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D E C I S I O N
of 9 March 1999

Case Number: T 0549/96 - 3.3.1

Application Number: 91917288.2

Publication Number: 0503035

IPC: C07C 401/00

Language of the proceedings: EN

Title of invention:
Novel 1α-hydroxy vitamin D_4 and novel intermediates and analogues

Applicant:
Bone Care International, Inc.

Opponent:
-

Headword:
Vitamin D derivatives/BONE CARE

Relevant legal provisions:
EPC Art. 56, 111(1)

Keyword:
"Inventive step (yes, regarding objected claims) - problem and solution approach - non-obvious solution"
"Remittal to the first instance for further prosecution"

Decisions cited:
-

Catchword:
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Case Number: T 0549/96 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 9 March 1999

Appellant: Bone Care International, Inc.
One Science Court
Madison, WI 53711 (US)

Representative: Ford, Michael Frederick
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 31 January 1996 refusing European patent application No. 91 917 288.2 pursuant to Article 97(1) EPC.

Composition of the Board:

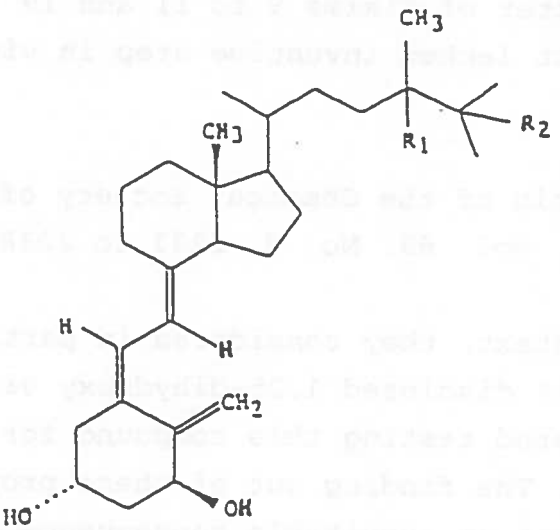
Chairman: A. J. Nuss
Members: J. M. Jonk
R. E. Teschemacher

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examination Division refusing the European patent application No. 91 917 288.2, having been published under number WO 92/05130, and relating to novel 1α-hydroxy vitamin D_4 and novel intermediates and analogues.

II. The decision was based on a main request and auxiliary requests 1 and 2 then on file, Claims 9, 19 and 20 of said main request reading as follows:

"9. A prophylactic or therapeutic pharmaceutical composition, comprising an amount of a compound of the formula (I):



(I)

wherein R1 is either H or OH and R2 is either H or OH in combination with a pharmaceutically acceptable vehicle."

"19. A feed for mammals comprising at least one compound of the formula (I) wherein R1 is either H or OH and R2 is either H or OH wherein normal consumption of the feed by the mammals provides about 0.01 to about 0.5 µg/kg/day of said compound."

"20. Use of a compound of formula (I) for the manufacture of a medicament for the treatment of vitamin D deficiency induced disease,
and/or osteoporosis,
and/or hyperproliferative skin disorders
and/or hypocalcemia,
and/or to control calcium metabolism in a mammal."

III. The Examination Division held, inter alia, that the subject-matter of Claims 9 to 11 and 19 to 23 of said main request lacked inventive step in view of the document

(1) Bulletin of the Chemical Society of Japan (August 1990), vol. 63, No. 8, 2233 to 2238.

In this context, they considered in particular that document (1) disclosed 1,25-dihydroxy vitamin D_4, and also suggested testing this compound for its biological properties. The finding out of these properties would then arise as an inevitable consequence of said suggestion and, therefore, could not justify an inventive activity.

They, also considered that the claims of the third auxiliary request then on file were allowable.

IV. Oral proceedings before this Board were held on 9 March 1999.

V. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or one of the auxiliary requests 1 to 3, all submitted with a letter dated 8 December 1995, or on the basis of auxiliary request 4, submitted on 8 February 1999.

