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Datasheet for the decision of 23 August 2018

Case Number: T 0142/15 - 3.3.01

Application Number: 00901483.8

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Language of the proceedings: EN

Title of invention:

NON-AQUEOUS PHARMACEUTICAL COMPOSITION FOR DERMAL USE TO TREAT PSORIASIS COMPRISING A VITAMIN D, A CORTICOSTEROID AND A SOLVENT COMPONENT

Patent Proprietor:

LEO PHARMA A/S

Opponents:

Teva Pharmaceutical Industries Ltd.
Sandoz AG
PENTAFARMA S.A.

Relevant legal provisions:

EPC Art. 123(2), 101(3), 83, 56

Keyword:

Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0142/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 August 2018

Respondent: (Patent Proprietor)	LEO PHARMA A/S Industriparken 55 2750 Ballerup (DK)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 5 Basel Street, P.O. Box 3190 Petah Tiqva 49131 (IL)
Representative:	D Young & Co LLP Briton House Briton Street Southampton SO14 3EB (GB)
Appellant: (Opponent 3)	PENTAFARMA S.A. Rua da Tapada Grande no. 2 Abrunheira 2710-089 Sintra (PT)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Party as of right: (Opponent 2)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Greiner, Elisabeth df-mp Dörries Frank-Molnia & Pohlman

Patentanwälte Rechtsanwälte PartG mbB
Theatinerstraße 16
80333 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 27 November 2014 concerning maintenance of the European Patent No. 1178808 in amended form.**

Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 178 808 was granted with a set of ten claims.

II. Three notices of opposition were filed, opposing the patent under Article 100(a), (b) and (c) EPC in particular on the grounds that the claimed subject-matter lacked an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

III. In the opposition proceedings, the patent proprietor requested the rejection of the oppositions (main request) and filed several sets of claims as auxiliary requests.

The sole independent claim of the first auxiliary request reads as follows:

"1. A non-aqueous pharmaceutical composition for dermal use to treat psoriasis sebopsoriasis and seborrhoic dermatitis in humans and other mammals, said composition comprising

a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and

a second pharmacologically active component B consisting of at least one corticosteroid

wherein the difference between the optimum stability pH of said first component A and the optimum pH of said second component B is at least 1;

and further comprising at least one solvent component C,

wherein said first component A is selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof and

wherein said second component B is selected from the group consisting of Betamethasone, Clobetasol, Clobetasone, Desoximethasone, Diflucortolon, Diflorasone, Fluocinonid, Flumethasone, Fluocinolon, Fluticasone, Fluprednidene, Halcinonide, Hydrocortisone, Momethasone, Triamcinolon, and pharmaceutically acceptable esters and acetonides as well as mixtures thereof, and

wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) and mixtures thereof, wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, and R^2 is straight chain or branched C_{1-20} alkyl or benzoyl."

IV. The documents cited in the course of the opposition proceedings included the following:

D4: British Journal of Dermatology 138, 254-258 (1998)

D11: WO 94/14453 A1

D12: J Am Acad Dermatol 38(6)-I, 1010-1011 (June 1998)

D22: US 4 083 974

D42: Declaration by Gert Høy (3 December 2008); Studies Involving Solvent Vehicles Containing Almond Oil

D46: A. Wade, P. Weller: Handbook of Pharmaceutical Excipients, 2nd ed, Washington 1994, pp. 407-408

D49: Expert Report of Professor Brown (22 April 2014)

D60: Van de Kerkhof (editor): Textbook of Psoriasis, Oxford 1999; Chapter 8 (pages 121 to 147)

V. The decision under appeal is the opposition division's interlocutory decision announced on 20 October 2014 and posted on 27 November 2014, rejecting the patent proprietor's main request and finding that the patent as amended in the form of the first auxiliary request met the requirements of the EPC.

VI. In the decision under appeal, the opposition division found that, while the grounds of opposition pursuant to Article 100(b) and (c) EPC did not prejudice the maintenance of the patent as granted, the claimed subject-matter did not however involve an inventive step starting from the technical teaching of prior-art document D12 (Articles 100(a), 52(1) and 56 EPC).

Claim 1 of the first auxiliary request differed from claim 1 as granted in that it restricted the group of compounds from which the mandatory solvent component C could be selected to those of formula (II). For the same reasons as set out in the context of the main request, the claimed subject-matter did not go beyond the content of the application as filed and was sufficiently disclosed for it to be carried out by a person skilled in the art. Starting from the teaching of documents D12 or D11, the person skilled in the art would have had no incentive and would have found no pointer in the prior art for employing such a solvent in order to solve the technical problem of providing a stable formulation comprising both components A and B. The claimed subject-matter was also inventive when starting from the technical teaching of document D22.

VII. Opponents 1 and 3 filed appeals against the opposition division's finding that the first auxiliary request met the requirements of the EPC.

Both requested that the decision under appeal be set aside and the patent be revoked.

The following documents were, *inter alia*, presented:

D65: J. Pharm. Sciences, 68(3), 275-280 (1979)

D67: "Almond Oil" pages 25-26 (title and date of publication missing)

VIII. The patent proprietor filed an appeal against the rejection of its main request, requesting that the decision under appeal be set aside and the oppositions be rejected.

In response to the appeals filed by opponents 1 and 3, the patent proprietor requested subsidiarily that the opponents' appeals be dismissed (first auxiliary request), and filed several sets of claims as lower-ranking auxiliary requests.

IX. Opponent 2 did not file an appeal and did not submit any arguments or requests in writing.

X. In reply to the summons to oral proceedings issued by the board, opponents 1 and 3 advised that they would not be attending the oral proceedings.

XI. Oral proceedings were held on 23 August 2018 in the absence of opponents 1 and 3.

During the oral proceedings, the patent proprietor withdrew its appeal, maintained the request that the appeals of opponents 1 and 3 be dismissed, and withdrew all lower-ranking requests. Accordingly, the former first auxiliary request (i.e. the request which was deemed allowable by the opposition division) remained as the patent proprietor's sole pending request in the appeal proceedings.

Opponent 2 stated that, in these circumstances, it had no requests.

XII. The arguments presented in writing by opponent 1 and opponent 3 (appellants) may be summarised as follows:

Amendments

The combination of technical features as defined in claim 1 was the result of multiple selections relative to the application as filed, which constituted added subject-matter in contravention of Article 123(2) EPC.

Sufficiency of disclosure

Claim 1 mentioned the parameters "optimum stability pH" (component A) and "optimum pH" (component B). It was not apparent how these parameters were defined, and in particular, how they should be measured and in what respect they differed. While the compositions as defined in claim 1 were non-aqueous, the patent in suit did not provide any guidance for determining the pH under non-aqueous conditions. If, for one or both components, the optimum stability pH was a pH range, there would be doubt about how to determine the pH difference according to claim 1. Identifying combinations of A and B with the required pH difference of at least 1 would present an undue burden to the person skilled in the art.

Inventive step

The compositions according to claim 1 differed from compositions disclosed in document D12 in that they contained a solvent component C of formula (II). Opponent 1 regarded the non-aqueous nature of the compositions as a further distinguishing feature. The technical effect of the claimed subject-matter as alleged by the patent proprietor was the stability of components A and B when contained in the same composition. The patent in suit did not actually

provide comparative data in respect of D12 (which disclosed a composition containing calcipotriol in combination with hydrocortisone-17-valerate). Assuming nevertheless that the patent provided sufficient information for the alleged technical effect to be plausibly disclosed, the objective technical problem could be defined as the provision of an improved (stable) formulation for the treatment of psoriasis.

The difference in the stability pH profiles of the two pharmacologically active components A and B was well recognised at the priority date of the patent in suit. Employing a non-aqueous vehicle was therefore an obvious measure for preventing the pH-related destabilisation of components A and/or B when both were to be combined in the same vehicle. In the absence of water, pH-mediated stability issues would be expected to be eliminated, or at least decreased to an extent that they would no longer be of concern. The evidence on file did not show conclusively that the presence of a solvent of formula (II) was essential for solving the problem of instability in the combination formulation. Within the limits of a few obvious restrictions, i.e. that the solvent did not contain acids or bases, that it was not hygroscopic and that it was able to dissolve the vitamin D analogue (component A), the selection of the solvent component was thus a routine matter within the normal activities of the skilled person, who disposed of a wide choice of suitable solvents.

Document D22 which disclosed non-aqueous corticosteroid ointments containing, for instance, polyoxypropylene-15 stearyl ether (Arlamol® E) conforming to formula (II), would be a reasonable alternative starting point for the assessment of inventive step. The teaching of

document D65 was in its essence identical to that of D22.

Document D60 concerning combination therapy with components A and B might also be considered as a starting point for the assessment of inventive step.

XIII. The arguments presented by the patent proprietor in its capacity as respondent to the opponents' appeal may be summarised as follows:

Amendments

The opposition division's analysis concerning support for claim 1 in the application as filed was correct (see the decision under appeal, 4.1 and 3.1). Specific reference was made to claims 20, 22 and 24 and the passages on page 3, lines 18 to 21, and page 11, lines 10 ff, in the application as filed.

Sufficiency of disclosure

It would immediately be evident to a person skilled in the art reading claim 1 that the "optimum pH" of compound B was indeed its "optimum stability pH". The determination of the optimum stability pH of a component was commonplace; it was self-evident that it must be examined at which pH value, in an aqueous medium, the component was most stable. The opponents' objection that finding suitable combinations of components A and B represented an undue burden was a mere unsubstantiated allegation.

Inventive step

Starting from the technical teaching of document D12, the technical problem to be solved was the provision of an improved stable formulation of a vitamin D analogue

(component A) and a corticosteroid (component B) for the treatment of psoriasis. Choosing a non-aqueous vehicle did not by itself ensure the desired stability - rather, the selection of the specific mandatory solvent component C, too, was relevant. The patent in suit showed that a polyoxypropylene alkyl ether conforming to formula (II) of claim 1 (namely, polyoxypropylene-15 stearyl ether available as "Arlamol® E") functioned as a solvent for a stable combined formulation of components A and B. The opponents had provided no convincing reason why the prior art would have prompted the person skilled in the art to use a compound of formula (II) as the solvent in such a formulation. At best, Arlamol® E was known to be a solvent for corticosteroids (i.e. components B) only, but that knowledge would not have provided any incentive to consider it as the solvent for a stable composition including both components A and B, as defined in claim 1.

The disclosure of document D22, which did not mention the treatment of psoriasis and which related to a mono-active formulation of component B rather than to a combination product containing both components A and B, was remote from the invention of the patent in suit and did not present a realistic starting point for the skilled formulator. The same argument applied to document D65 (with a content similar to that of D22).

Unlike document D12, document D60 (on page 132 cited by opponent 3) did not disclose a mixture including both "A" and "B" components within a single composition, but instead referred to morning/evening separate administration of A and B as reported in document D4. Thus there was no good reason to select D60 as the closest prior art.

XIV. The present decision is based upon the following final requests by the parties:

(a) Opponents 1 and 3 (appellants) requested that the decision under appeal be set aside and the patent be revoked.

(b) Opponent 2 (party as of right pursuant to Article 107 EPC) did not submit any requests.

(c) The patent proprietor (respondent) requested that the appeals of opponents 1 and 3 be dismissed.

Reasons for the Decision

1. Non-attendance at oral proceedings

1.1 As announced in their letters dated 9 July 2018 and 26 July 2018, opponents 1 and 3, who had been duly summoned to oral proceedings pursuant to Rule 115(1) EPC, did not attend the oral proceedings (see points X and XI above).

1.2 In accordance with Rule 115(2) EPC, the board decided that the proceedings be continued in their absence and, pursuant to Article 15(3) RPBA, that they be treated as relying only on their written cases.

2. Amendments

2.1 Claim 18 of the application as filed (PCT/DK00/00033) is directed to a pharmaceutical composition for dermal use comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid, characterised in that the difference

between the optimum stability pH of said first component A and the optimum pH of said second component B is at least 1; and at least one solvent component C which may be selected from six specified classes of compounds (covering, *inter alia*, compounds of formula (II)).

This embodiment is also described on page 11, lines 10 to 30, of the application as filed, restricted to its non-aqueous version, as a preferred embodiment.
In view of this, the board considers that the distinct non-aqueous embodiment, as generally disclosed on page 11, may be combined with the subject-matter of the claims dependent on, or referring back to, claim 18.

Claim 20, which is dependent on claim 18, restricts the selection of the mandatory solvent component C to the class of compounds conforming to formula (II), as defined in present claim 1.

Claim 22, which is dependent on claims 18 to 21, additionally restricts the selection of component B to the members of the group defined in present claim 1.

2.2 The description as filed contains a general disclosure of preferred components A (see page 3, lines 18 to 21) corresponding to the list of eligible components A defined in present claim 1.

The medical indications psoriasis, sebo-psoriasis and seborrhoic dermatitis in humans and other mammals are supported by page 9, lines 20 to 26, and also by claims 28 and 29 (both addressing the topical treatment of psoriasis and related skin diseases or disorders and referring back to any of claims 1 to 27 of the application as filed).

Since these are general disclosures, they also apply to the embodiment discussed in point 2.1.

2.3 In consideration of points 2.1 and 2.2 above, the board arrived at the conclusion that the features of the cited claims and passages were indeed disclosed in combination, and that therefore the subject-matter of present claim 1 does not go beyond the content of the application as filed (Article 123(2) EPC).

2.4 As far as the dependent claims are concerned, the opponents did not raise specific objections, and the board sees no reason for objection pursuant to Article 123(2) EPC.

3. Claim analysis and sufficiency of disclosure

3.1 It is undisputed that the combined formulation of components A and B is an effective treatment for psoriasis. While the word "and" is used in the list of diseases to be treated, the board understands claim 1 in the sense that the treatment of psoriasis, sebopsoriasis or seborrhoic dermatitis is addressed. It was not contested that it is plausible that the claimed composition would be useful in treating the other two diseases.

3.2 With regard to the objections raised by opponents 1 and 3 on the issue of sufficiency (see point XII above):

- The board considers that the term "optimum stability pH" is self-explanatory and designates the pH value (or, if applicable, the pH range) at which a component is most stable.

- The reader of claim 1 would also understand that "optimum pH" means the same as "optimum stability pH": It is, after all, the stated object of the patent in suit to combine, in a single stable formulation, components A and B which might normally be expected

to be instable in each other's presence due to their incompatible stability pH profiles. The pH difference of at least 1 is the criterion for identifying such "problematic" pairs of components. Thus it is immediately evident to the reader that the pH difference relates to values of the same pH parameter (namely, the optimum stability pH), as respectively determined for component A and component B.

- Since according to claim 1, the optimum stability pH values characterise the individual components A and B, it will be inferred that those parametric values will be determined for each component separately. It is furthermore implicit, in view of the common general knowledge, that the pH must be measured in an aqueous medium. Contrary to the opponents' assumption, claim 1 does not imply that the optimum stability pH should be determined in a non-aqueous medium, because there is no logical connection between the determination of the optimum stability pH of the separate components A and B and the technical feature specifying that the finished combination preparation is non-aqueous.

- Methods for stability testing and for measuring pH values are commonly known.

- The opponents did not identify specific examples of components A or B showing a plateau of constant optimum stability over a broader pH range. Should the case nevertheless arise that pH ranges must be compared, it is self-evident that the upper endpoint of the lower range should be subtracted from the lower endpoint of the higher range to calculate the difference in optimum stability pH.

- The objection that identifying suitable combinations of components A and B would present an undue burden to

the person skilled in the art is not plausible, since components A and B can only be selected from two lists of limited size, and as to the methodology, nothing more than conventional stability testing and the routine determination of pH values appears to be called for.

3.3 For these reasons, the opponents' objections regarding insufficiency of disclosure must fail (Articles 101(3) and 83 EPC).

4. Inventive step

Patent in suit

4.1 The patent in suit acknowledges that it was known to employ vitamin D analogues (component A) and corticosteroids (component B) in combination in the topical treatment of psoriasis, albeit formulated and administered in separate preparations. A topical pharmaceutical composition comprising a combination of components A and B had not been described. For easier administration and improved compliance, the person skilled in the art would wish to combine the two pharmacologically active components in a single formulation while maintaining good stability of the active components. However, practical difficulties were encountered due to the fact that components A, e.g. calcipotriol, required a pH value above 8 for maximum stability, while components B such as betamethasone required pH values in the range of 4 to 6 (see paragraphs [0001] to [0004] of the patent specification).

4.2 The technical solution suggested in present claim 1 for overcoming this incompatibility involves combining components A and B in a single formulation which

is non-aqueous and comprises a solvent component C of formula (II).

Starting point in the prior art

4.3 Documents D12 or D22 were proposed by the parties as possible starting points for the assessment of inventive step. Opponent 3 also mentioned document D60, but did not go on to develop a chain of reasoning consistent with the problem-and-solution approach on that basis. It was also mentioned that the teaching of document D65 was identical to that of document D22.

4.4 As already mentioned (see point 4.1. above), it is acknowledged in the patent in suit that it was common to use a combination treatment involving a vitamin D analogue (component A) and a steroid (component B) in the topical treatment of psoriasis. The board takes the view that a realistic starting point for the assessment of inventive step must contain these elements.

4.5 Documents D22 and D65

4.5.1 Document D22 teaches that topical steroid formulations in the form of ointments or non-aqueous solutions may contain polyoxypropylene-15 stearyl ether marketed under the trademark "Arlamol® E" (i.e. a solvent component C according to formula (II) of claim 1). According to D22, that solvent is used to replace propylene glycol; it has the function of solubilising the steroid component, is non-irritating and has lubricant properties (see D22: claims, examples, column 1, lines 54 to 63). The steroid of D22 may be a component B as defined in present claim 1.

4.5.2 No mention is made, however, of vitamin D analogues (component A) or combination therapy, and D22 provides

no incentive for adding a second pharmacologically active agent to the formulations.

4.5.3 Thus the board considers that an assessment starting from the teaching of document D22 cannot lead the way, without hindsight, to the subject-matter of claim 1.

4.5.4 The same conclusion applies to document D65, which describes compositions containing diflorasone diacetate (component B) and polyoxypropylene-15 stearyl ether (solvent component C) in a mineral oil base.

4.6 Document D12

4.6.1 It is common ground that document D12 is a suitable starting point for the assessment of inventive step. D12 discloses that calcipotriol is a widely prescribed topical treatment for psoriasis. For better convenience, pharmacists and patients have been known to mix calcipotriol ointment and other psoriasis medications in a single container. Calcipotriol is however inactivated by an acidic pH and can be unstable when mixed with other topical preparations (see D12: page 1010, column 1, paragraph 1).

That was found to be the case for a mixture of calcipotriol (component A) 0.005% ointment and hydrocortisone-17-valerate (component B) 0.2% ointment (see D12: page 1010, column 2, Figure 1, "Results"; page 1011: "Discussion").

4.6.2 Thus the teaching of document D12 corresponds to the starting point identified in the patent in suit, namely, stability problems are encountered when it is attempted to combine both components A and B in a single formulation.

4.7 Document D60

4.7.1 The board observes that the passage on page 132 of D60 cited by opponent 3 merely summarises the content of another document relating to combination therapy (D4), but does not disclose a single formulation containing components A and B. The treatment schedule according to the referenced document D4 involved the administration of calcipotriol (component A) in the morning and bethamethasone valerate (component B) in the evening (see D4: page 255, column 1).

4.7.2 Thus document D60 cannot provide a more promising starting point for the development of a combination preparation than document D12.

4.8 In view of these considerations, document D12 is regarded as the most suitable starting point for the assessement of inventive step.

Technical problem and solution

4.9 The technical features distinguishing the subject-matter of present claim 1 from the disclosure of document D12 (in particular, the mixture of calcipotriol 0.005% ointment and hydrocortisone-17-valerate 0.2% ointment) are:

1) the non-aqueous nature of the composition (since D12 does not disclose a non-aqueous vehicle), and

2) the presence of a solvent component C conforming to formula (II).

4.10 The technical effect allegedly achieved by the claimed subject-matter is the acceptable stability of components A and B when present in a single formulation. In that context, the patent in suit mentions in paragraphs [0008] and [0015] that non-

aqueous preparations are specifically envisaged and ointment-type preparations are preferred, and furthermore states in paragraph [0016]: "It has been found that in such combination compositions containing a solvent component C, the active components can co-exist without degradation, despite their different pH/stability profiles. The tendencies of the active compounds to affect one another with regard to pH is minimised or eliminated."

4.11 Example 1 of the patent in suit (see paragraphs [0027] to [0028]) describes an ointment formulation containing calcipotriol (component A), betamethasone dipropionate (component B) and polyoxypropylene-15 stearyl ether (solvent component C) in a non-aqueous, paraffin-based vehicle.

According to paragraph [0004] of the patent in suit, the optimum stability pH is above 8 for calcipotriol and between 4 and 6 for corticosteroids such as betamethasone. In addition, the patent proprietor referred to document D49 (see points 99 and 100) which confirms that betamethasone dipropionate is most stable at a pH value of 4. Hence the composition of example 1 meets the pH criterion defined in claim 1.

Example 2 of the patent in suit (see paragraphs [0029] to [0035]) reads on to example 1 and relates to stability tests carried out with, presumably, the same composition. This was undisputed. Both calcipotriol and betamethasone remained stable under the test conditions (storage at 25°C during three months or at 40°C during one month or three months; see Table 1).

4.12 In a similar non-aqueous ointment also containing calcipotriol and betamethasone dipropionate in a paraffin-based vehicle, but containing propylene glycol

and lanolin instead of a solvent of formula (II), the calcipotriol showed strong degradation when that composition was stored for 2.5 months at either 5°C or 40°C (see example 2: paragraph [0034] and Table 2 of the patent in suit).

4.13 Example 2 demonstrates that a composition as defined in claim 1 presented a satisfactory stability of both components A and B. While the corticosteroid (component B) of example 2 is not the same as in document D12, it is structurally similar and there is no reason to assume that this would be a crucial factor. On the other hand, the desired stability was not achieved when a different vehicle was used which did not contain a solvent according to formula (II) (see point 4.12 above).

4.14 Thus the objective technical problem is the provision of a composition for dermal use which combines a vitamin D analogue and a corticosteroid selected from components A and B as defined in claim 1 in a single preparation, while avoiding pH-related instability of the pharmacologically active components.

4.15 That problem is solved by compositions according to claim 1.

Obviousness of the solution

4.16 In view of the incompatible stability pH profiles of components A and B (defined as a technical feature in claim 1), the board considers that it would have been obvious for a person skilled in the art to choose a non-aqueous vehicle in order to minimise pH-related stability issues. As a consequence, whether an inventive step can be acknowledged depends upon the role of solvent component C.

4.17 According to the comparative test described in example 2 of the patent in suit (see paragraphs [0034] to [0035] and point 4.12 above), the calcipotriol (component A) degraded when a non-aqueous vehicle was used which did not contain a solvent component C according to formula (II).

According to document D42, similar tests were carried out with compositions containing a combination of hydrocortisone acetate (component B) and either calcipotriol or calcitriol (component A) in a mixture of white paraffin and almond oil. Document D42 reports that a significant degradation of the calcipotriol and calcitriol occurred after storage at 40°C for one month or three months.

These test results suggest that the composition of the non-aqueous vehicle is indeed relevant at least to the stability of component A.

4.18 In that context, the opponents argued that the test results obtained with the comparative samples were neither representative nor conclusive and, in a second approach, that it had not been shown that solvent components C of formula (II) presented any advantages in comparison with the larger group of solvent components C originally encompassed in the definition of the solvent according to claim 1 as granted.

4.18.1 With regard to the first issue, the opponents submitted that it was well known that almond oil contained free fatty acids, and the person skilled in the art would therefore not use this material together with an acid-sensitive vitamin D analogue such as calcipotriol. The same was true for propylene glycol, which was known to form acidic impurities. Furthermore, since propylene glycol was hygroscopic, it would not be selected by a

skilled person for preparing a non-aqueous composition. Hence, in addition to the fact that only very limited data had been provided, the comparative tests of example 2 and of document D42 were also artificial and unrealistic.

The patent proprietor argued that Arlamol® E had the same acid value as almond oil (D22: column 4, line 35; D67: Table 1). If the skilled person would avoid almond oil, they would avoid Arlamol® E for the same reason. Propylene glycol was a well-known standard solvent which formed acidic impurities only under specific unfavourable storage conditions which would not be applied to a pharmaceutical material; furthermore, both Arlamol® E and propylene glycol could contain small amounts of water (see D22: column 4, line 33; D46: column 2, table).

On that basis, the board arrived at the conclusion that the opponents' doubts are of a rather speculative nature and do not prove that the person skilled in the art would have ruled out propylene glycol or almond oil as clearly unsuitable for the non-aqueous vehicle. Thus the comparative examples are valid and the board accepts on that basis that there are non-aqueous vehicles containing plausible solvents which nevertheless do not achieve the desired stability.

4.18.2 With regard to the second issue, the board considers that it is not relevant whether other groups of structurally different solvents, previously claimed as alternatives to the solvents of formula (II), may also be suitable for solving the technical problem.

The important point is that, on the basis of example 2 and of the tests reported in document D42, it can be acknowledged that not all solvents are suitable for

providing compositions in which components A and B can co-exist without stability problems.

In a further step, it has to be determined whether the prior art discloses or suggests that solvents of formula (II) will solve the objective technical problem.

4.19 Document D12 itself does not disclose a specific vehicle composition nor does it suggest the use of solvents of formula (II).

4.20 While document D22 relates to formulations of corticosteroids (covering components B of claim 1) containing polyoxypropylene-15 stearyl ether ("Arlamol® E") as a solvent, it does not disclose how solvents of that class would interact with vitamin D analogues (i.e. component A of claim 1). Since this type of solvent was not in common use as a pharmaceutical solvent at the priority date of the patent in suit, the board considers that the person skilled in the art attempting to solve the objective technical problem would not have included it in sample formulations for pre-formulation stability testing without any specific incentive in the prior art to suggest that it would be a particularly good candidate solvent.

4.21 As a consequence, the subject-matter of claim 1 of the patent proprietor's sole request involves an inventive step within the meaning of Article 56 EPC. The same applies to the dependent claims (claims 2 to 9).

Order

For these reasons it is decided that:

The appeals of opponents 1 and 3 are dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated