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**Datasheet for the decision
of 30 May 2012**

Case Number: T 0097/11 - 3.3.01

Application Number: 08101985.3

Publication Number: 2098525

IPC: C07D 477/20, A61K 31/4025,
A61P 31/04

Language of the proceedings: EN

Title of invention:
Crystalline carbapenem compound and produced method thereof

Applicant:
Savior Lifetec Corporation

Headword:
Crystalline Meropenem/SAVIOR LIFETEC CORP.

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure (no) - Disclosure to prepare the
claimed crystalline form not sufficient given that the seed is
not available"

Decisions cited:
-

Catchword:
-



Case Number: T 0097/11 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 30 May 2012

Appellant:
(Applicant)

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted 20 July 2010
refusing European patent application
No. 08101985.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: P. Ranguis
Members: J.-B. Ousset
C.-P. Brandt

Summary of Facts and Submissions

I. An appeal was lodged against the decision of the examining division refusing the European patent application EP-08 101 985.3. This application related to Meropenem, i.e. "Compound A" in the crystalline "form B", and a method for preparing it. "Compound A" in the crystalline "form A" was known from document

(1) EP-A-0 256 377

(see application as filed, page 2, lines 4 to 10).

II. The decision under appeal was based on a main request and four auxiliary requests all filed with letter dated 7 May 2012 and a further auxiliary request (5th) submitted during the oral proceedings.

The different requests were rejected on various grounds, only one of which is relevant for the present decision (which does not mean that the others were not well-substantiated).

The sole ground for rejecting the present application relevant for the present decision was based on Article 83 EPC with respect to Claim 2 of the main request (Claim 1 of auxiliary request 5).

Claim 2 of the main request reads:

"2. A produced method of crystalline carbapenem compound comprising the steps of:

(1) activated carbon being added to solution and stirring, the solution containing crude product of

(4R,5S,6S)-3-[[(3S,5S)-5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid and water;

(2) the activated carbon being removed from the solution by a filtration and filtrate being washed with water to form aqueous solution;

(3) the aqueous solution being concentrated by a reverse osmosis condensing apparatus and resulting condensate being cooled;

(4) a seed being added to the resulting condensate;

(5) solvent being added thereto and then stirring; and

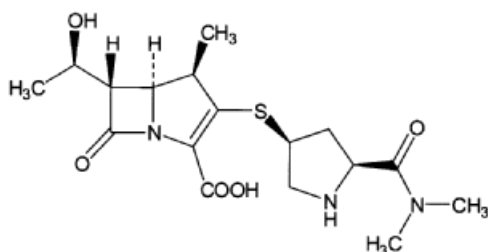
(6) precipitated crystals being collected, washed and dried to get crystalline (4R,5S,6S)-3-[[(3S,5S)-5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, which is characterized by an X-ray powder diffraction pattern (omitted for the sake of conciseness)"

III. The examining division considered that the feature "seed" in the mandatory step of seeding defined as "95% Meropenem" in the description did not give any information as to the crystals used in order to produce compound A in crystalline form B. Therefore, the person skilled in the art would be unable to produce compound A in crystalline form B. The argument of the applicant that the seeding crystals are preferably crystalline form B intensified the objection under Article 83 EPC since without seeds of form B the skilled person would not be able to prepare the intended form B.

IV. With its statement of grounds of appeal the appellant filed the main request and the five auxiliary requests already refused by the examining division.

Claim 1 of the main request reads as follows:

"1. A crystalline carbapenem compound comprising:
crystalline (4R,5S,6S)-3-[[[(3S,5S)-5-
[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-
1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylic acid of the formula



Wherein the crystalline (4R,5S,6S)-3-[[[(3S,5S)-5-
[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-
1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylic acid is characterized by an X-ray
powder diffraction pattern (omitted for the sake of
conciseness)".

