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# D E C I S I O N
# of 11 July 2006

**Case Number:** T 1066/03 - 3.3.01

**Application Number:** 96924553.9

**Publication Number:** 0839132

**IPC:** C07D 207/34

**Language of the proceedings:** EN

**Title of invention:**
NOVEL PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1)

**Patentee:**
Warner-Lambert Company LLC

**Opponent:**
Dr. Robert Waldraff
-Patente, Strategien, Märkte-

**Headword:**
Polymorphic Atorvastatin/WARNER-LAMBERT

**Relevant legal provisions:**
EPC Art. 100(b), 83

**Keyword:**
"Sufficiency of disclosure (no) - undue burden in carrying out the claimed invention - research program"

**Decisions cited:**
T 0737/90

**Catchword:**
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**Case Number:** T 1066/03 - 3.3.01

# D E C I S I O N
**of the Technical Board of Appeal 3.3.01**
**of 11 July 2006**

**Appellant:** (Patent Proprietor)
Warner-Lambert Company LLC
201 Tabor Road
Morris Plains, NJ 07950 (US)

**Representative:**
Henkel, Feiler & Hänzel
Patentanwälte
Maximiliansplatz 21
D-80333 München (DE)

**Respondent:** (Opponent)
Dr. Robert Waldraff
-Patente, Strategien, Märkte-
Dr. Berndl-Strasse 3
D-87700 Memmingen (DE)

**Representative:**
Becker Kurig Straus
Patentanwälte
Bavariastrasse 7
D-80336 München (DE)

**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 29 July 2003 revoking European patent No. 0839132 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** A. J. Nuss
**Members:** C. M. Radke
J. Van Moer

## Summary of Facts and Submissions

I. The Appellant (Proprietor of the Patent) lodged an appeal on 29 September 2003 against the decision of the Opposition Division posted on 29 July 2003 revoking European patent No. 0 839 132 and on 8 December 2003 filed a written statement setting out the grounds for appeal.

II. The decision under appeal was based on claims 1 to 8 as granted, the only independent claim reading as follows:

"1. A process for the preparation of amorphous atorvastatin and hydrates thereof which comprises:
(a) dissolving crystalline Form I atorvastatin in a non-hydroxylic solvent; and
(b) removing the solvent to afford amorphous atorvastatin."

The Opposition Division held that grounds under Article 100(b) EPC prejudiced the maintenance of the patent as the starting material to be employed in the process claimed (i.e. crystalline form I of atorvastatin) was neither available at the filing date of the patent in suit nor was a process for making it sufficiently described in the patent in suit or in

(D3) WO-A-97 03 959

referred to in the patent in suit, as was deemed to be evident from

(D9) Experimental report of Lek Pharmaceuticals d.d. .

III. Inter alia, the following additional documents were cited during appeal proceedings:

(D8) Report "Synthesis of Form I Atorvastatin Calcium, dated "12/01/2003"

(D11) Experimental Report of Pfizer dated June 8, 2006,

IV. The Appellant argued that an expert would have repeated example 1 of the patent in suit without the use of seed crystals knowing that seed crystals only accelerate crystallisation. In addition to that he submitted that the present application as originally filed referred to (D3) as far as the synthesis of crystalline form I of atorvastatin was concerned. This cross-reference was deemed to satisfy the conditions laid out in the Guidelines at C-II, 4.18 and thus to form part of the disclosure for the purpose of Article 100(b) EPC.

Document(D3) disclosed on pages 20 to 22 three different processes for making crystalline form I of atorvastatin including all the process conditions necessary in order to obtain the desired product in the absence of seed crystals.

According to the Appellant, (D8) showed that these processes reliably yield crystalline form I of atorvastatin.

Furthermore, he expressed the view that document (D11) showed that method A of example 1 of (D3) yielded crystalline form I of atorvastatin even in the absence of seed crystals.

V. The Respondent (Opponent) denied that (D3) belonged to the disclosure of the present patent as it was cited in the part of the description describing the background art and there was no indication that it was to be incorporated by reference. In addition to that, the examples of (D3) required seed crystals to yield crystalline form I of atorvastatin as was evident from (D9).

He argued that the processes outlined on pages 20 to 22 of the description were not described in such a precise manner as to allow the person skilled in the art to rework them. In the report (D8) additional parameters had been used which were not disclosed in (D3).

He mentioned that claim 1 as granted also covered a process for making the respective hydrates. As the solvent in this process was to be non-hydroxylic and no water content of the starting material is defined, there was no disclosure how hydrates might be produced.

VI. Oral proceedings were held on 11 July 2006.

VII. The Appellant requested to set aside the decision of the opposition division and to maintain the patent as granted (Main Request) or to remit the case to the opposition division to decide on the objections under Article 100(a) EPC (Auxiliary Request).

The Respondent requested to reject the appeal and to reject the request to remit the case to the opposition division.

(The request of the Respondent for apportionment of costs was withdrawn during oral proceedings.)

VIII. At the end of the oral proceedings the decision of the Board was announced.

## Reasons for the Decision

1. The appeal is admissible.

2. Insufficiency of disclosure of the invention (Article 100(b) EPC)

2.1 To be patentable under the EPC, the European patent must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

It is established jurisprudence that a person skilled in the art is neither the nor an "expert" in the field concerned but is presumed to be an ordinary practitioner aware of what was common general knowledge in the art at the relevant date.

In the present case, the Appellant submitted at no stage of the opposition or appeal proceedings any evidence of common general knowledge relevant to the issue of sufficiency of disclosure. In the absence of such evidence it must be concluded that the claimed invention must be capable of being carried out by following the instructions in the patent in suit.

In this context it is to be noted that it was undisputed that crystalline form I of atorvastatin was not disclosed prior to the filing date of the patent in suit (see section [0006] of the patent in suit).

2.2 The patent in suit describes a method for preparing crystalline form I of atorvastatin only in example 1. In this example, seed crystals of crystalline form I of atorvastatin were employed, whereby the instruction to do so reads as follows:

"The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C."

This shows that seeding is carried out in a controlled manner by a slurry of crystals of form I of atorvastatin, namely by a particular crystal concentration in a particular mixture of water and methanol.

A person skilled in the art would thus consider this step of adding seed crystals as essential for obtaining the desired form I, and not as an optional measure.

The Board does therefore not accept the Appellant's unsupported allegation that a person skilled in the art would have considered that the process described in said example would yield crystalline form I of atorvastatin even if the seed crystals of the same crystalline form were omitted, and this all the more since atorvastatin exists in at least four polymorphic

crystalline forms (see section [0006] of the patent in suit). Different reaction conditions thus may yield different crystalline forms.

There is thus no reason for the skilled person, when trying to carry out the claimed invention, to consider omitting the seeding with crystals in the process of example 1 of the patent in suit. Therefore, the only disclosure in the patent in suit in respect of the preparation of crystalline form I of atorvastatin (example 1) does not give all the necessary information to the person skilled in the art as to how to produce that crystalline form.

2.3 A further argument of the Appellant was that in the application as originally filed reference was made to a document which sets out all the process conditions necessary for obtaining form I crystals without necessarily using seed crystals.

The application on which the patent in suit is based (i.e. WO-A-97 03 960) mentions on page 2, lines 13 to 25 (cf. section [0006] of the patent in suit) the titles of two concurrently filed U.S. patent applications said to disclose crystalline forms I, II, III and IV of atorvastatin, the title of the second one only referring to form III.

Even though these documents were not formally stated to be incorporated by reference, it is likely that the person skilled in the art would have tried to consult the first of these documents as this was the only reference in the patent in suit other than example 1 to obtaining crystalline form I of atorvastatin.

It was undisputed that document (D3) was easily retrievable from the information given on page 2, lines 13 to 25 of the application on which the patent in suit was based (i.e. of WO-A-97 03 960), which disclosure corresponds to that on page 2, lines 22 to 27 of the patent in suit. Therefore, document (D3) may be taken into account for the purpose of Article 100(b) EPC (see T 737/90 of 9 September 1993 (not published in the O. J. of the EPO), point 5 of the reasons).

2.4 The only examples in (D3) that yield crystalline form I of atorvastatin are Methods A and B of its example 1. Like in the patent in suit, these Methods require seed crystals of crystalline form I of atorvastatin. Consequently, the conclusion drawn in point 2.2 above also applies to these Methods.

2.5 The last point to be considered by the Board is whether the general teaching of document (D3) referred to by the Appellant (i.e. in particular the three processes described on page 20, lines 31, to page 22, line 3) provides the person skilled in the art with information that is sufficient to produce crystalline form I of atorvastatin without any undue effort.

When trying to carry out the claimed invention, the skilled person would take into account what the worked examples teach, namely that even small changes in the process conditions may yield crystalline form II (see (D3), example 2 as compared to Method B of example 1) or crystalline form IV (see (D3), example 3 as compared

to Method A of example 1) instead of form I of atorvastatin.

For the Board, in a situation where the operating conditions are shown to be highly critical, it would not be realistic to accept that the process need not be described in much detail.

2.5.1 The first two of the processes described in (D3) on page 20, line 31, to page 22, line 3, preferably employ seed crystals (see (D3), page 21, lines 14 to 18, and page 21, lines 27 to 32). Even if it were assumed that the addition of seed crystals was not mandatory, the person skilled in the art would realize that the most preferred operating conditions of these two processes as described in (D3) were those to be employed when seed crystals were to be used. In the absence of detailed technical information on how to proceed if no seeding is done, the skilled person is left without any clear guidance, which means that he has to start a research program in order to find out how those process conditions have to be modified in order to yield the desired crystalline form without making use of seed crystals.

This is in line with the experiments presented by the Appellant in (D8). In experiment B of (D8) (corresponding to the first process of (D3); see (D3), page 20, line 31, to page 21, line 18) the reaction mixture was treated as follows after the addition of the calcium actetate solution:

"When the addition was completed, the resulting mixture was stirred overnight at 52-57 °C."

Document (D3) only gives a general guidance on the process conditions during crystallisation (see (D3), page 21, lines 8 to 11).

The combination of the process features during crystallisation as employed in experiment B of (D8), i.e. the stirring during a particular crystallisation time at a particular crystallisation temperature, is, however, not derivable from the first process described in (D3) on page 20, line 31, to page 21, line 18.

In experiment C of (D8) (corresponding to the second process of (D3); see (D3), page 21, lines 19 to 32) no co-solvent is employed although its use is recommended in (D3)(see page 21, lines 23 to 25).

Moreover, the specific reaction conditions employed in experiment C of (D3), i.e. that the amorphous atorvastatin was slurried "for 3 days at ambient temperature", are also not derivable (D3); the disclosure on page 21, lines 19 to 32 of (D3) is silent on the crystallisation temperature and the crystallisation time.

2.5.2 The third process (see (D3), page 21, line 32, to page, line 3) teaches to heat a "water-wet cake consisting principally of amorphous atorvastatin" at elevated temperatures, most preferably to 65-70 °C "until a significant amount of crystalline Form I atorvastatin is present".

In this process, the starting (amorphous) atorvastatin is to be used in form of a "water-wet cake" so that the

presence of water appears to be a mandatory feature. The amount of water to be present is, however, not defined in (D3). It is unclear how to interpret under these circumstances the instruction to heat a water-wet cake until a significant amount of desired form I is present . How this is to be monitored is nowhere said; nor does (D3) disclose if a constant amount of residual water is to be maintained or not in the "water-wet cake". Therefore, this process is deficient in that it is silent in respect to essential process conditions. Hence, also this disclosure cannot be considered to enable the person skilled in the art to produce crystalline form I of atorvastatin.

Experiment D of (D8), where this third process is said to be repeated, does not contradict this finding as also in this experiment the amount of water is not defined and particular reaction conditions not disclosed in (D3), such as heating in a closed container for 22.5 h, had been chosen.

2.5.3 Document (D9) describes experiments using seed crystals; (D11) concerns experiments which had been carried out on the basis of operating conditions which cannot be derived from the disclosure of (D3) or that of the patent in suit. Those two documents are thus irrelevant as evidence.

2.6 Consequently the Board comes to the conclusion that neither the patent in suit nor document (D3) cited therein enabled the skilled person to produce without undue burden crystalline form I of atorvastatin, i.e. the starting material to be employed in the process of present claim 1.

The decision of the Opposition Division to revoke the patent in suit based on grounds under Article 100(b) EPC thus was justified.

2.7 In the light of the above findings, there is no need to decide whether or not the patent in suit enabled the person skilled in the art to produce all the hydrates of amorphous atorvastatin according to the process of claim 1.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. J. Nuss