VI. With respect to the main request, which corresponded to the main request forming the basis of the decision of the Examination Division, and in particular regarding the subject-matter of the objected Claims 9 to 11 and 19 to 23 of this request, the Appellant argued that the vitamin D_4 derivatives according to the patent application in suit displayed biological activities comparable to those of corresponding vitamin D_2 and D_3 derivatives, and that they showed toxicity properties similar to those of corresponding vitamin D_2 derivatives and lower than those of corresponding vitamin D_3 derivatives. In this context, he referred to Example 3 of the present patent application and the test-report as submitted on 10 June 1996. Moreover, he argued that on the basis of document (1) a skilled person was in no position to predict a good combination of activity and toxicity before carrying out research work which was not reported in this document. He also referred to the prior art discussed in the patent application in suit, in particular:

(2) De Luca, et al., Archives of Biochemistry and Biophysics, 124 (1968), 122-128, and

(3) The Merck Index, 11th Edition (1989), page 1579,

indicating that a skilled person would expect that the present vitamin D_4 derivatives had an unsatisfying biological activity.

With respect to the procedure at the oral proceedings before the Examining Division, in which the Appellant was given an opportunity to withdraw his main request and his auxiliary requests 1 and 2, so as to allow the Examination Division to grant a patent on the basis of the third auxiliary request, the Appellant submitted that such a procedure was not correct. In this context, he submitted in particular that according to the principle of *reformatio in peius* the applicants should have received a decision allowing the third auxiliary request while explaining the grounds on which the other requests were refused, instead of a decision to refuse the patent application.

VII. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 The substantive issue to be dealt with is whether the subject-matter of Claims 9 to 11 and 19 to 23 involves an inventive step.

2.2 Article 56 EPC sets forth that an invention involves an inventive step if, having regard to the state of the art (in the sense of Article 54(2) EPC), it is not obvious to a person skilled in the art.

2.3 For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the "problem-solution-approach", which consists essentially in (a) identifying the closest prior art, (b) assessing the technical results (or effects) achieved by the claimed invention when compared with the closest state of the art established, (c) defining the technical problem to be solved as the object of the invention to achieve these results, and (d) examining whether or not a skilled person starting from the closest prior art **would** arrive at something falling within the claimed invention by following the suggestions made in the prior art in the sense of Article 54(2) EPC.

2.4 According to the consistent case law of the Boards of Appeal the closest prior art for assessing inventive step is normally a prior art document **disclosing subject-matter conceived for the same purpose as the claimed invention** and having the most relevant technical features in common.

2.5 Moreover, it is observed by the Board that, in applying the "problem-solution-approach", the technical problem to be considered is likely to be that apparent from the patent application or patent in suit, unless strong reasons would speak against this, such as starting from an inappropriate state of the art for defining the technical problem to be solved, the absence of sufficient evidence that the stated problem has been

solved by the claimed invention, or the fact that the technical problem as indicated in the application or patent in suit has already been solved in the state of the art. In such cases, a reformulation of the underlying technical problem may become necessary.

2.6 In the present case, the **technical problem as apparent from the present patent application** has been seen in the provision of vitamin D derivatives having a satisfying biopotency, while being **less toxic**, as well as pharmaceutical and feed compositions containing such derivatives (see page 2, last line but one, to page 3, first line; page 3, first whole paragraph; page 6, third paragraph; and page 8, last but one paragraph; of the originally filed application).

2.7 Given this objective, the Board considers - in agreement with the Appellant - that the **closest state of the art** is represented by the summary in **document (1)** of the well established knowledge in the field of vitamin D indicating:

(a) that vitamin D_3 and vitamin D_2 must be hydroxylated at the C-25 position in the liver, and subsequently at the C-1α position in the kidney, before eliciting their physiological activity;

(b) that the activity of 1α,25-dihydroxyvitamin D_2 is similar to that of the corresponding vitamin D_3 derivative in mammals; and

(c) that, though 1α-hydroxyvitamin D_2 is equally potent to 1α-hydroxyvitamin D_3 regarding biological activity, the former is 5 to 10 times less toxic than the latter in rats (see page 2233, left column, first paragraph).

Moreover, this document relates in particular to **the chemical synthesis** of 22,23-dihydro-1α,25-dihydroxyvitamin D_2, i.e. **1α,25-dihydroxyvitamin D_4, in order to study the effect of unsaturation at the 22,23-position** (see page 2233, left column, second paragraph). Furthermore, it is stated that **the biological activities of this compound will be reported elsewhere** (see page 2235, left column, last paragraph before the experimental part).

2.8 Thus, having regard to the fact that the technical problem as indicated in the present patent application has already been solved by a specific vitamin D_2 derivative disclosed in document (1) (see in this respect points 2.6 and 2.7 above), the Board sees the technical problem underlying the present patent application - in agreement with the Appellant - in the provision of vitamin D derivatives having a biological activity and toxicity comparable to 1α-hydroxyvitamin D_2.

2.9 The present patent application suggests, as the solution to this problem, pharmaceutical as well as feed compositions according to Claims 9 and 19 comprising vitamin D_4 derivatives of formula (I) as defined in these claims, i.e. vitamin D_4 derivatives including 1α,25-dihydroxyvitamin D_4 disclosed in document (1).

2.10 In view of Example 3 of the patent application in suit, the Board considers it plausible that 1α-hydroxyvitamin D_4 has about the same low toxicity as 1α-hydroxyvitamin D_2, because this example shows LD_{50} values for 1α-hydroxyvitamin D_4 in male and female rats of 1.0 mg/kg and 3.0 mg/kg, respectively, and for 1α-hydroxyvitamin D_2 in male and female rats of 1.7 mg/kg and 1.8 mg/kg, respectively. Moreover, the test-report as submitted on 10 June 1996 demonstrates that with rats 1α-

hydroxyvitamin D_4 is metabolised biologically to the 1α,25-dihydroxyvitamin D_4 derivative. Thus, in view of said Example 3 showing a low toxicity for 1α-hydroxyvitamin D_4 and having regard to the fact that this compound is metabolised *in vivo* to 1α,25-dihydroxyvitamin D_4, the Board concludes that this last mentioned compound also has a low toxicity.

Moreover, said test-report also shows in the vitamin receptor binding (VDR binding) assay, i.e. a standard test for examining the binding ability of a vitamin D compound, that 1α,25-dihydroxyvitamin D_4 has a slightly better activity than 1α,25-dihydroxyvitamin D_3 (see in particular the attached graph). Therefore, having regard to the fact that for 1α,25-dihydroxyvitamin D_4 and 1α,25-dihydroxyvitamin D_3 similar biological activities have been demonstrated, and in view of the fact that it was known that vitamin D_3 and vitamin D_2, and their *in vivo* formed active hydroxy analogues, also display similar biological activities (see e.g. document (1), first paragraph), the Board is satisfied that the present vitamin D_4 derivatives have about the same biological activities as the corresponding vitamin D_2 derivatives.

Thus, in these circumstances, the Board considers it plausible that the technical problem as defined above has been solved.

2.11 The question now is whether the prior art would have suggested to a person skilled in the art solving the above-indicated technical problem in the proposed way.

2.12 Document (1) discloses - as indicated above under point 2.7, second paragraph - a process for the preparation of 22,23-dihydro-1α,25-dihydroxyvitamin D_2, i.e. of 1α,25-dihydroxyvitamin D_4, **in order to study the**

effect of unsaturation at the 22,23-position. However, while indicating that **the biological activity of this compound will be reported elsewhere**, it clearly does not provide any information about its biological activity, let alone about its toxicity. Therefore, in the Board's judgment, document (1) does not give any pointer to the skilled person how the technical problem underlying the present patent application as defined above could be solved.

2.13 The Board notes in this respect that in view of the teaching of document (1) a skilled person indeed **could** have tested 1α,25-dihydroxyvitamin D_4 on its activity. However, according to the consistent case law of the Boards of Appeal for determining lack of inventive step, it is necessary to show that considering the teaching of the relevant prior art as a whole, without using hindsight based on the knowledge of the claimed invention, the skilled person **would** have arrived at the **claimed solution of the technical problem to be solved**. However, as indicated above, a skilled person, when trying to solve the technical problem underlying the patent in suit, would not have found any reason in the state of the art to replace vitamin D_2 or its active derivatives by the vitamin D_4 derivatives as defined in the objected claims.

2.14 In this context, the Board notes that document (2) reports that in rats vitamin D_4 is two-thirds as active as vitamin D_3 or vitamin D_2, and that the skilled person in reading this document would have expected that the *in vivo* formed hydroxy derivatives of these vitamins would display about the same activities. Moreover, document (3) discloses with respect to vitamin D_4 that its biological activity seems doubtful. Therefore, as

submitted by the Appellant, documents (2) and (3) clearly suggest that vitamin D_4 derivatives have an unsatisfying biological activity, and therefore rather lead away from the solution of the problem underlying the present application as claimed.

2.15 Furthermore, the Examining Division held that according to document (1) the inventive work had already been done by preparing the compound 1α,25-dihydroxyvitamin D_4 with the intention to test it for vitamin D type properties. However, this conclusion neglects that there is nothing in document (1) casting any doubts on the correctness of the above indicated information derivable from documents (2) and (3) (see the preceding paragraph). For this reason, the fact that testing of said compound was announced in document (1) cannot be considered as a hint that the preparation of said compound was done in the expectation of any useful pharmaceutical effect.

2.16 In conclusion, the Board finds that the compositions according to present Claims 9 and 19 involve an inventive step in the sense of Article 56 EPC.

Furthermore, since the subject-matter of Claim 20 concerns the use of a compound of formula (I) for the manufacture of a medicament for the treatment of vitamin D deficiency induced diseases, this claim is also considered allowable for the same reasons.

Since Claims 9 and 10, and Claims 21 to 23 relate to particular embodiments of the independent Claims 9 and 19, respectively, they are also allowable.

2.17 According to the decision of the Examining Division the claims of the main request being objected to were Claims 9 to 11 and 19 to 23. However, in the Board's judgment, this does not mean that the Examining

Division examined the formal and substantive allowability of all the other claims of the present main request up to the hilt. Therefore, the Board makes use of its competence under Article 111(1) and remits the case to the first instance EPC for further prosecution.

Auxiliary requests

3. In the light of the above findings, it is not necessary to consider the Appellant's auxiliary requests.

Procedural issues

4. The Appellant also submitted that according to the prohibition of *reformatio in peius* in appeal proceedings the applicants should have received a decision allowing the third auxiliary request while explaining the grounds on which the other requests were refused, instead of a decision to refuse the patent application.

4.1 In this context, the Board notes that according to Article 113(2) EPC the Examining Division should decide upon an application only in the text agreed by the applicant. It follows therefrom that an applicant must unambiguously indicate at the end of the proceedings, which text he proposes. Otherwise, the Examining Division would be unable to decide on the basis of which version it should proceed and the application would eventually have to be refused, since there would be no clear request at all. Thus, if an applicant fails to indicate his approval of the text of an allowable subsidiary request, e.g. by express disapproval or by maintaining one or more unallowable higher-preference requests, the Examining Division can refuse the application under Article 97(1) EPC.

4.2 Moreover, the Board notes that the situation in opposition proceedings differs from that in grant proceedings in that in the case of an allowable auxiliary request in opposition proceedings an interlocutory decision is taken under Article 106(3) EPC to the effect that the European patent meets the requirements of the EPC, account being taken of the amendments made by the patent proprietor. This interlocutory decision must then also contain the reasons why the preceding requests do not meet the requirements of the Convention. The purpose of such an interlocutory decision in opposition proceedings is to save the proprietor the further costs of fulfilling the formal requirements under Rule 58(5) EPC before there is a final decision on the version in which the patent can be maintained. No comparable situation exists in grant proceedings. On the contrary, in *ex parte* appeal proceedings the principle of examination *ex officio* applies (see G 10/93, OJ EPO 1995, 172, point 3 of the Reasons). Up to the grant stage it has to be ensured that the conditions for patentability are met. An interlocutory decision, stating that the application in a certain version meets the requirements of the Convention, would be in conflict with this purpose (see also T 839/95, dated 23 June 1998, not published in the OJ EPO).

4.3 The above considerations lead the Board to draw the Appellant's attention to the Legal Advice from the European Patent Office, No. 15/98 (OJ EPO 3/1998, 133) dealing with various aspects and procedural consequences of filing auxiliary requests, inter alia, in the examining proceedings under 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 first instance for further prosecution.

The Registrar: The Chairman:

E. Görgmaier A. Nuss