Claim 1 of the first auxiliary request differs from the wording of claim 1 of the main request in that the table listing the spacings and the relative intensities has been replaced by a X-ray diagram.

Claim 1 of the second, third and fourth auxiliary requests differs from the wording of Claim 1 of the main request in that it specifies that the claimed compound is trihydrate.

Claim 1 of the fifth auxiliary request is the same as claim 2 of the main request before the examining division (see point II above).

- V. With letter dated 8 November 2011, the appellant argued, in particular, that the seed comprises Meropenem with 98% content, 1g (in the Examples 1 to 4 of the specification) that is, the Meropenem seed crystals could be in crystalline form A or B. The Meropenem seed crystals synthesized by the applicants in their plant facilities are crystalline form A as the first seed. And after the claimed recrystallization process used crystalline form A as a seed to obtain crystalline form B, the crystalline form B is substituted for the crystalline form A as the seed in the claimed recrystallization process. The applicants discovered that when crystalline form A is the seed used in the claimed recrystallisation process, the yield and purity of the final product crystalline form B are lower. Thus, the disclosure "the seed comprises Meropenem with 98% content, 1 g provides that the seed is inherently crystalline form A or B, preferably crystalline form B.
- VI. In the annex to the invitation to oral proceedings, the board expressed the view that the subject-matter of the present invention did not fulfil the requirement of Article 83 EPC, in particular because if compound A in the crystalline form A as described in document (1) had been used as seeding crystal, the same crystal would have been obtained, i.e. crystalline form A and not a new one, i.e. crystalline form B, as evidenced by document

(8) Römpf Lexikon, Chemie, 10. Auflage, 1997 Georg Thieme Verlag, page 1896, "Impfen"

VII. With its letter of 25 May 2012, the appellant filed the following documents:

(9) Struct Bond (2009) 132: 25, 30-31, Springer-Verlag Berlin Heidelberg 2009. Published online: 25 February 2009

(10) Alfred Y. Lee, Deniz Erdemir, Allan S. Myerson, "Crystal polymorphism in Chemical Process Development" in Annu. Rev. Chem. Biomol. Eng. 2001. pages 259 and 269-270.

(11) European Pharmacopoeia 7.0

VIII. During oral proceedings, which took place on 30 May 2012, the appellant submitted two further sets of claims.

Claim 1 of the sixth auxiliary request corresponds to claim 1 of the main request in which the expression "... of Fig. 2 of the specification." was added at the end of the wording of this claim.

Claim 1 of the seventh auxiliary request corresponds to claim 1 of the fifth auxiliary request in that the expression "wherein the seed comprises 95 wt% Meropenem" was added to point (4) of this claim.

The appellant also submitted a complete document (9), namely pages 25-50.

IX. The appellant's arguments in the written proceedings and during oral proceedings, as far as they are relevant for the present decision, can be summarised as follows:

Contrary to the board preliminary opinion based on document (8), the seed and the crystalline compound do not have necessarily the same crystalline form because polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at particular conditions, namely crystallisation conditions or choice of solvents. Only one polymorph was thermodynamically stable; however, due to kinetic considerations, metastable forms could coexist additionally to the stable one as evidenced by document (9), bridging paragraph, pages 30-31 and page 27, last paragraph.

It is known that the nature of the solid-state phase is also dependent on the driving force for crystallisation, supersaturation; and the level of supersaturation influences both the crystal nucleation and growth rate; generally, stable polymorphs are the slowest to nucleate and tend to precipitate at low supersaturation as evidenced by documents (10), bridging paragraph, pages 269-270.

It is important to note that the level of supersaturation influences the crystal nucleation to get the crystalline form B. In that respect, in Examples 1-4 the crystallisation process is carried out with a starting volume of 6.7 L and thus supersaturation is relatively lower as compared to the prior art. The crystalline form B was obtained by

adding the seed (either crystalline form A or B) at the above-mentioned supersaturation.

In the prior art (document (1)), the polymorph started to nucleate in the 1st hour whereas in the applicant's process the formation of crystalline form B started after the 4th hour. Therefore, the polymorph produced by the claimed process was more stable than that of document (1). Table 1 submitted with letter of 25 May 2012 showed that it was possible to prepare a polymorph, crystalline form B, different from the polymorph crystalline form A described in document (1). Document (2), i.e. WO 2007/031858, was also relied upon in that respect.

Furthermore, "Meropenem with 98% content, 1g" is known from document (11).

- X. The appellant requested that the decision under appeal be set aside and that a patent be granted either on the basis of the main request or on the basis of one of the auxiliary requests 1 to 5 filed with letter of 19 November 2010 or on the basis of auxiliary requests 6 or 7 filed during oral proceedings of 30 May 2012.

- XI. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

- 1. The appeal is admissible.

Main request - Sufficiency of disclosure

2. A European patent application must disclose the invention in manner sufficiently clear and complete for it to be carried out by a person skilled in the art (see Article 83 EPC).

2.1 In all examples as well as in the description as originally filed, the process described to obtain the crystalline form B as claimed in claim 1 requires the use of a seed (see claims 3 and 6; page 4, line 17 and page 7, line 13). The nature of the seed was specified on page 8, lines 9-10: "The seed comprises > 95 wt% Meropenem", and in the different examples 1 to 4 (see page 9, lines 4 and 19 and page 10, lines 7 and 22: "Meropenem with 98% content, 1g.").

2.2 The question to be decided is thus whether the person skilled in the art can obtain crystalline form B in view of the description as originally filed and common general knowledge by using a seeding.

2.2.1 The appellant submitted that the seeding can be made either by using known crystalline form A or claimed crystalline form B.

Although the seed crystalline form A was not explicitly mentioned as the seed to be used, the board can accept that the person skilled in the art had sufficient information to use crystalline form A, since Compound A in the crystalline form A is highlighted in the description of the related art, namely document (1) (see point I above).

2.2.2 However, as pointed out in the annex to the invitation to oral proceedings (see point VI above), document (8), which is an excerpt from a textbook and thus represents the person skilled in the art's general knowledge, recites that if it is intended to obtain a crystalline form of a compound, the seed must have the same crystalline form as the compound to be obtained (see page 1896, left-hand column, middle of the paragraph 2, "Bei der ... Reinstoff").

That crystalline form A can be used as seeding to obtain another crystalline form of Meropenem is in clear contradiction with the well-accepted common general knowledge as reflected by document (8).

2.3 To rebut this finding, the appellant relied on specific passages of documents (9), (10) and (11).

2.3.1 Document (9), bridging paragraph, pages 30-31, relates to the search for various crystals forms and states that it requires that the behaviour of a solid phase be investigated as a function of the variables that can influence or determine the outcome of the crystallisation process, e.g. temperature, choice of solvents, crystallisation conditions, rate of precipitation, interconversion between solid forms (from solvate to un-solvate and vice-versa), pressure and mechanical treatment, absorption and release of vapour. In other words, the well-known methods of screening of polymorphs are to be used. This passage does not address the point, because it says nothing about the possibility of obtaining a specific crystalline form from another specific crystalline form of seeding.

2.3.2 The passage of document (9), page 27, last paragraph states that from thermodynamic principles, under specified conditions only one polymorph is the stable form. In practice, however, due to kinetic considerations, metastable forms can exist or coexist in the presence of more stable forms. The relative stability of the various crystal forms and the possibility of interconversion between crystal forms, between crystals with different degrees of solvation, and between an amorphous phase and a crystalline phase, can have very serious consequences.

However, there is nothing in the description as originally filed or in document (1) indicating that crystalline form A is metastable (unstable). On the contrary, the application as filed states that Compound A in such crystalline form A is much more stable than in a non-crystalline form and suitable for storage (see page 2, lines 4-7). Furthermore, this passage says nothing about the possibility of obtaining a specific crystalline form from another specific crystalline form of seeding.

2.3.3 The appellant also submitted that in view of the disclosure of document (10) (see paragraph bridging pages 269 and 270), the level of supersaturation has an influence on the crystal nucleation and on the growth rate. Generally, stable polymorphs are the slowest to nucleate and tend to precipitate at low supersaturation levels, whereas kinetic polymorphs favour a high degree of supersaturation. It pointed to the experimental results provided with its letter of 25 May 2012 (see below) from which it concluded that the lower level of

supersaturation for the formation of crystalline form B would allow its formation from crystalline form A having a higher level of supersaturation.

Table 1.

Prior art	EP0256377	WO2007/031858	Claimed invention
Applicant	Sumitomo	Orchid	Savior Lifetec
Crystallizing concentration	100mg/mL	77mg/mL	ca. 30mg/mL
Crystalline formation time point	1hr	Not disclosed	4-8hr
Crystalline form	Form A	Form A	Form B

2.3.4 Regarding document (1), (table above, left-hand column, EP0256377), the appellant referred to example 1, page 10, lines 19-25). However, this example describes a crystallisation process wherein non-crystalline compound A (5.0g) was dissolved in water (50ml) at 30°C and cooled in a water bath, whereupon precipitation of a small amount of crystals was observed. Acetone (250ml) was added thereto, and the resultant mixture was stirred for 1 hour. The precipitated crystals were collected.

The appellant contends that the supersaturation is 100mg/ml, i.e. 5.0g/50ml. This assertion is not sufficiently substantiated since it appears that the supersaturation state is obtained by incorporation of a water-miscible solvent such as acetone (see page 3, lines 46 to 53 and page 4, lines 11-12). Therefore, it might equally well be concluded that the supersaturation level is $5.0g / (50ml + 250 ml) =$

17mg/ml. For this reason the argument of the appellant must fail.

2.3.5 Furthermore, the general information that the level of supersaturation has an influence on the crystal nucleation and on the growth rate refers to the general methods of screening which do not provide any evidence that from crystalline form A, crystalline form B can be obtained.

2.3.6 Document (2), page 19, lines 1-19, example 5(c) is still more subject to doubt. The appellant started from the hypothesis that the two reaction steps were quantitative. Starting from 0.08mol of Reactant 1, 0.08mmol of Meropenem would be obtained. The calculated ratio of 30.68g of Meropenem (0.08) / 400ml water would be lower if the yield is lower. Furthermore, the appellant bases its assertion on 400ml of water. However, the passage at issue states: "To the aqueous filtrate was added slowly cold THF. The product was filtered and washed with aqueous THF to afford the title compound (22.0g) as off white crystal". There is no evidence that 400ml of water is involved in the crystallisation process.

2.3.7 As for document (11), which discloses Meropenem trihydrate with 97.5% to 102.0% content, 1g, even if it is accepted that it relates to crystalline form A, that does not show that starting from a seed having the crystalline form A one could obtain the claimed crystalline form.

2.4 In conclusion, none of the documents (9), (10) or (11) can rebut the finding of the board based on document (8)

that it is not credible that the person skilled in the art starting from a seed having the crystalline form A could obtain the claimed crystalline form.

- 2.5 The appellant further contended that once crystalline form B was obtained, it could be used for making the claimed compound.

This is true but the description as originally filed does not disclose how this form B can be made by the person skilled in the art using the content of the said description and his common general knowledge.

3. For these reasons, the board concludes that the disclosure of the present application is not enabling and thus the main request does not fulfil the requirements of Article 83 EPC.
4. Since the appellant did not have any further arguments concerning auxiliary requests 1 to 7, the board has no reason to depart from its opinion as stated above, and also concludes that auxiliary requests 1 to 7 do not fulfil the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar

The Chairman

M. Schalow

P. Ranguis