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Case Number: T 0826/12 - 3.3.07

Application Number: 06737018.9

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Title of invention:
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

Applicant:
Banner Pharmacaps Inc.

Headword:
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS/Banner Pharmacaps

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

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Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0826/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 September 2014

Appellant: (Applicant)	Banner Pharmacaps Inc. 4125 Premier Drive High Point, NC 27265-8144 (US)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 29 November 2011 refusing European patent application No. 06737018.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	W. Ungler

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division refusing European patent application No. 06 737 018.9.

II. The decision was based on the sets of claims of the main request and auxiliary requests 1-5 filed with the letter of 16 September 2011 and the auxiliary request 6 filed with the letter of 4 October 2011.

Claim 1 of the main request read as follows:

"1. A pharmaceutical composition comprising
a) a salt of an acidic pharmaceutical agent;
b) a deionizing agent which is a hydrogen ion species in an amount to cause partial deionisation of the salt of from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent;
c) polyethylene glycol; and optional
d) water."

The independent claims of subsequent requests differed from claim 1 of the main request mainly in the category of the claim ("A softgel capsule...", "A pharmaceutical composition obtainable by a method...", "A method of making a pharmaceutical composition, and the use of the composition). Only according to the sixth auxiliary request was the acidic pharmaceutical agent limited to naproxen sodium.

III. In the decision under appeal, the following documents were cited *inter alia*:
D1: US-A-5 360 615
D2: WO-A-95/31979
D3: US-A-2001/007668

IV. The decision under appeal, as far as relevant to the present decision, may be summarised as follows:

a) Claim 1 of the main request was not novel in view of D3, which disclosed a composition comprising naproxen sodium.

b) Inventive step of the main request was also assessed by the Examining Division despite the finding that claim 1 was not novel. The closest prior art was seen as being either D1 or D3. The distinguishing feature was the presence of the additional acid. The experimental data provided with the letter of 16 September 2011, when compared with the information provided in D2 regarding the instability of a formulation according to D1, did not provide evidence of a technical effect since there were too many differences between the formulations in question, and an effect could not be attributed to the distinguishing feature. The problem was consequently identified as the provision of a further composition. In order to solve the problem of providing an alternative, the addition of any compound to the composition, including an acid, was seen as obvious and in view of this, inventive step was denied.

c) Auxiliary requests 1-5 failed for the same reasons as those provided for the main request.

d) Claim 1 of auxiliary request 6 did not fulfill the requirements of Article 123(2) EPC. Novelty was also denied in view of D3.

V. The applicant (appellant) filed an appeal against that decision. With the statement setting out the grounds of appeal, the appellant filed a new main request and thirteen auxiliary requests, and submitted the following item of evidence:

D7: Annex to grounds of Appeal: Report on comparative studies.

VI. With the communication sent in preparation for oral proceedings, the Board expressed a preliminary view with respect to novelty, added subject-matter and inventive step, in particular stating that the experimental tests provided as D7 appeared to show less PEG ester formation using the compositions according to the application. The Board also noted that said tests appeared to demonstrate that the compositions alleged prepared according to the application, with the exception of samples 8 and 11, were characterised by phase separation and precipitation, and questioned whether they could be considered suitable for the intended purpose, i.e. encapsulation into softgel capsules.

VII. With the letter of 22 August 2014 the appellant submitted further arguments, a new main request and auxiliary requests 1-7 to replace all previous requests on file.

VIII. Oral proceedings were held on 16 September 2014 during which a new set of claims 1-13 was submitted as main and sole request, all previous requests being withdrawn.

Claims 1 and 13 of the main request read as follows:

"1. A softgel capsule comprising a fill material where the fill material comprises
(a) naproxen sodium
(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
(c) polyethylene glycol;
(d) water; and
(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof."

"13. The use of
(a) naproxen sodium;
(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
(c) polyethylene glycol;
(d) water; and
(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

IX. The appellant's arguments, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step

D1 is the closest prior art. The tests submitted as D7 demonstrated that when subjected to accelerated stress conditions, the amount of polyethylene glycol (PEG) esters present in the pharmaceutical compositions prepared in accordance with the application is lower than that present in the compositions prepared in accordance with the teaching of D1 under the same conditions.

Although samples 1-15 of D7 were, with the exception of samples 8 and 11, for the most part physically characterised by the formation of a phase separated precipitate which would not be suitable for encapsulation in a softgel capsule, the purpose of the tests had been merely to demonstrate the improvement over D1 with respect to the decreased production of PEG esters; the composition of said samples lacked the solubilizers required by claim 1, which would produce solutions suitable for encapsulation into softgel capsules. One such capsule according to the application had been produced according to the experimental report filed before the first instance with the letter of 16 September 2011. The capsules produced according to the application consequently provided unexpected advantages in that the fill material contains less PEG esters both initially and after stability studies, when compared with the corresponding formulations of D1. These advantages could not have been predicted starting from D1 as the closest prior art.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims 1 to 13 of the main and sole

request, filed during oral proceedings before the Board on 16 September 2014.

Reasons for the Decision

Basis in the application as filed

1. Claim 1 originates from independent claim 19 of the application as filed with the limitation that the pharmaceutically active agent is the preferred agent naproxen sodium, employed in all 12 examples.

1.1 The "deionising agent" referred to in claim 19, ingredient (b) as originally filed, is limited to some of the acids chosen from the list disclosed on page 6, lines 17-21 of the application as filed. That said acid is present "in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium" is supported by claim 21 as originally filed, which depends on claim 19. The presence of further ingredients of the fill material in claim 1, namely PEG (component (c)) and water (component (d)) finds support in the application as filed in reference to the preparation of the fill material (page 8, lines 25-27; page 10, lines 14-16). Finally, the presence of a solubilizer according to claim 1, step (e) is supported by the passage in the description as filed on page 7, lines 13-15.

1.2 Since a capsule comprising the fill material according to claim 1 finds support in the application documents as filed, it follows that the use of said fill material in the manufacture of a medicament in the form of a capsule according to claim 13 is also supported.

1.3 It follows that the claims of the main request fulfill the requirements of Article 123(2) EPC.

Novelty - main request

2. Claim 1

2.1 D1 discloses a solvent system for enhancing the solubility of pharmaceutical agents suitable for encapsulation in softgels (column 2, lines 29-33). Example IV concerns the preparation of a concentrated solution of naproxen in which naproxen free acid is mixed with 0.50 mole equivalents of 50% aqueous potassium hydroxide (KOH) and PEG-600.

Claim 1 of the main request differs from example IV of D1 in that:

a) a softgel capsule is claimed; D1 merely discloses solutions (filling mixtures) suitable for filling softgels;
b) naproxen sodium is used instead of naproxen free acid;
c) an acid chosen from the list provided in claim 1, part (b) is added to the naproxen sodium, rather than adding KOH to naproxen free acid; and
d) a solubilizer is employed.

2.1.1 It follows that the subject-matter of claim 1 is novel over the disclosure of D1.

2.2 D3, specifically example 17 thereof, discloses a solution formulation consisting of 21.67 % naproxen sodium, 72.40 % PEG-300, 0.05 % KOH (as a solution of 6.8g KOH in 100 ml of water) and 5.88% sodium

propionate (as a solution of 500 g sodium propionate in 700 ml of water). The formulations of D3 are intended as concentrated solutions of pharmaceutical agents suitable for encapsulation into softgel capsules (paragraph [0013]).

2.2.1 The fill material of claim 1 of the main request differs from example 17 of D3 in that the latter:

a) does not employ an acid chosen from the list provided in claim 1, part (b) in the mole equivalent required; and
b) does not disclose the use of a solubilizer as required by claim 1, ingredient (e).

2.2.2 With respect to difference a), although sodium propionate in aqueous solution exists in equilibrium with propionic acid (denoted "proprionic acid" according to claim 1), the amount of the acid present at equilibrium in the formulation of example 17 of D3 can only be far below the lower limit of 0.2 mole equivalents required by claim 1. Furthermore, although D3 mentions that the pH of the propionate solution may be adjusted by the addition of propionic acid in an amount of 1-2 % by weight of the propionate solution (paragraph [0032]), such a minor proportion would not significantly affect the amount of acid present at equilibrium.

2.2.3 It follows that the subject-matter of claim 1 is novel over the disclosure of D3.

3. Claim 13

3.1 In order to assess novelty of claim 13, its subject-matter needs first to be defined, as discussed during

the oral proceedings. Said claim is drafted in a manner resembling the so-called Swiss-type second medical use claim as instituted by decision G5/83 (OJ EPO 1985, 64), a claim form which would still be permissible in the present application by virtue of the priority date thereof (decision G2/08, order, answer to question 3). A so-called Swiss-type claim may be construed as a purpose-limited process claim, and was introduced specifically to overcome the absence of a specific provision in EPC 1973 allowing purpose-limited product claims for further medical indications (the use-related product claim was allowable for the first medical indication according to Article 54(5) EPC 1973).

3.1.1 The subject-matter of claim 13 is thus not a Swiss-type claim defining a second medical use, but a mere process claim, deriving its novelty from the novelty of the composition of the fill material comprised therein, and not from a new therapeutic use of naproxen sodium. This is evident since the claim fails to identify a specific therapeutic indication for naproxen sodium. Not comprising such a use, the feature "for administration of the naproxen sodium to a patient in need thereof" remains *de facto* purely illustrative and does not limit the scope of the claim to that specific application.

Inventive step

4. Closest prior art

4.1 Both D1 and D3 were seen as suitable closest prior art documents according to the appealed decision, while the appellant has focused on D1 as the closest prior art in

relation to which comparative tests have been provided as D7.

4.2 D3, by virtue of the fact that it discloses in example 17 a formulation comprising naproxen sodium (see section 2.2, above), as well as the salt of an acid listed in claim 1, might appear at first sight to represent a more suitable starting point for the skilled person. However, the remaining 16 examples thereof concern different pharmaceutically active agents, none of which are employed in the salt form. The possibility of using a salt of the pharmaceutical agent is not mentioned at all in the description (D3, paragraphs [0035] and [0040]), and no explanation whatsoever is provided as to the purpose of the added KOH in example 17. Furthermore, D3 explains by way of mechanism that the purpose of the salt of the organic acid used (sodium propionate according to the examples) is to help ionise the medicament (paragraphs [0028] and [0041]). This proposed mechanism does not make logical sense in the context of example 17 in which the naproxen is added as the sodium salt, i.e. already fully ionised. Given this contradiction between on the one hand the use of naproxen sodium in example 17 and on the other hand, the teaching in the description with respect to the role of sodium propionate, coupled with the apparent lack of explanation regarding the use of KOH, example 17 represents an unrealistic starting point which the skilled person, on reading D3, would discard as being inconsistent with the teaching of the remainder of said document.

4.3 For these reasons, D1 is chosen as representing the closest prior art. Example IV of D1, the embodiment closest to the subject-matter of claim 1, does not disclose a softgel capsule comprising specifically the

sodium salt of naproxen, the addition of an acid thereto, nor the use of a solubilizer (see section 2.1, above).

Problem solved

5. According to the appellant, the problem to be solved is the provision of a stable solvent system for naproxen sodium which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

5.1 As a solution to this problem, the appellant proposes a softgel capsule according to claim 1 of the main request comprising *inter alia* naproxen sodium and an organic acid chosen from a list in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium.

5.2 The experimental tests provided by the appellant as D7 compare the production of undesired PEG esters in samples 16-21 prepared according to D1 with samples 1-15 according to the application. Samples 7-15 correspond to compositions prepared in accordance with claim 1 of the main request with the exception that component (e) thereof is missing, while samples 1-6 employ HCl, an acid which does not fall under the alternatives listed in claim 1, part (b). After being subjected to accelerated stability testing at 60 °C for 7 days, no PEG ester formation was detected in samples 7-12 and 15, while minor amounts were observed in samples 13 and 14. In the solutions of samples 16-21, PEG ester formation was detected (D7, table on pages 6 and 7).

5.2.1 While samples 8 and 11 were physically characterised as clear solutions after the stability tests, samples 7, 9, 10 and 12-15, despite displaying no detectable PEG ester formation, were all physically characterised by either a phase separated precipitate or a semi-solid paste, physical states unfavourable for encapsulation into softgel capsules. The explanation provided by the appellant that the tests of D7 were carried out specifically for the purpose of demonstrating the reduction in PEG ester formation *vis à vis* the compositions prepared according to D1, rather than necessarily to produce clear solutions suitable for incorporation into a softgel capsule, is plausible. Addition of the solubilizer required by claim 1, step (e) to said samples would indeed be expected to provide the desired clear solutions.

5.2.2 It is also plausible that the effect of a reduction in PEG ester formation displayed by samples 7, 9, 10 and 12-15 would remain had the required solubilizer of claim 1, component (e) been included therein, thus producing a clear solution. Furthermore, said effect is credible not only for softgel capsule fill material prepared using lactic acid or citric acid according to comparative samples 7-15, but also for fill materials prepared using the alternative closely related organic acids listed in claim 1, component (b). The effect of a reduction in PEG ester formation is consequently recognised in respect of the whole scope of claim 1.

5.3 On the basis of the effect, the problem has been credibly solved by the subject-matter of claim 1.

Obviousness

6. Although D1 is also concerned with the preparation of a solvent system for enhancing the solubility of naproxen in order to produce concentrated solutions thereof suitable for encapsulation in a softgel, the problem of undesirable PEG ester formation is not recognised nor addressed therein.

6.1 Furthermore, according to D1 it is presumed that the increase in solubility is accomplished by increasing the number of species of naproxen (ionised and unionised) that are available to go into solution, thereby using both the hydrophobic and hydrophilic binding sites of PEG (D1, column 6, line 26 - column 7, line 26). D1 also suggests that the same effect can be achieved by simply adding in the appropriate ratio to PEG and water both the salt and the free acid, without the need for an ionising agent (column 10, lines 39-48).

6.2 Thus D1 teaches that in order to provide the concentrated solution of naproxen desired, the presence of both the free acid and the salt thereof is a prerequisite; how this mixture is obtained is less crucial. It follows that even if the skilled person were to recognise that the (partial) treatment of naproxen sodium with an acid would be a further method leading to the formation of the desired mixture of ionised and unionised naproxen, he would not expect the resultant solution to differ in any of its properties to that produced according to the options provided in D1. Consequently, there is nothing in D1 which would lead the skilled person looking to solve the above problem to the solution of claim 1 of the main request.

6.3 On that basis claim 1 of the main request involves an inventive step.

6.4 Since claim 1 directed to a capsule comprising a fill material involves an inventive step, the same conclusion applies to the use of said fill material in the manufacture of a medicament in the form of a capsule according to claim 13.

6.5 On that basis claim 13 of the main request involves an inventive step.

Conclusion

7. The subject-matter of independent claims 1 and 13 of the main and sole request fulfill the requirements of the EPC.

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 with the order to grant a patent on the basis of the claims of the main request filed during the oral proceedings of 16 September 2014 and a description to be adapted thereto.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated