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Datasheet for the decision of 14 November 2024

Case Number: T 0239/22 - 3.3.10

Application Number: 10800762.6

Publication Number: 2658840

IPC: C07C213/10, C07C215/28

Language of the proceedings: EN

Title of invention:
PROCESS FOR MAKING FINGOLIMOD HYDROCHLORIDE CRYSTALS

Patent Proprietor:
Synthon BV

Opponent:
KELTIE LLP

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes) - non-obvious alternative

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0239/22 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 14 November 2024

Appellant: (Opponent)	KELTIE LLP No.1 London Bridge London SE1 9BA (GB)
Representative:	Moore, Michael Richard Keltie LLP No.1 London Bridge London SE1 9BA (GB)
Respondent: (Patent Proprietor)	Synthon BV Microweg 22 6545 CM Nijmegen (NL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 18 November 2021 rejecting the opposition filed against European patent No. 2658840 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	P. Gryczka
Members:	M. Kollmannsberger
	T. Bokor

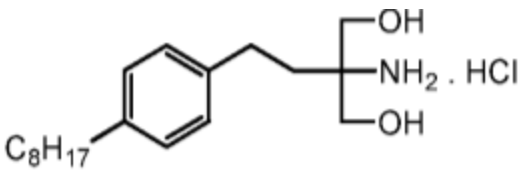
Summary of Facts and Submissions

I. The opponent (appellant) appealed the Opposition Division's decision to reject its opposition against European Patent 2 658 840 pursuant to Article 101(2) EPC.

II. The patent deals with the crystallisation of fingolimod hydrochloride form I by using a solvent/antisolvent precipitation wherein the solvent is a C_1-C_6 aliphatic alcohol and the antisolvent n-heptane.

III. The independent claim of the patent reads as follows:

"A process of making crystalline fingolimod hydrochloride Form 1 of formula (1a).



(1a)

represented by the XRPD pattern

[XRPD pattern, details irrelevant for the decision]

comprising a sequence of steps of

a) contacting a solution of fingolimod hydrochloride in a solvent with an antisolvent at a temperature of at least 50°C wherein the temperature of the antisolvent before and during contacting it with the solvent is at least 40°C,

b) cooling the obtained solution to a temperature of below 40°C, whereby crystalline fingolimod hydrochloride precipitates, and
c) isolating crystalline fingolimod hydrochloride from the mixture

wherein
the solvent is a C_1-C_6 aliphatic alcohol and the antisolvent is n-heptane."

IV. Reference is made to following documents:

D1: EP 0627406 A1

D2: WO 00/27798 A1

D4: Kim, S. et al., "Efficient Synthesis of the Immunosuppressive Agent FTY720", Synthesis 2006(5), 753-755

D5: CN 1814583 A

D6: CN 1765872 A1

D6a: Machine translation of D6

D7: JP H11-310556

D7a: Machine translation of D7

D8: Sugiyama, S. et al., "A convenient Synthesis of Immunosuppressive Agent FTY710 Using the Petasis Reaction", Chem.&Pharm.Bull. 2005(53(1), 100-102

D9: CN 1528738 A

D10: Kiuchi, M., et al. "Synthesis and Immunosuppressive Activity of 2-substituted 2-Aminopropane-1,3-diols and 2-Aminoethanols" J.Med.Chem 2000, 43, 2946-2961

D11: CN 1266844 A

D12: EP 0989113 A

D13: CN 1483721 A

D15: Myerson, Allan S., "Handbook of Industrial Crystallization", Butterworth Heinemann, 2002

D17: Becker Heinz G.O. et al., "Organikum, Organisch-chemisches Grundpraktikum", Deutscher Verlag der Wissenschaften, 1976

D21: Gordon, A.J. and Ford, R.A., "The Chemist's Companion: A Handbook of Practical Data, Techniques and References", 1972, pages 442-443 "Common solvents for crystallization"

V. The patent had been opposed under Articles 100(a) and 100(b) EPC for lack of inventive step (Article 56 EPC) and insufficient disclosure (Article 83 EPC). The Opposition Division rejected the opposition. With respect to inventive step the Opposition Division held that in view of the prior art processes using ethanol either in combination with ethyl acetate (D2, D10) or with diethyl ether (D6, D7) as solvent mixtures for crystallisation of fingolimod hydrochloride form 1, the use of n-heptane as an antisolvent was not a routine modification (point 15.17 of the reasoning). Moreover, also some of the process steps, in particular the temperature of the antisolvent upon addition, were not arbitrary (point 15.18 of the reasoning). The Opposition Division thus found that the claimed process was a non-obvious solution to the objective technical problem of providing an alternative recrystallisation process for preparing form I of fingolimod hydrochloride (point 15.14 of the reasoning). Improvements achieved by the claimed process resulting in better processable crystal habits of the resulting product, as invoked by the patent proprietor, were not found to be conclusively proven and were thus not taken into account (points 15.8 to 15.13 of the reasoning).

VI. In its statement setting out the grounds of appeal and in the further course of the appeal proceedings the appellant submitted that the Opposition Division's decision was incorrect. While it was correct to find that the claimed crystallisation process did not lead to any improvements with respect to the processes known from D2/D10 or D6/D7, the proposed alternative was obviously derivable from the cited prior art. In particular, the use of heptane as an antisolvent did not require any inventive activity, and any differing process features in the claims resulted from routine experimentation.

VII. The respondent (patent proprietor) submitted that the claimed process involved an inventive step. The use of heptane as an antisolvent and the pre-heating of the antisolvent as defined in the claim lead to a more favourable morphology of the crystals obtained in this way. Even if it were to be seen only as an alternative to the processes known from the prior art, the claimed process was not obvious, as the Opposition Division had correctly found. This was so because the use of n-heptane as an anti-solvent and its pre-heating before the addition to the fingolimod hydrochloride solution were not derivable from the prior art in an obvious manner.

VIII. The appellant requested the appealed decision to be set aside and the patent to be revoked.

The respondent requested the appeal to be dismissed.

IX. Oral proceedings were held on 14 November 2024. The decision was announced at the end of the proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The Opposition Division found that the claimed invention is sufficiently disclosed in the patent, Articles 100(b) and 83 EPC. This was uncontested in appeal proceedings.

3. Inventive step (Article 100(a) and 56 EPC)

3.1 Closest prior art

In the prior art, fingolimod hydrochloride has been crystallized in various ways. The cited documents show crystallisations from single solvents like ethanol, isopropanol or tetrahydrofuran (D1, D4, D5, D8, D9, D11-D13). Crystallisations using a solvent/antisolvent system are described in D2/D10 and in D6/D7. D2/D10 use a mixture of ethanol and ethyl acetate, D6/D7 use a mixture of ethanol and diethyl ether. That all of these crystallisations lead to fingolimod hydrochloride in crystalline form 1 was undisputed.

Since the claimed process likewise uses a solvent/ antisolvent mixture, the processes described in D2/D10 and D6/D7 can be considered to represent the closest state of the art. D6a and D7a are their translations.

It was undisputed between the parties that the claimed process differs from these disclosures at least in the choice of n-heptane as an antisolvent.

3.2 Objective technical problem and its solution

The appellant and the respondent disagreed on whether the choice of n-heptane as an antisolvent leads to improvements compared with the processes disclosed in D6/D7 or D2/D10. The Opposition Division considered that such improvements had not been proven, see points 15.8 to 15.13 of the decision under appeal.

This issue does not need to be analysed in detail by the Board. The Board assumes, in the appellant's favour, that such improvements are not demonstrated.

The objective technical problem to be solved was thus the provision of an alternative crystallisation process for the preparation of fingolimod hydrochloride form 1, in line with the formulation of the problem used by the Opposition Division (point 15.14 of the decision under appeal).

This problem is solved by the process defined in claim 1 which is characterized in that n-heptane is used as an antisolvent.

That this problem was indeed solved, i. e. that the claimed process allows to obtain fingolimod hydrochloride form 1 in crystalline form in a suitable morphology, is shown in the examples of the patent and in other documents submitted during grant and opposition proceedings.

3.3 Obviousness

3.3.1 Thus, the decisive question is whether the use of n-heptane as an antisolvent would have been obvious for a skilled person in view of the prior art.

The appellant submitted various lines of arguments in this respect.

3.3.2 The appellant argued that the solvent systems used in D2/D10 and D6/D7 already contain a non-polar antisolvent, namely ethyl acetate or diethyl ether. A skilled person would thus know that a solvent/ antisolvent crystallisation gives suitable results. Therefore, a skilled person would have expected that the use of a further non-polar solvent would likewise lead to the crystallisation of fingolimod hydrochloride. In particular, as evident from claim 5 of the patent application as filed, at least when filing the patent application the respondent itself considered diethyl ether and n-heptane to be equivalents.

However, polarity is a relative term. While ethyl acetate or diethyl ether are less polar than the ethanol used as a solvent part of the mixture, they are still considerably more polar than the n-heptane defined in the claim. In none of the documents on file is fingolimod hydrochloride recrystallised from a solvent system containing a hydrocarbon as an anti-solvent. A skilled person would therefore have no information as to whether or not such a process would yield useful results.

Moreover, in order to solve the objective technical problem defined above in the manner as claimed, a skilled person would have had to first decide that the solvent system should be changed, instead of e.g. changing process parameters while continuing to use solvent systems which are known to lead to crystallisation of the product. The objective technical problem to be solved was not the provision of a

different solvent system suitable for crystallisation of fingolimod hydrochloride, but the provision of an alternative crystallisation process for this compound.

With regard to claim 5 as filed the Board notes that the deletion of unpatentable subject-matter from a claim has no influence on the patentability assessment of the remaining claim. Article 56 EPC refers to the skilled person and the state of the art, not to the inventor's opinion and the content of the original application documents.

3.3.3 The appellant referred to the handbook D17, in particular to the chapter on the choice of suitable solvents in crystallisation processes, and to the table on page 33. They argued that from this table it could be derived that salts, such as fingolimod hydrochloride, were likely to be soluble in polar solvents, such as ethanol, whereas they were not likely to be soluble in hydrocarbons. The appellant also referred to D15, chapter 11.2.3 which stated that water or an alkane (heptane) may be used to precipitate compounds from organic solutions.

It is undisputed that a skilled person would have known that salts are likely to be soluble in polar and insoluble in non-polar solvents like alkanes. However, this does not mean that a salt will necessarily crystallize in a suitable form upon the addition of any non-polar solvent to a solution of it in a polar solvent. It may as well precipitate with an undesirable crystal morphology or in amorphous form. A skilled person would not have obtained any information from D15 or D17 on the suitability of alcohol/heptane mixtures for use in crystallizing the title compound of the

patent. Such mixtures are not even specifically mentioned in these documents.

3.3.4 The appellant referred to D21, newly filed in appeal, for general guidance on recrystallization solvents. It referred in particular to the table titled "*common solvents for crystallisation*" on pages 442 and 443.

However, independent of the question of admittance of such a document to the appeal proceedings under Articles 12(2),(4) or (6) RPBA, no relevant information supporting the appellant's case can be derived from D21. On the contrary, D21 proposes water or acetic acid containing mixtures for recrystallisation of salts. For "highly associated solids" like amides or alcohols (fingolimod is an amino alcohol, and hydrochloride salts are at least as associated as the free bases) the table header proposes mixtures of diethyl ether and methanol or ethanol, which in is fact the system used in D6/D7. Several second solvents are proposed for ethanol as a (first) solvent in a solvent mixture, among others hydrocarbons in general. However, these systems are said to be good for "*general, esters, nitro and bromo compounds*", not specifically for alcohols or salts. The table mentions n-heptane as the last entry, but as a solvent for hydrocarbons, not as an antisolvent for precipitating polar compounds. D21 does not contain any hint to use the solvent system defined in the claims for fingolimod hydrochloride or similar compounds.

3.3.5 During the oral proceedings before the Board the applicant argued that solvent screening was a routine activity for the crystallisation of new pharmaceutical entities. Such tests were fast and easy to carry out. This resulted in a "try and see situation" which,

according to the jurisprudence of the Boards, regularly lead to a lack of inventive step. Reference was made to the CLBA, 10th edition 2022, I.D.7.2. Since the solvent combination defined in the claims was certainly part of such routine screenings, the finding that it was suitable for crystallisation of fingolimod hydrochloride form 1 was the result of simple routine experimentation.

In essence, the appellant's submissions boil down to the argument that the mere existence of solvent screening methods leads to any solvent system found useful for the crystallisation of a new pharmaceutical active ingredient to lack inventive step. However, such an argument, whether valid or not, does not apply to the situation that a skilled person would be confronted with in the present case. Fingolimod hydrochloride existed already before the present patent was filed, and it had been crystallized in various ways from a variety of solvents or solvent mixtures, as outlined above. Thus, a skilled person did not have to start from scratch looking for suitable solvent systems for crystallisation using solvent screening. The skilled person had already some knowledge about which kind of solvents or solvent mixtures were proven to be useful for the crystallisation of the title compound, e. g. in the documents D2/D10 or D6/D7 defined as closest state of the art above. That the use of n-heptane as an alternative antisolvent in order to solve the objective technical problem starting from these documents was not obvious to the skilled person has been set out above.

3.4 In summary, none of the arguments submitted by the appellant convinces the Board to hold the claimed crystallisation process obvious over the cited prior art. The use of the solvent system as defined in the

claims was already non-obvious. It is not necessary to decide whether other technical features of the claims, e.g. the process steps, also constitute an inventive difference over the prior art.

4. Thus, the Board agrees agrees with the Opposition Division's decision to reject the opposition, so that the request to set aside the decision cannot succeed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated