor of the patent) argued essentially as follows: the emulsions according to Claim 1 of the contested patent allowed intravenous administration of PGE_1 and simultaneous protection of the active compound PGE_1 from inactivation in the lung, accompanied by reduced manifestation of side effects in the administered region. In contrast hereto, the known α-cyclodextrin clathrate of PGE_1, which had been prepared with the aim of improving the stability of PGE_1, was unsuitable for intravenous administration since PGE_1, as the active compound of the clathrate, has the disadvantage of being inactivated by 15-hydroxydehydrogenase present in the lung, kidney and liver.

At the time Claim 1 was formulated it was altogether surprising that PGE_1 could be incorporated into an emulsion and that the active compound contained therein, would thus be applicable more advantageously than in prior art preparations.

The technical problem underlying document (2) was clearly different from the one solved by the contested patent. In the prior art, intravenous administration of aqueous solutions was applied so as to achieve the maximum systemic effect, and it was pointed out in document (2) that the use of the agents in a water-soluble form has often had several disadvantages,

because aqueous solutions thereof may, for instance, cause side effects due to their pH value or may not be tolerated by the patient. It has to be seen in this particular context that document (2) was faced with a different problem, which was to enhance the parenteral administration of water-insoluble pharmacologically active agents. Therefore the invention underlying document (2) was directed to administering water-soluble agents.

Since document (2) is related to water-insoluble agents, the latter are taken up into the oil phase (hydrophobic phase) of that carrier system. In this context it had to be emphasised that PGE_1 was not water-insoluble, contrary to the active agents of document (2), but it was even more soluble in water than it was in (fatty) oil.

So there was not the remotest suggestion in document (2) that applying its carrier system to PGE_1 might be one way to solve the problem underlying the contested patent.

The skilled person knew from **The Extra Pharmacopoeia**, a recognised handbook edited by Martindale in 1978, that prostaglandins are soluble in water as well as in lipids. This clearly confirmed that the solubility properties of PGE_1 differed significantly from those of the water-insoluble agents to which the teaching of document (2) was applicable. There was no suggestion in document (2) that an agent which was more water-soluble than oil-soluble might be incorporated into such a carrier system to overcome the difficulties of PGE_1 administration known from the prior art, instead of the water-insoluble agents to whose administration document (2) was specifically addressed.

From the fact that PGE_1 - a very important vasodilator - was not mentioned in document (2), but only cyclandelate was given there as an example of a vasodilating agent, it could be taken that the skilled person would not consider the teaching of document (2) as being applicable to PGE_1.

The significant difference between the carrier system containing water-insoluble active agents according to document (2) and the emulsions of the disputed patent containing PGE_1, which is highly soluble in water, as an agent was corroborated by the much higher water content of the emulsion prepared according to Example 1 of the patent (30g of purified soybean oil together with small quantities of other components made up with water to 300ml) compared to the composition according to Example 2 of document (2) (10g of soybean oil and 25g of ethanol together with minor quantities of other ingredients, made up with water to 100ml only).

The Patentee's view that the teaching of document (2) was confined to water-insoluble agents had been endorsed by Opponent 2 in its submissions in opposition proceedings EP-B-123 027 where it had stated, again referring to the **Martindale Pharmacopoeia**, that PGE_1 is soluble in water and lipids, concluding as follows: "PGE_1 can therefore not be used in an emulsion". In actual fact, the reason for preparing esters from PGE_1, according to EP-B-132 027 had been that PGE_1, contrary to the water-insoluble agents adressed in document (2), is water-soluble. As a result, the skilled person saw no reason to try to put a water-soluble drug (PGE_1 according to the patent) into a carrier system specifically designed for water-insoluble agents according to document (2).

The skilled person had to expect that most of the PGE_1 added to the emulsion would be accumulated in the aqueous phase, the more so as the emulsions according to Claim 1 of the patent contained a high percentage of water, whereas, surprisingly, PGE_1 occurred mainly in the oil phase. This is also the reason for the great improvement in administering PGE_1 and its protection against inactivation by enzymic action.

Rather than acknowledge the marked difference between the technical problems underlying document (2) and the contested patent on the one hand, and the clear difference in solubility of water-insoluble agents on one hand and PGE_1 on the other, the Appellant had picked out a number of passages in document (2) in an attempt to demonstrate with the benefit of hindsight, on the basis of results disclosed for the first time in the contested patent, that the patent lacked inventive step.

Moreover, document (2) was published more than four years before the priority date.

Had document (2) anywhere suggested providing an emulsion for intravenous application of PGE_1 as a way to overcome the prior art difficulties of administering PGE_1, the skilled person would have sought to accomplish this, all the more so as PGE_1 was such an important drug.

VII. The Appellant requested that the decision under appeal be set aside and the patent revoked.

The Respondent requested that the appeal be dismissed and the patent be maintained unamended.

At the end of the oral proceedings the Board announced its decision to revoke the patent.

Reasons for the Decision

1. The appeal is admissible.

2. The only issue to be decided in these appeal proceedings is that of inventive step.

2.2 At the priority date prostaglandin E_1 (PGE_1) was known to exhibit a strong vasodilating action in mammals, but its insufficient chemical stability had hindered PGE_1 from clinical application to chronic arteriostenosis diseases. To improve the stability of PGE_1 a clathrate has been prepared from α-cyclodextrin and PGE_1. This clathrate, however, was also unsuitable for intravenous administration because a considerable part of PGE_1 is inactivated particularly upon passing through the lung. Moreover, when the clathrate from α-cyclodextrin and PGE_1 is administered by continuous intra-arterial infusion, side effects are sometimes manifested in the administered region (see contested patent, column 1, lines 14-48).

Although no document has been cited to illustrate the state of the art from which the above problem has been defined, in the oral hearing all parties accepted that this state of the art was properly described in the description of the patent in suit.

2.3 To overcome the shortcomings of the prior art as stated above, the technical problem which the patent sets out to solve was to make available a pharmaceutical preparation which allows intravenous administration of PGE_1 with concomitant protection of the pharmacologically active compound PGE_1 from inactivation

(in the patient's body particularly) in the lung, accompanied by reduced manifestation of side effects in the administered region (see contested patent, column 1, lines 49-59).

2.4 The patent proposed solving this problem by providing an emulsion comprising 5-50% (W/V) of soybean oil containing an effective amount of prostaglandin E_1, 1-50 parts by weight of a phospholipid per 100 parts by weight of the soybean oil, and a suitable amount of water according to Claim 1.

Having regard to the examples contained in the patent specification, the Board is satisfied that the above technical problem has thereby been effectively solved.

2.5 It is agreed that documents (1) and (2) are the most relevant documents for the purpose of evaluating inventive step in this case.

2.5.1 Document (2) relates to the parenteral administration of water-insoluble pharmacologically active agents, whereby parenteral is to be understood as "preferably then intravenously" (see column 3, lines 32-33; also the contested patent, column 3, lines 46-47). The method reported there makes it possible to administer water-insoluble agents in high concentrations, and thus a lower dose, whereby a rapid onset of the pharmacological effect is accompanied by a markedly reduced incidence of injury to body tissues.

However, contrary to what the Respondent put forward, document (2) is not confined to the administration of water-insoluble agents only, but also considers that:

"It may occur that the active agent is not completely dissolved in the hydrophobic phase. It may have a

greater affinity to the hydrophobic phase on account of its hydrophobic properties, but depending upon the distribution equilibria, both of the phases may contain the active agent." (See column 3, lines 21-26).

For the skilled person, it follows from the characterisation of prostaglandins in **The Extra Pharmacopoeia** as "being fatty acids which are soluble in water as well as (in) lipids which is probably an important feature in determining their different properties" (see page 1328, right-hand column, paragraph 6, first sentence) that PGE_1 belongs to the group of active agents addressed in document (2), column 3, lines 21-26, which is not completely dissolved in the hydrophobic phase. So, in line with document (2), the skilled person would expect both phases of the emulsion in question, i.e. the hydrophobic as well as the hydrophilic phase, to contain the active agent (see column 3, lines 24-26).

On these grounds the skilled person would not consider PGE_1 to be a "very special drug" (see decision of the Opposition Division under 4.2, paragraph 4).

2.5.2 The solubility data of PGE_1 reported by the Respondent show that PGE_1 was more soluble in distilled water than it was in soybean oil. The Respondent put forward that it therefore had to be expected that most of the PGE_1 incorporated into the emulsions of the contested patent would be in the water phase and drew attention to Example 1 of the contested patent (in comparison to Example 2 of document (2)) emphasising the high water content.

However, this argument that a high content of PGE_1 is to be expected in the water phase, cannot support inventive step for the following reason: the subject-matter of

Claim 1 also (equally well) comprises emulsions with a content of soybean oil up to 50% (W/V) and beside the compulsory content of a phospholipid the emulsions concerned (see Example 1), according to Claims 2 to 4, may contain additional components classified as emulsifying adjuvant, stabilizer and stabilizing adjuvant. Considering the great variety of emulsions there is no reason to expect a priori that most of the PGE_1 would be in the aqueous phase and therefore be susceptible to enzymic inactivation after administration.

2.5.3 If this had been obvious, the skilled person would have noticed that a part of the technical problem set out by the contested patent, namely protection of PGE_1 from inactivation by 15-hydroxydehydrogenase present in the lung, kidney and liver (see contested patent, column 1, lines 31-33), could not be solved by preparing (and subsequently administering intravenously) such emulsions containing the major quantity of PGE_1 in the aqueous phase.

However, as reasoned above, the expected distribution of a given quantity of PGE_1 between the hydrophilic and hydrophobic phases of one of the carrier emulsions known from document (2) or document (1) cannot be construed as an impediment such as to prevent the skilled person from trying to find out whether PGE_1 could, with the technical problem of the contested patent in mind, be administered in a carrier emulsion. There is nothing in document (2) or in the **Martindale Pharmacopoeia** to indicate that PGE_1 would accumulate mainly in the aqueous phase therefore making an experiment aimed at distributing PGE_1 in such a carrier system a priori, appear unsuitable for the intended administration.

2.5.4 Document (2) further mentions that a longer duration of the effect is also obtained in those cases where the agent is normally attacked rapidly by enzymes in metabolic processes (see column 2, lines 63-65). Although, as the Opposition Division pointed out, there are a very large number of different kinds of enzyme-catalysed reactions in metabolism, no reason was given as to why the skilled person would not have inferred from the above that, by incorporating PGE_1 into a carrier emulsion, its pharmacological effect(s) might also be expected to last longer, since it was already known that PGE_1 is inactivated by an enzyme (15-hydroxydehydrogenase) present in the lung, kidney and liver (see contested patent, column 1, lines 31-33, and E.W. Horton, **Prostaglandins**, Springer Verlag Berlin 1972, page 75).

2.5.5 Finally, it could be expected from document (2) that parenterally administering an active agent in a carrier emulsion might lead to reduced manifestation of side effects in the administered region (see contested patent column 1, lines 57-59) because it is pointed out there that the method of administration in a carrier system according to document (2) will cause a lower incidence of injury to body tissues (see column 2, lines 53-55).

2.5.6 Document (2) was published in February 1978, i.e. about four years before the priority date of the patent in suit. The teaching of this document, namely administering water-insoluble pharmacologically active agents or, additionally, an active agent which is not completely dissolved in the hydrophobic phase (see column 3, lines 21-22) in a carrier emulsion, is not confined to the examples given there but has found

broader acceptance as it has been applied, according to Claims 1 and 2 of document (1), published in December 1981, to any steroid having an anti-inflammatory activity.

On these grounds the skilled person can conclude from document (2) that the teaching given there is directed towards solving a technical problem in relation to the parenteral administration of a variety of pharmacologically active agents. The problem underlying document (2) has, however, as outlined above, several aspects in common with the specific problem related to parenteral PGE_1 administration underlying the patent in suit.

In particular, the combined teachings of documents (2) and (1) are an incentive to the skilled person to try to find out whether just a carrier system available from the Respondent's prior document (1) would be suitable for parenteral PGE_1 administration. As a result of such an experiment incited by similarities in solubility between any steroid having an anti-inflammatory activity, as in document (1), including such steroids which may not be completely dissolved in the hydrophobic phase, and PGE_1, the skilled person would have noticed that the carrier system known from document (1) is in fact also suitable for parenteral administration of PGE_1.

2.5.7 When referring to Opponent 2's submission in opposition proceedings EP-B-132 027, reading as follows: "PGE_1 can therefore not be used in an emulsion", the Respondent, in the oral hearing before the Board, did not convincingly explain why the skilled person would have concluded that PGE_1 could not be used in an emulsion.

Later considerations in relation to further improvements in PGE_1 administration, like those underlying EP-B-132 027, cannot support inventive step of the subject-matter of Claim 1 at the priority date.

3. The Board, contrary to the Opposition Division, concludes that the technical problem underlying the contested patent is addressed by the technical teachings of documents (2) and (1) such that a person of ordinary skill in the art would have been led by these documents to try to incorporate PGE_1 as a pharmacologically active agent into a carrier emulsion.

4. Hence, it is concluded that, with regard to the subject-matter of Claim 1 of the patent in suit, the requirement of Article 56 EPC is not met.

Dependent Claims 2 to 12 share the same fate as the independent claim to which they refer.

Order

For these reasons, it is decided that:

1. The decision of the Opposition Division is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

P. Martorana P.A.M. Lançon