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**D E C I S I O N**  
**of 14 July 2004**

**Case Number:** T 0433/02 - 3.3.1

**Application Number:** 98922693.1

**Publication Number:** 0970087

**IPC:** C07D 503/00

**Language of the proceedings:** EN

**Title of invention:**

A process for the preparation of a metal salt of clavulanic acid

**Applicant:**

SmithKline Beecham plc

**Opponent:**

-

**Headword:**

Potassium clavulate/SMITHKLINE BEECHAM

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Main request: inventive step (yes) - non obvious solution"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0433/02 - 3.3.1

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.1  
of 14 July 2004

**Appellant:** SmithKline Beecham plc  
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**Representative:** Walter, Ralph Francis, Dr.  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 15 October 2001  
refusing European application No. 98922693.1  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** A. J. Nuss  
**Members:** P. P. Bracke  
S. C. Perryman

## Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision refusing European patent application No. 98 922 693.1, published as WO 98/45300, since the then pending set of claims lacked inventive step over the disclosure of document

(3) EP-A-0 594 099,

taken alone or in combination with the disclosure of document

(2) WO 93/25557.

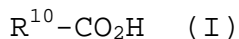
In particular, the Examining Division found that document (3) represented the closest state of the art and that the claimed process differed from the process disclosed in document (3) only by the use of a liquid medium comprising a fluorinated hydrocarbon. Since it was stated in document (3) that other solvents than isopropanol may be used and document (2) mentions halogenated hydrocarbons as solvent for the formation of amino salts of clavulanic acid, it was obvious to use fluorinated hydrocarbons.

Furthermore, the Opposition Division observed that the data provided with letter of 15 August 2001 did not result from a valid comparison with the closest state of the art. In the absence of any valid showing of a surprising effect, the claimed process was not inventive.

II. With letter of 14 February 2002 the Appellant filed sets of claims according to a main request and a first and second auxiliary request.

The set of claims according to the main request consisted of 10 claims with the only independent claim reading:

"1. A process for the preparation of potassium clavulanate which comprises the reaction between an organic amine salt of clavulanic acid and a salt of potassium with an organic carboxylic acid of formula (I):



wherein  $R^{10}$  is an alkyl group containing from 1 to 20 carbon atoms, the reaction taking place in a liquid medium which comprises a liquid fluorinated hydrocarbon which is a gas at ambient temperature which can be liquefied at ambient temperature by pressure, the reaction being performed at a pressure at which the fluorinated hydrocarbon is a liquid."

III. The Appellant essentially argued that the use of fluorinated hydrocarbons, which are neither solvents for the organic amine salts of clavulanic acid nor for the potassium organic carboxylic acid salts of formula (I), was not suggested in the cited prior art.

Moreover, with letter of 14 February 2002 the Appellant filed data resulting from the reaction of tertiary-octylamin clavulanate with potassium 2-ethylhexanoate in isopropanol and/or 1,1,1,2-tetrafluoroethane with

different ratios of isopropanol and 1,1,1,2-tetrafluoroethane.

- IV. The Appellant requested that the application be granted on the basis of the claims of the main request, or on the basis of the first or second auxiliary request.

Oral proceedings were requested if the Board did not intend to grant a patent on the basis of any of these requests.

### **Reasons for the Decision**

1. The appeal is admissible.
2. *Main request*
- 2.1 Article 123(2) EPC

Present Claim 1 results from the combination of features of original Claim 1 with the following features described in the application as filed:

- the selection of the potassium salt of a carboxylic acid of formula (I) and of clavulanic acid (Claims 4 and 5 of the application as filed);
- the restriction to those liquid fluorinated hydrocarbons which are a gas at ambient temperature which can be liquefied at ambient temperature by pressure (page 7, lines 9 and 10, of the application as filed); and

- the specification that the reaction is performed at a pressure at which the fluorinated hydrocarbon is liquid (page 8, lines 24 to 27, of the application as filed).

Claims 2, 3 and 6 correspond with original Claims 2, 6 and 13 respectively.

Claim 4 is supported by the pressure of 5 bar cited on page 7, line 35, of the application as filed.

Claim 5 is a combination of the process features described in original Claims 11 and 12.

Claims 7 to 9 are supported in the application as filed by the organic solvents and ratio-range disclosed on page 8, lines 1 to 12.

Claim 10 finds support on page 8, lines 36 to 39, of the application as filed.

## 2.2 Novelty

Since none of the cited documents discloses the use of fluorinated hydrocarbons in the conversion of an organic amine salt of clavulanic acid and a salt of potassium with an organic carboxylic acid, the claims meet the requirement of novelty. This has not been contested.

## 2.3 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.

2.3.1 Document (3), which indisputably represents the closest state of the art, discloses in column 3, especially lines 42 to 52, and in example 3 a process for preparing potassium clavulanate by adding a solution of potassium 2-ethylhexanoate in isopropanol to a solution of tertiary-octylamin clavulanate in an organic solvent such as an alcohol, especially isopropanol containing up to 5% of water.

2.3.2 There was dispute, whether starting from the disclosure of document (3) the problem underlying the invention could be seen as the provision of a process having an unexpected effect or, less ambitiously, as the provision of a further process for preparing potassium clavulanate from an organic amine salt of clavulanic acid and a salt of potassium with an organic carboxylic acid of formula (I). In particular, the Examining Division doubted that with the data provided in the application and those provided with letter of 15 August 2001 an unexpected effect had been made plausible.

However, since the Board comes to the conclusion that it has been made plausible that with the claimed process the less ambitious problem, namely the provision of a **further** process for preparing potassium clavulanate from an organic amine salt of clavulanic

acid and a salt of potassium with an organic carboxylic acid of formula (I), is solved and that the use of fluorinated hydrocarbons according to Claim 1 was not obviously derivable from the cited prior art, it is, in the present case, not relevant whether an **unexpected** effect has been made plausible.

2.3.3 It follows namely from the data provided with letter of 14 February 2002 that by reacting tertiary-octylamin clavulanate with potassium 2-ethylhexanoate in mixtures of 1,1,1,2-tetrafluoroethane and isopropanol in v:v proportions differing from 1:0.07 to 1:21.12 potassium clavulanate has effectively been prepared. Moreover, with the data provided with letter of 15 August 2001 it has been made plausible that potassium clavulanate was obtained not only by reacting tertiary-octylamin but also by reacting tertiary-butylamine or bis(2-dimethylaminoethyl)ether salt of clavulanic acid with potassium 2-ethylhexanoate in 1,1,1,2-tetrafluoroethane in admixture with alcohols such as methanol, ethanol and isopropanol.

In the absence of any indication to the contrary, the Board does not have any reason to question that it has been made plausible, that potassium 2-ethylhexanoate may effectively be obtained by the claimed process over its complete claimed scope.

2.3.4 In such case, the question arises whether in the light of the teachings of the cited documents a skilled person seeking a further process for preparing potassium clavulanate would have arrived at the claimed process in an obvious way, in particular, whether a skilled person would have chosen a liquid medium



comprising a fluorinated hydrocarbon as defined in Claim 1.

- 2.3.5 Document (3) only specifically cites isopropanol as a suitable solvent for the reaction of tertiary-octylamin clavulanate with potassium 2-ethylhexanoate (see column 3, lines 42 to 52).

The Board concurs with the Examining Division that it is also stated in column 4, lines 2 to 7, of document (3) that not only isopropanol but also other similar solvents or mixtures of solvents may be equally useful. However, such disclosure cannot be considered as suggesting any solvent, let alone, a liquid medium as now claimed.

Therefore, a skilled person could not have been suggested by document (3), taken alone, to use a liquid medium as defined in Claim 1.

- 2.3.6 Document (2) describes the reaction of clavulanic acid with amines and the subsequent conversion of the formed amine salts of clavulanic acid into an alkali or alkaline earth metal salt of clavulanic acid, such as its potassium salt (see page 2, lines 2 to 8, and page 10, lines 6 to 16).

Since halogenated solvents, such as dichloromethane and chloroform, were mentioned on page 7, line 26 and on page 9, line 10, as suitable solvents, the Examining Division was of the opinion that a skilled person would have got a hint to use the liquid medium as defined in Claim 1 in the claimed process.

However, both passages referred to by the Examining Division describe solvents in which clavulanic acid may be contacted with the amine and not the liquid media suitable for converting the amine salts of clavulanic acid into an alkali metal salt of clavulanic acid, such as potassium clavulanate. The only general information about the nature of the liquid medium suitable for converting the amine salts of clavulanic acid into the potassium clavulanate can be found in the paragraph bridging pages 10 and 11, where it is stated that suitable solvents may for example be an organic solvent, water or mixture of water and an organic solvent, such as isopropanol. Moreover, in the sole examples related to the conversion of amine salts of clavulanic acid into an alkali metal salt of clavulanic acid, namely examples 12, 15, 17 and 19, a solution of potassium 2-ethylhexanoate in isopropanol is added to the amine salt of clavulanic acid dissolved in water or isopropanol.

Thus, a skilled person could not get any hint from document (2) to use a halogenated solvent in the conversion reaction of amine salts of clavulanic acid into its potassium salt, let alone, to use a liquid medium as defined in Claim 1.

Consequently, the claimed process was also not obviously derivable from the combined teaching of documents (2) and (3).

2.3.7 Since also in the remaining documents cited by the Examining Division a hint to the use of a liquid medium as defined in Claim 1 cannot be found, the Board comes

to the conclusion, that the claimed process is not obviously derivable from the cited state of the art.

3. In the light of the above findings, there is no need for the Appellant to be heard in oral proceedings nor to consider the auxiliary requests.
4. The description is not yet adapted to the allowable claims. The Board deems it appropriate to make use of its power under Article 111(1) EPC and to remit the case for the purpose of this adaptation to the Examining Division.

## **Order**

### **For these reasons it is decided that:**

1. The contested decision is set aside.
2. The case is remitted to the Examining Division with the order to grant a patent on the basis of the main request and a description to be adapted.

The Registrar:

The Chairman

N. Maslin

A. Nuss