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D E C I S I O N
of 1 March 2005

Case Number: T 1038/02 - 3.3.2

Application Number: 94901593.7

Publication Number: 0674510

IPC: A61K 31/335

Language of the proceedings: EN

Title of invention:
Injectable composition comprising paclitaxel

Patentee:
Mayne Pharma (USA) Inc.

Opponent:
BASF Aktiengesellschaft
Frohwitter, Bernhard, Dipl.-Ing, RA

Headword:
Taxol composition/MAYNE PHARMA INC.

Relevant legal provisions:
EPC Art. 54, 123

Keyword:
"Main, first, second and third auxiliary requests - added matter - yes: unallowable combination of different parts of the application as filed"
"Fourth auxiliary request - novelty - no: broad term in the claim encompasses a prior art embodiment"
"Fifth and sixth auxiliary requests - added matter - yes: unallowable generalisation"

Decisions cited:
-

Catchword:-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1038/02 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 1 March 2005

Appellant: (Proprietor of the patent)	Mayne Pharma (USA) Inc. 650 From Road, Mack-Cali Centre II Second Floor Paramus, NJ 07652 (US)
Representative:	Baldock, Sharon Claire BOULT WADE TENNANT Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Respondent: (Opponent)	BASF Aktiengesellschaft Patente, Marken und Lizenzen D-67056 Ludwigshafen (DE)
Representative:	-
Respondent: (Opponent)	Frohwitter, Bernhard, Dipl.-Ing, RA Possartstrasse 20 D-81679 München (DE)
Representative:	-
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 10 October 2002 revoking European patent No. 0674510 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
J. H. P. Willems

Summary of Facts and Submissions

I. European patent No. 0 674 510, based on application No. 94 901 593.7, was granted on the basis of 21 claims comprising five independent claims, namely claims 1, 9, 14, 15 and 16.

Of particular interest in the present case are independent claims 1 and 9 which read:

"1. A pharmaceutical composition suitable for use in treating cancer and comprising paclitaxel (taxol), polyethoxylated castor oil and an acidifying agent, the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1."

"9. Use of an acidifying agent as a stabilizer for paclitaxel in a pharmaceutical composition in which paclitaxel is carried by polyethoxylated castor oil, said acidifying agent being employed in such use in such proportion that said composition has a resulting pH less than 8.1."

II. Notice of opposition was filed against the granted patent by the respondents.

The patent was opposed under Article 100(a) EPC for lack of novelty and lack of an inventive step and because the patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

The following documents, inter alia, were cited during the proceedings before the opposition division and the board of appeal:

(1) Waugh et al. in AMERICAN JOURNAL OF HOSPITAL PHARMACY, volume 48, pages 1520-1524, 1991

(16) The NCI Clinical Brochure on Taxol published in 1991

(34) Technical leaflet of Cremophor EL by BASF, September 1987

(64) US patent 5504102

III. The appeal lies from a decision of the opposition division revoking the patent under Article 102(1) EPC pronounced at the oral proceedings held on 2 July 2002. The opposition division held that neither the claims as granted of the patent in suit nor the claims of auxiliary requests 1 to 4 met the requirements of the EPC.

Thus the opposition division took the view that

- claim 1 of the patent as granted did not meet the requirements of novelty,
- the claims of the auxiliary requests 1 to 3 contravened Article 123(2) EPC
- the claims of the auxiliary request 4 did not meet the requirements of inventive step.

The opposition division thus considered claim 1 as granted to encompass both diluted and undiluted taxol compositions and that Cremophor was the only compound

having an influence on the pH, which, according to document 34, was of 6-8 in aqueous solution, and that thus Cremophor played the role of the "acidifying agent".

The opposition division therefore concluded that diluted taxol compositions of document 1 possessed all the technical features of claim 1.

As to Article 123(2) EPC, the opposition division furthermore considered that, among other things, the introduction into claim 1 of auxiliary requests 1 to 3 of the stability requirement "and a volume of said composition retaining at least 86.7% and 96.6% respectively, of the paclitaxel potency when said volume is filled into a clear glass 5ml vial sealed with a rubber bung and stored at 40 degrees Celcius for 7 days" introduced added matter.

As regards inventive step with respect to auxiliary request 4, the opposition division saw the technical problem solved by the patent in suit as the provision of a non-aqueous taxol solution with an improved storage stability. It considered that the patent in suit did not belong to the category of "problem-inventions" on account of the comments on page 4 of document (16) stating that shelf-life surveillance of the ampoules and vials was ongoing.

The opposition division concluded that the claimed matter was obvious over document (1) or over document (16) because (1) mentioned that taxol was more stable at acidic pH, more particularly between pH 4 and 8.

IV. The appellant (patentee) lodged an appeal against the said decision and filed arguments.

V. In the communication of 2 November 2004 accompanying the summons to the oral proceedings, the opinion was expressed that the subject-matter of claim 1 as granted lacked novelty and that the amendment of claim 1 in the auxiliary request "in the form of a substantially non-aqueous solution" contravened Article 123(2) EPC.

VI. On 3 February 2005, the appellant filed a main and three auxiliary requests.

Claim 1 of the main request reads:

"1. A pharmaceutical composition suitable for use in treating cancer, which is a solution consisting of paclitaxel (taxol), ethanol, polyethoxylated castor oil and an acidifying agent, the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1."

Claim 1 of the first auxiliary request reads:

"1. A pharmaceutical composition suitable for use in treating cancer, which is a solution consisting of paclitaxel (taxol), ethanol, polyethoxylated castor oil and an acidifying agent, the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1, and a volume of said composition retaining at least 96.6% of the paclitaxel potency when said volume is filled into a clear glass 5ml vial and the vial sealed with a

rubber bung and stored at 40 degrees Celcius for 7 days"."

Claim 1 of the second auxiliary request and third auxiliary request only differs from claim 1 of the first auxiliary request in that the pH of the claimed composition has been restricted to 5-7 and 6.1 respectively.

VII. Oral proceedings were held before the board on 1 March 2005.

During the oral proceedings, the respondent filed six other auxiliary requests, namely auxiliary requests 4 to 9. Auxiliary requests 8 and 9 were rejected by the board as late-filed.

Claim 1 of auxiliary requests 4 to 7 differs from claim 1 of the main and auxiliary requests 1-3 respectively only in that the expression polyethoxylated castor oil has been replaced by "Cremophor EL".

Thus, claim 1 of the fourth auxiliary request reads:

"1. A pharmaceutical composition suitable for use in treating cancer, which is a solution consisting of paclitaxel (taxol), ethanol, Cremophor EL and an acidifying agent, the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1."

Claim 1 of the eighth auxiliary request reads:

"Use of an acidifying agent as a stabilizer for paclitaxel in a pharmaceutical composition in which said paclitaxel is carried by Cremophor EL, said acidifying agent being employed in such use as to provide a pharmaceutical composition said pharmaceutical composition being suitable for use in treating cancer, and which is a solution consisting of paclitaxel (taxol), ethanol, Cremophor EL and the acidifying agent, the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1."

Claim 1 of the ninth auxiliary request differs from the that of the eighth auxiliary request in that it contains the stability requirements as a claim 1 of auxiliary request 5.

VIII. The submissions of the appellant can be summarised as follows:

As regards added matter, the appellant was of the opinion that the compositions restricted by the combination of ethanol and polyethoxylated castor oil were supported by the original disclosure, more particularly by original claims 2, 5 and 6 in combination with the general part of the description and the examples. In this respect, it submitted that for the skilled man at the priority date of the patent Cremophor EL and polyethoxylated castor oil were synonymous.

With respect to the introduction of a stability requirement that the compositions have to meet in auxiliary requests 5-7, he submitted that it was a

generalisation of the stability test of the examples and that the value of 96.6 corresponded to a value for which it could be considered that the composition was stable. In support of its argument, it referred to the stability data of documents (1) and (64).

IX. Respondent 02 contested these arguments.

In its view, claim 1 as granted contravened Article 123(2) and (3) with respect to the amendment of "comprising" to "consisting of"

It furthermore maintained that the claimed matter lacked novelty and an inventive step over the cited prior art, since the claimed compositions still encompassed aqueous solutions.

X. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with letter of 3 February 2005 or, alternatively, of one of the auxiliary requests 1-3, filed with a letter of 3 February 2005, or auxiliary requests 4-9 filed during the oral proceedings.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Admissibility of the auxiliary requests filed during the oral proceedings.

2.1 Auxiliary requests 4 to 7

As these auxiliary requests were filed in direct response to the board's observation made during the oral proceedings that the combination of ethanol with polyethoxylated castor oil may infringe Article 123(2) EPC and since they only differ from the main and auxiliary requests 1-3 in the amendment consisting in replacing polyethoxylated castor oil by Cremophor EL, these sets of claims are admitted into the procedure.

2.2 Auxiliary requests 8 to 9 filed at the end of the oral proceedings

The argument submitted by the respondent for the filing of these requests at that stage was that there was a reaction to the argument heard for the first time, ie that water can play the role of the acidifying agent in the claimed compositions and that the claimed compositions may therefore lack novelty.

The claims of these requests are use claims based principally on claim 6 of auxiliary request 4 and claim 7 of auxiliary request 5 respectively and concern the use of an acidifying agent as a stabilizer for paclitaxel in a pharmaceutical composition. The board observes that the term acidifying agent has not been clarified in the claims of these requests.

Furthermore, the claimed compositions have been objected to for lack of novelty over document (1) throughout the opposition and appeal procedure. The filing of an auxiliary request directed to the use of a class of compounds in order to overcome this novelty objection directed to compositions per se could have been done before.

In the absence of any valid arguments from the appellant as to why these requests were not filed earlier and since it is not immediately apparent whether they are allowable, they are considered as late-filed and are not therefore admitted into the proceedings.

3. *Main request: added matter*

Claim 1 has been amended in such a way that the claimed compositions now contain the combination of ethanol with polyethoxylated castor oil.

The appellant argued that the support of this amendment was to be found in originally filed claims 2, 5 and 6 which read:

"2. A method of formulating a taxol solution for injection in which the taxol does not readily degrade, comprising the following steps:
mixing acid with a carrier material to form a first carrier solution; and
mixing taxol with the first carrier solution to form a taxol solution having a pH of less than 8.1 whereby the taxol in the taxol solution does not readily degrade."

"5. A method according to claim 2 wherein said carrier material is polyethoxylated castor oil"

"6. A method according to claim 2 including the step of slurrying said taxol in alcohol before mixing said taxol with the first carrier solution".

The board however notes that these claims do not disclose the combination of polyethoxylated castor oil with ethanol. Claims 2 and 5 do not refer at all to an alcohol.
Claim 6 is only dependent upon claim 2 and discloses the combination of an alcohol with an unspecified carrier.

The appellant further contended that Cremophor EL and polyethoxylated castor oil were synonymous at the priority date of the patent and that at that date Cremophor EL was the only pharmaceutically acceptable polyethoxylated castor oil available for dissolving taxol. By Cremophor EL the skilled person would thus have understood polyethoxylated castor oil.

This argument is however not convincing in the present case. Indeed as Cremophor EL is a specific polyethoxylated castor oil obtained by reacting castor oil with ethylene oxide in the specific molar ratio of 1:35 (see document (34)), the amendment of Cremophor EL into polyethoxylated castor results in a broadening of this term.

It is established case law of the Boards of Appeal that the content of the application as originally filed only

encompasses what is directly and unambiguously disclosed in the application as filed either explicitly or implicitly (see eg the Case Law of the Boards of Appeal of the EPO, 4th edition, III.A.3.3). In this context "implicit disclosure" means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content (eg in view of general scientific laws, common general knowledge in the relevant technical field or purely logical necessity arising from the relationships among distinguished portions of the application as filed).

Accordingly, even if at the filing date of the patent the skilled person would have considered Cremophor EL as necessarily implied in the explicit content of the patent, ie as being the only pharmaceutically acceptable polyethoxylated castor oil available for the purpose of dissolving paclitaxel, this would not have supported an amendment involving replacing the specific Cremophor EL which the skilled person would have considered mandatory by any polyethoxylated castor oil.

It follows that the board is unable to see any support for the combination of ethanol with polyethoxylated castor oil in the original specification. Accordingly, claim 1 of auxiliary request 1 contravenes Article 123(2) EPC.

4. *Auxiliary requests 1 to 3*

As claim 1 of these auxiliary requests is directed to compositions still containing the specific combination of polyethoxylated castor oil with ethanol, the

reasoning and conclusion in point 3 hold good for these requests as well.

5. *Auxiliary request 4*

5.1 Article 123 EPC

The board is satisfied that claim 1 of this request is supported by the original disclosure, more particularly by the combination of original claim 1 with page 2, lines 4 to 7 of the description.

Respondent 02 submitted that claim 1 of this request infringed Article 123(3) EPC, since claim 1 now requires the presence of two acidifying agents, that which is inevitably present in Cremophor and that which is required by the claim.

The board cannot agree with this interpretation since the amendment "comprising" to "consisting of" together with "polyethoxylated castor oil" to "Cremophor" results in a clear restriction of the claimed scope. Moreover, as this request fails for lack of novelty (see point 5.3), the board does not consider it necessary to develop this point further.

5.2 Clarity (Article 84 EPC)

Claim 1 of this request now encompasses the term Cremophor EL which is the trade name of a product commercially available. As Cremophor EL is a complex mixture, the board has serious doubts about whether a claim directed to a composition defined by a complex commercial product only identified by its trade name

would be clear. Since claim 1 of this request lacks novelty (see point 5.3), there is no need to answer this point.

5.3 Novelty

5.3.1 Claim 1 of auxiliary request 4 is directed to a pharmaceutical composition suitable for use in treating cancer consisting of
1. paclitaxel (taxol),
2. ethanol,
3. Cremophor EL
4. an acidifying agent and
5. the components of the composition being mixed in such proportion that said composition has a resulting pH less than 8.1.

5.3.2 Document (1) is concerned with the stability of a diluted clinical formulation containing paclitaxel for treating cancer.
Document (1) discloses diluted taxol compositions which are obtained by diluting the NCI composition (6 mg taxol dissolved in 0.5 ml Cremophor EL and absolute alcohol to 1 ml) to taxol nominal concentrations of 0.3, 0.6, 0.9 and 1.2 mg/ml with a 0.9% sodium chloride solution for injection (NS) (see table 1 on page 1522 of document (1)).

In particular, a 0.6 mg/ml taxol composition corresponds to a dilution 1:10 of the NCI composition with a 0.9% sodium chloride solution.

Thus, document (1) discloses a pharmaceutical composition suitable for use in treating cancer comprising

1. paclitaxel (taxol),
2. ethanol,
3. Cremophor EL and
4. water containing 0.9% NaCl

5.3.3 Having regard to characteristics 4 and 5 of the analysis of claim 1, it remains to be examined whether water containing 0.9% NaCl may be regarded as an acidifying agent and whether the pH of the solution is less than 8.1. Neither the appellant nor the respondents have provided the board with the pH value of this prior art composition. It must therefore be decided whether these features of the solution of document (1) comply with the requirements of claim 1.

5.3.4 Together with its letter dated 23 February 2005 the appellant filed pH data on sample 2 (the NCI composition) and on sample 2 diluted with water for injection (making a 10% solution), showing that the pH is lowered from about 8.50 for the undiluted NCI composition to about 5.75 for the water-diluted solution.

From these data the board concludes that water acts as an acidifying agent for the NCI composition.

5.3.5 Water-diluted sample 2 according to the experimental data provided by the appellant differs from the diluted composition disclosed in document (1) only in that the latter contains some sodium chloride (0.9% in the aqueous phase).

It therefore remains to be determined whether the dilution of the NCI composition with a normal saline solution (ie having 0.9% NaCl) will have an equivalent pH-decreasing effect as water. In the absence of any evidence to the contrary and as it is common general knowledge that NaCl is a salt derived from a strong acid (HCl) and a strong base (NaOH), the board is convinced that the resulting salt NaCl will have no significant influence on the pH value when dissolved in an aqueous solution. There is therefore no doubt that the effect on the pH achieved with the dilution with water of the NCI composition will also be achieved with a dilution with water containing 0.9% NaCl.

It must therefore be concluded that a normal saline solution should also be regarded as an acidifying agent for the NCI composition and that the pH of the aqueous solution disclosed in document (1) should be less than 8.1.

5.3.6 The appellant contended that the claimed compositions were novel over document (1) since they could not contain water.
The appellant stressed that water is neutral and thus could not be regarded as an acidifying agent, the sole effect achieved by the addition of water to the NCI composition being a dissociation which explains the observed decrease in the pH-value.

The board observes that the description does not contain any definition for the expression "acidifying agent". Accordingly, in the absence of any definition, this expression has to be interpreted according to its broadest sense, ie an agent which lowers the pH value.

As set out in paragraph 5.3.4, water lowers the pH value of the NCI composition and therefore is to be regarded as an acidifying agent for this composition.

5.3.7 The appellant further pointed out that the diluted composition disclosed in document (1) contains further components, ie sodium salt or dextrose.

Again, given that there is no definition for the expression "acidifying agent", an acidifying agent cannot be construed as a single component.

Moreover, example 2 of the patent in suit supports the broader interpretation, since the acidifying agent is a solution of 1M acetic acid, ie the couple water/acetic acid.

5.4 Under these circumstances, the board concludes that the subject-matter of claim 1 of auxiliary request 4 lacks novelty under Article 54 EPC.

6. *Auxiliary request 5*

Added matter

Claim 1 differs from claim 1 of the preceding auxiliary request 5 only in that it has been further restricted by a condition to be met, ie a stability test which reads "and a volume of said composition retaining at least **96.6%** of the paclitaxel potency when said volume is filled into a clear glass 5ml vial and the vial sealed with a rubber bung and stored at 40 degrees Celcius for 7 days".

According to the appellant, the support for this condition to be met, more particularly the value of 96.6%, should be found in the result of sample 1 obtained in the said stability test.

The board notes that this requirement is neither disclosed in the general part of the original description nor is it disclosed in the claims as originally filed.
By this feature, a narrower scope of claim 1 has now been defined, since the compositions which do not meet this requirement are no longer claimed.
This amendment should *inter alia* exclude aqueous compositions since, according to the appellant, taxol has an obviously lower stability in diluted aqueous solution than in concentrates form.

In examples 1 and 2, the stability of samples 1 to 3 were assessed by a method in which the composition was filled into a clear glass 5 ml vial sealed with a rubber bung and stored at 40 degrees Celcius for 7 days. For sample 1, a retention of the paclitaxel potency of 96.6% was observed while for sample 3 it was 97.5%.

The board considers however that examples which concern compositions consisting of four particular components in a given ratio and showing that a specific stabilizing effect is achieved cannot form the basis for defining a novel sub-group of compositions as now defined in claim 1, all the more so because in the preamble to the working examples it was pointed out expressis verbis "*In a preferred procedure adopted by the applicant, which it will be clearly understood* ***is***

non-limiting *[emphasis added by the board], the following steps were carried out…"* while at the end of the examples it is again stressed that ***"****It will be clearly understood that the invention in its general aspects is not limited to the specific details referred to hereinabove****".***

Nor is the argument by reference to documents (1) and (64) relevant to that end. The board does not contest that, as shown in these documents, the skilled person would understand that a composition is regarded as being stabilized by a retention of a specific value between 62.8 and 100% of the activity of paclitaxel (see document (1), page 1522, table 1; document (64), example 3, tables 4 and 5). This information is however not relevant for the question of whether or not the application as originally filed disclosed the specific functional feature which was added to auxiliary request 5.

As a consequence, the board takes the view that claim 1 according to the fifth auxiliary request constitutes an unallowable generalisation of what was originally disclosed, so that this request must be rejected pursuant to Article 123(2) EPC.

7. *Auxiliary request 6*

As claim 1 of this request contains the same condition to be met as in claim 1 of auxiliary request 5, the reasoning and conclusion in point 6 hold good for this request as well.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald