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D E C I S I O N
of 12 July 2005

Case Number: T 1139/02 - 3.3.1

Application Number: 97901158.2

Publication Number: 0883608

IPC: C07D 211/34

Language of the proceedings: EN

Title of invention:
Optical resolution of methylphenidate by 0,0'-bisaroyl tartaric acids

Applicant:
Celltech Pharma Europe Limited

Opponent:
-

Headword:
Methylphenidate/CELLTECH

Relevant legal provisions:
EPC Art. 56, 84
EPC R. 29(1)

Keyword:
"Main request: clarity (no)"
"Sole auxiliary request: inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1139/02 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 12 July 2005

Appellant: Celltech Pharma Europe Limited
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 23 May 2002 refusing European application No. 97901158.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
R. T. Menapace

Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision refusing European patent application No. 97 901 158.2, published as WO 97/27176, due to lack of inventive step.

The claims underlying the decision under appeal were identical with those as originally filed and consisted of product-, composition-, use- and process claims. The only independent process claim read:

"1. A process for preparing substantially single enantiomer *d*- or *l*-*threo*-methylphenidate, which comprises resolution of a mixture of enantiomers using an *O,O*-diaroyltartaric acid as resolving agent."

In particular, the Examining Division found that an advantageous effect over the process disclosed in document

(1) US-A-2 957 880

had not been shown. Therefore, the problem underlying the invention could only be seen as the provision of a further process for preparing single enantiomers of d- or l-threo-methylphenidate. Since *O,O'*-diaroyltartaric acids were known to be useful as resolving agents, it was obvious to substitute the 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate in the process of document (1) as resolving agent by a *O,O'*-diaroyltartaric acid.

II. At the oral proceedings before the Board, which took place on 12 July 2005, the Appellant filed, as a main request, a set of two claims. The only independent claim read:

"1. A process for preparing substantially single enantiomer *d*- or *l-threo*-methylphenidate by a classical salt reduction procedure, which comprises resolution of a mixture of enantiomers using, as resolving agent, D- or L-*O,O*-ditoluoyltartaric acid."

During the previous written procedure the Appellant filed on 1 July 2005 a set of two claims titled "auxiliary request 2". The claims read:

"1. A process of preparing substantially single enantiomer d-threo-methylphenidate wherein a mixture of threo-methylphenidate and 1 molar equivalent of D-0,0-ditoluoyltartaric acid in an inert organic solvent is heated and then allowed to cool; the resultant precipitate is filtered, washed with an appropriate solvent and dried to afford directly a salt enriched in at least 97% enantiomeric excess d-threo-methylphenidate."

"2. A process according to claim 1, which additionally comprises salt cracking using aqueous alkali metal hydroxide."

III. As far as clarity is concerned, the Appellant submitted that Claim 1 according to the main request clearly defined the essence of the invention, namely that by using *D*- or *L-O,O'*-ditoluoyltartaric acid as resolving agent *d*- or *l-threo*-methylphenidate may be prepared

from a mixture of enantiomers thereof in very high chemical and enantiomeric purity.

IV. Moreover, the Appellant argued that document

(3) The Journal of Pharmacology and Experimental Therapeutics, 1987, 241(1), pages 152 to 158

represented the closest state of the art, that an advantageous effect had been shown with the data presented in the sole example of the application and that such advantageous effect could not have been deduced from the cited prior art.

V. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 and 2 as filed during the oral proceedings (main request) or Claims 1 and 2 filed as "auxiliary request 2" on 1 July 2005 (sole auxiliary request).

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Article 84 EPC - clarity

2.1.1 Article 84 EPC in combination with Rule 29(1) EPC requires that the matter for which protection is sought be defined in the claims in a clear manner. This means not only that a claim must be non-ambiguous and comprehensible, but also that all the essential

features of the claimed invention have to be indicated in the claim. Since a process is claimed in Claim 1, that process must be defined in the same claim by concrete process steps as essential features.

As Claim 1 describes a process of preparing an enantiomer by a classical salt resolution procedure wherein a specific resolving agent is used, the only feature which could define a concrete process step is the feature referring to "the classical salt resolution procedure". Therefore, the question arises whether such feature defines one or more concrete process steps.

The Appellant himself submitted that a classical salt resolution procedure should not be interpreted as being restricted to the process steps described on page 2, lines 16 to 20, of the published description, namely of heating a mixture of a racemate and 1 molar equivalent of a resolving agent in a solvent, allowing to cool, filtering the precipitate, washing and drying. However, the Appellant did not provide any evidence which concrete process steps were necessarily or inevitably defined by a classical salt resolution procedure. In the absence of any such evidence, a skilled reader is not taught, without ambiguity, of which concrete process steps the process defined in Claim 1 consists. Thus, Claim 1 cannot be considered to meet the requirement of clarity.

2.1.2 The Board cannot follow the Appellant's submission that it would be sufficient that the essence of the invention is defined in Claim 1 (see point III above).

Since patent claims are directed to concrete subject-matter, it is the practical meaning of the language of the claims to a skilled person which counts. The skilled person should thus understand without ambiguity from the wording of the claim the matter for which protection is sought in terms of the technical features of the invention (Rule 29(1) EPC).

3. *Sole auxiliary request*

3.1 Clarity

As the process is now incontestably defined by concrete process features, the requirement of clarity is fulfilled.

3.2 Article 123(2) EPC

Since the process parameters in Claim 1 are identical to the ones disclosed on page 2, lines 14 to 20, and Claim 2 corresponds with original Claim 16, the requirement of Article 123(2) EPC is met.

3.3 Novelty

Since the claimed process differs from the process disclosed in the cited prior art documents at least by the use of *D-O,O*-ditoluoyltartaric acid for resolving *threo*-methylphenidate, the claimed process is novel over the cited prior art.

3.4 Inventive step

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

3.4.1 The "closest state of the art" is normally a prior art document disclosing subject-matter aimed at the same objective as the claimed invention and having the most relevant technical features in common.

Since document (1) is concerned with resolving methylphenidate in an a- and a b-racemate, whereas the claimed process is concerned with the resolution of a racemate of methylphenidate into its single enantiomers, document (1) does not disclose subject-matter aimed at the same objective as the claimed invention.

Document (3), which is the only cited prior art document disclosing the resolution of *threo*-methylphenidate into its enantiomers, represents the closest state of the art.

Indeed, document (3), which is mentioned on page 1, lines 17 to 20, of the present description, discloses a process for resolving *dl-threo*-methylphenidate into its enantiomers by using 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as resolving agent (see, in particular,

page 153, under the heading "Preparative separation of *threo*-MPH isomers").

3.4.2 According to the present description, page 2, lines 1 to 12, the process disclosed in document (3) has the disadvantage that the enantiomers are contaminated with resolving agent, which can only be removed by repeated extractions causing hydrolysis of the ester, thus leaving ritalinic acid as a contaminant.

3.4.3 It has not been contested that, starting from document (3), the problem to be solved consisted of providing a process for preparing single enantiomer *d-threo*-methylphenidate in very high chemical and enantiomeric purity, free of resolving agent.

The application in suit claims to solve this problem by the claimed process.

It has been made plausible in the sole example of the present application that the enantiomers of *threo*-methylphenidate are effectively obtained in high optical purity and free of resolving agent when using *D-O,O'*-ditoluoyl tartaric acid, whereas the enantiomers contain resolving agent as a contaminant when using the process described in document (3).

3.4.4 Therefore, it remains to be decided whether in the light of the teachings of the cited documents a skilled person seeking to solve the problem as described in point 3.4.3 above would have arrived at the claimed process in an obvious way or not.

3.4.5 Since document (3) only discloses a resolution of *threo*-methylphenidate by using 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as resolving agent, no indication at all could be found concerning other resolving agents which could be used, let alone, which would be suitable for avoiding contamination of the enantiomer with the resolving agent.

3.4.6 From all the prior art documents cited in the International Search Report, document

(4) WO-A-95/31436

is the only one which describes the use of ditoluoyl tartaric acid as resolving agent.

Document (4) discloses the use of di-para-ditoluoyl tartaric acid as resolving agent for compounds, such as terfenadine, which have a completely different chemical structure as methylphenidate. The second to the fourth paragraph on page 3 of document (4) teach that by using di-para-ditoluoyl tartaric acid instead of 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as resolving agent the resolution process is more efficient and economical.

However, document (4) is completely silent about the problem of enantiomers contaminated with the resolving agent. Therefore, a skilled person could not find any hint therein that the problem of avoiding contamination of the enantiomers with the resolving agent could be solved by using D-*O,O'*-ditoluoyl tartaric acid.

3.4.7 Consequently, the claimed process is not rendered obvious by the cited prior art documents.

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 Claims 1 and 2 filed as "auxiliary request 2" on 1 July 2005 and the description as originally filed.

The Registrar: The Chairman:

N. Maslin A. Nuss