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Datasheet for the decision of 15 April 2024

Case Number: T 0672/21 - 3.3.02

Application Number: 10792183.5

Publication Number: 2447254

IPC: C07D241/20, A61K31/4965, A61P3/06, A61P7/00, A61P7/02, A61P9/08, A61P9/10, A61P9/12, A61P11/06, A61P11/08, A61P13/12, A61P17/02, A61P25/00, A61P37/00, A61P37/02, A61P43/00

Language of the proceedings: EN

Title of invention:
CRYSTALS

Patent Proprietor:
Nippon Shinyaku Co., Ltd.

Opponents:
Alfred E. Tiefenbacher (GmbH & Co. KG)
Generics [UK] Ltd
Hexal AG

Headword:

Relevant legal provisions:
EPC 1973 Art. 56

Keyword:
Inventive step

Decisions cited:
T 0990/96, T 0777/08, T 2007/11, T 1684/16, T 0041/17

Catchword:
Inventive step: unexpected balance of beneficial properties - yes (points 1.4.5 and 1.5 of the Reasons). In contrast: see parallel case T 1994/22 (points 1.7 and 1.8 of the Reasons)

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Case Number: T 0672/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 15 April 2024

Appellant: (Opponent 2)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Nippon Shinyaku Co., Ltd. 14, Kisshoin Nishinosho Monguchicho Minami-ku Kyoto-shi Kyoto 601-8550 (JP)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Party as of right: (Opponent 1)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Party as of right: (Opponent 3)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 31 March 2021 rejecting the opposition filed against European patent No. 2447254 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman M. O. Müller
Members: S. Bertrand
L. Bühler

Summary of Facts and Submissions

I. The appeal by opponent 2 ("appellant") lies from the opposition division's decision to reject the oppositions filed against European patent No. 2 447 254.

II. Claim 1 of the patent as granted reads as follows:

"*1. A Form-I crystal of 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl) acetamide, showing diffraction peaks in its X-ray powder diffraction spectrum at least at the following angles of diffraction 2θ: 9.4 degrees, 9.8 degrees, 17.2 degrees and 19.4 degrees, wherein the X-ray powder diffraction diagram is obtained by using Cu Kα radiation.*"

III. The following documents are referred to in the present decision:

D4	S. Byrn *et al.*, Polymorphism - A Critical Consideration in Pharmaceutical Development, Manufacturing, and Stability, Pharmaceutical Solids, pages 15-23
D10	EP 1 400 518 A1
D21	Selexipag crystal slurry experiment
A034	Certificate of experimental results

IV. In the impugned decision, the opposition division's conclusions included that the subject-matter of the claims of the patent as granted involved an inventive step in view of D10 as the closest prior art.

V. In its statement of grounds of appeal, the appellant contested the opposition division's reasoning regarding the grounds for opposition under Article 100(a) in combination with Article 56 EPC. It submitted that the subject-matter of claim 1 as granted lacked inventive step in view of D10 as the closest prior art.

VI. In its reply to the grounds of appeal, the patent proprietor ("respondent") provided counter-arguments to the appellant's objection. It submitted claim sets in accordance with auxiliary requests 1 to 3.

VII. In a further letter, the appellant made further submissions.

VIII. In further letters, the respondent filed auxiliary request 4 (by letter dated 16 September 2022), A034 and further submissions.

IX. The board summoned the parties to oral proceedings as per their requests, and issued a communication under Article 15(1) RPBA.

X. Opponents 1 and 3 did not file any submission and did not submit any request. Opponent 1 informed the board and the parties that it would not be attending the oral proceedings.

XI. Oral proceedings before the board were held by videoconference on 15 April 2024, in the presence of the appellant and the respondent and in the absence of opponents 1 and 3, in accordance with Rule 115(2) EPC.

XII. The parties' requests, where relevant to the decision, were as follows:

The appellant requested that the decision under appeal be set aside, and the patent be revoked in its

entirety, and that document A034 not be admitted into the proceedings.

The respondent requested that the appeal be dismissed, implying that the opposition be rejected, or, alternatively, that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 3 filed with the reply to the appeal, and auxiliary request 4, filed with the letter dated 16 September 2022.

XIII. The appellant's case and the respondent's case, in so far as relevant to the present decision, are summarised in the Reasons below.

Reasons for the Decision

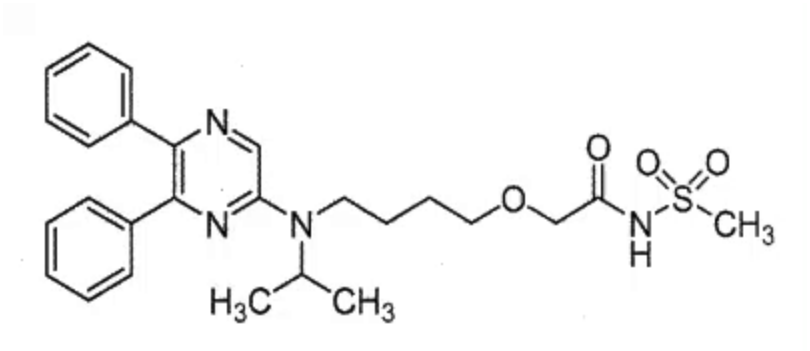
Main request

1. Inventive step - claim 1

1.1 Claim 1 of the main request relates to Form I of 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl) acetamide.

2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide is known as selexipag, which is an agonist of the prostaglandin receptor PGI2. PGI2 is known for its roles in mediating inflammation and in maintaining homeostasis, and acts as a vasodilator and a potent inhibitor of platelet aggregation.

Selexipag has the following formula:



In the following, "Form I", "Form II" and "Form III" refer to Form I, Form II and Form III crystals of selexipag.

1.2 The appellant made an objection to inventive step of the subject-matter of claim 1 of the main request in view of D10 as the closest prior art.

It was also common ground that example 84 of D10 could be regarded as a starting point for assessing inventive step within this document.

Example 84 of D10 discloses the preparation of selexipag. In this example, selexipag was purified by column chromatography. When referring to the product obtained after chromatographic purification, example 84 of D10 only refers to "*272 mg to the desired compound*" and does not disclose what type of solid form of selexipag, if any, is obtained.

1.3 Distinguishing feature

Considering the above, the distinguishing feature of claim 1 of the main request in view of example 84 of D10 is the crystalline form, namely Form I of selexipag.

1.4 Technical effect and objective technical problem

The following four properties as regards the technical effects achieved by the distinguishing feature were relied on by the respondent:

- stability,
- particle size distribution and, linked thereto, industrial processability,
- reduced concentration of residual solvents, and
- reduced level of impurities.

1.4.1 Stability

As regards stability, the parties relied on D21.

D21 is a document filed by the respondent, discussing a stability test. More specifically, D21 shows the relative stability of crystal Forms I to III of selexipag in a mixture of ethanol and methyl ethyl ketone. From this stability test, it is concluded that Form I (in accordance with claim 1 of the main request) is less thermodynamically stable than Form II (not in accordance with claim 1) and more thermodynamically stable than Form III (not in accordance with claim 1). Hence, as discussed during oral proceedings, in terms of thermodynamic stability, the claimed Form I takes an intermediate position between comparative Forms II and III.

1.4.2 Particle size distribution

The respondent relied on table 1 of the patent. Table 1 of the patent compares the particle size distribution of Forms I to III of selexipag (see below).

[Table 1]

	Crystal Form	D10	D50	D90
1	Form-I Crystal of the Invention	5.6	12.8	25.8
2	Form-II Crystal	5.2	11.3	22.0
3	Form-III Crystal	4.3	8.0	14.4

D10 : Cumulative undersize particle diameter at 10% of volumetric ratio [μm]
D50 : Cumulative undersize particle diameter at 50% of volumetric ratio [μm]
D90 : Cumulative undersize particle diameter at 90% of volumetric ratio [μm]

As apparent from the above table and as stated in paragraph [0063] of the patent, the particle size of Form I (in accordance with claim 1 of the main request) is larger than those of Form II and Form III (both comparative). It follows that the particle size distribution of Form I (in accordance with claim 1 of the main request) is shifted to larger particle sizes compared with those of Form II and Form III (both comparative).

As submitted by the respondent, based on this shift of the particle size distribution to higher particle sizes, industrial processability including filtration, drying, scattering and cross-contamination of Form I (in accordance with claim 1 of the main request) is improved over Form II and Form III (both comparative).

This was disputed by the appellant.

First, the appellant submitted that the comparison of Form I in accordance with claim 1 of the main request with Form III was irrelevant, since Form III was not the form disclosed in example 84 of D10. There was thus no comparison available with the closest prior art.

The board disagrees. It is established case law that a comparison of the claimed subject-matter may be made with variants of the closest state of the art, in order to have a variant lying closer to the invention so that the advantageous effect attributable to the

distinguishing feature is thereby more clearly demonstrated. In the current case, as set out above, example 84 of D10 discloses selexipag, but not its form, let alone a crystalline form thereof. In table 1 of the patent, the claimed Form I is compared with comparative crystalline Form II and crystalline Form III, which may be considered variants lying closer to the invention than unspecified selexipag as disclosed in example 84 of D10. Anyway, the claimed Form I can be regarded as a selection from the host of alternatives covered by the generic disclosure of example 84 of D10. Based on the above results, it can be concluded that this selection leads to the effects discussed above.

The appellant further submitted that the particle size could be measured in many ways other than that used in the patent, and that the results of table 1 of the patent only showed that the particle size distribution of Form I in accordance with claim 1 of the main request was similar to that of Form II and Form III and provided no technical "real-world" advantage.

The board does not share the appellant's view. The results set out in table 1 of the patent are the only experimental results on file regarding the particle size distribution. The board sees no reason to question these results. The burden would have been on the appellant to show that other measurement methods, the application of which would have led to results that contradict those reported in the patent, existed. In the same way, the burden of proof was with the appellant to show that the particle size measurement conducted in the patent is so inaccurate that the results reported therein are virtually identical. In the absence of any such proof, it follows that table 1 of the patent clearly shows a difference in the particle size distribution between the claimed Form I

and the comparative Form II and Form III. The board also sees no reason, in the absence of any evidence to the contrary, to question the technical advantages regarding industrial processing including filtration, drying, reduced scattering and cross-contamination achieved by the shift of the particle size distribution of Form I to larger particle sizes.

Finally, the appellant submitted that the particle size of the crystals was not inherent in Form I and was not a limitation to the claim in line with T 2007/11 (D11), but was inherent in the specific process by which the particles were obtained in the patent. The advantages based on the particle size distribution could therefore not be taken into consideration in assessing inventive step.

The appellant's submission is not convincing. In T 2007/11, the claim in question related to an unspecified crystalline form defined by five XRPD peaks. The board held that claim 1 encompassed different crystalline forms and the particular shape, size or size distribution shown for one crystalline form of claim 1 could not be taken into account in the assessment of inventive step, since the claim was not restricted to a crystalline form having a particular shape, size or size distribution (point 7.4 of the Reasons). Contrary to claim 1 in T 2007/11, claim 1 of the main request does not encompass different crystalline forms and is limited to a single specific polymorph (Form I). It thus follows that the facts underlying T 2007/11 are different and this decision is not applicable in the current case. Furthermore, in the same way as above, the appellant has not provided any proof that the advantages discussed are due to

differences in the way the claimed Form I has been prepared rather than due to its crystal habit.

Thus the improved industrial processability for Form I (as claimed) in comparison with Form II and Form III (both comparative) may be taken into account in formulating the objective technical problem.

1.4.3 Reduced concentration of residual solvents

The respondent relied on table 2 of the patent.

Table 2 of the patent (reproduced below) discloses the concentration of residual solvents contained in Form I, Form II and Form III of selexipag.

[Table 2]

	Crystal Form	Solvent	Content (ppm)
1	Form-I Crystal of the Invention	Ethanol Methyl-ethyl-ketone	371 82
2	Form-II Crystal	Ethanol	2169
		Methyl-ethyl-ketone	246
3	Form-III Crystal	Isopropyl acetate n-Butyl acetate	93 2781

As discussed during the oral proceedings, it is apparent from the above table and stated in paragraph [0066] of the patent that the amount of residual solvents in Form I (in accordance with claim 1 of the main request) is less than that of Form II and Form III (both comparative).

The relevance of these data was disputed by the appellant. First, it submitted that the comparison of Form I in accordance with claim 1 of the main request with Form III was irrelevant, since Form III was not

the form disclosed in example 84 of D10. There was thus no comparison available with the closest prior art.

For the reasons given in point 1.4.2 above, the board does not agree.

The appellant further submitted that the solvents used for preparing Form III in the patent had a higher boiling point than those of the solvents used for preparing Form I. The data presented in table 2 of the patent were thus a result of the solvent applied in the process of preparation rather than inherent in Form I, and were thus irrelevant.

The board does not agree. In table 2 of the patent, a mixture of ethanol and methyl ethyl ketone was used to prepare Form I and Form II. As submitted by the respondent, both solvents have similar boiling points (78.4 vs 79.6°C). Nevertheless, the amount of residual ethanol in Form I and Form II is almost five and nine times higher, respectively, than the residual amount of methyl ethyl ketone (371 vs 82 ppm for Form I and 2169 vs 246 ppm for Form II). This fact underlines that a higher boiling point of the solvent does not necessarily imply a higher residual amount of this solvent contained in the crystalline form.

Even if the difference in residual solvent concentration was due to the type of solvent used in preparing Forms I to III of table 2 of the patent, as submitted by the respondent, the choice of solvent systems for crystallisation depends on the crystalline form to be obtained. This means that particular forms are only accessible via crystallisation from specific solvent systems. The lower content of residual solvent is thus an intrinsic property of the claimed polymorph.

The data presented in table 2 of the patent are thus inherent in Form I.

The appellant also disputed the practical usefulness of a reduced concentration of residual solvents. However, as set out by the respondent, the very low concentration of residual solvents observed for Form I has a significant impact on the safety of selexipag as an active pharmaceutical ingredient (API). There can thus be no doubt about practical usefulness.

Therefore the reduced concentration of residual solvents observed for Form I (in accordance with claim 1 of the main request) in comparison with Form II and Form III (both comparative) may be taken into account in formulating the objective technical problem.

1.4.4 Residual impurities

Table 3 of the patent (reproduced below), relied on by the respondent, sets out the purity and the ratio of impurity removal of Form I, Form II and Form III of selexipag.

[Table 3]

	Crystal Form	Purity of Compound A (%)	Ratio of Impurity Removal (%)
	Crude Material	98.04	
1	Form-I Crystal of the Invention	99.51	75
2	Form-II Crystal	99.33	66
3	Form-III Crystal	98.97	47

As is apparent from the third column of the above table, and as stated in paragraph [0072] of the patent, the effectiveness of removing impurities for Form I (in accordance with claim 1 of the main request) is higher than that for Form II and Form III (both comparative). In the same vein, the purity level of Form I is higher

than that of Form II and Form III (second column). Form I thus has the lowest level of impurity.

The relevance of these data was disputed by the appellant.

First, the appellant submitted that the comparison of Form I with Form III was irrelevant, since Form III was not the form disclosed in example 84 of D10. There was thus no comparison available with the closest prior art.

For the reasons given in point 1.4.2 above, the board does not agree.

The appellant further submitted that the level of purity depended on the method of preparation and was not a property of the polymorph per se. Furthermore, it submitted that a small molecule could be prepared at any level of purity, based on T 990/96, so the low level of impurity of Form I could not be an effect to be considered in formulating the objective technical problem.

The board disagrees. As submitted by the respondent, in the absence of evidence that the lower impurity level depends on the method of preparation, the appellant's submission is seen only as an allegation which, due to its unsubstantiated nature, has to be disregarded. The level of impurity is thus a property of the polymorph per se. Furthermore, it cannot be held that any crystal of any given compound which comprises impurities within the crystal lattice can be prepared at any level of purity. In the absence of any evidence to the contrary, the appellant's submission is not convincing.

The appellant lastly submitted that the low amount of impurities did not lead to any real-world advantage. The board does not agree. As set out by the respondent, it is desirable to lower the amount of impurities included in a crystal to the greatest possible extent, and the increased purity facilitates the further processing of selexipag as an API.

The lower amount of residual impurities in Form I (as claimed) compared with Form II and Form III (both comparative) may therefore be taken into account in formulating the objective technical problem.

1.4.5 Objective technical problem

Based on the above, and as discussed during the oral proceedings, the objective technical problem is the provision of a crystalline form of selexipag with a balance of beneficial properties, namely an intermediate stability and at the same time improved industrial processability and improved purity in terms of reduced amounts of residual solvents and residual impurities.

1.5 Obviousness

The appellant provided submissions on obviousness based on the assumption that any improved property was absent, so that the objective technical problem was the mere provision of a further polymorph. It relied in this respect on decision T 777/08.

As set out above, the board has defined the objective technical problem in a more ambitious way. For this reason alone, the appellant's submission on obviousness must fail.

For completeness' sake, the board notes that according to T 777/08 "*in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step*" (headnote 1) and "*the arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step*" (headnote 2). However, in the present case there is no absence of unexpected properties and the selection is not arbitrary, since the selected Form I has a balance of beneficial properties in terms of stability, industrial processability and purity in comparison with Form II and Form III. There is nothing in the prior art which points to the fact that the claimed Form I would have this balance of beneficial properties. This balance of beneficial properties is thus not expected. The present case thus differs from the situation at issue in decision T 777/08.

The appellant further relied on T 41/17 and submitted that, based on D4, the alleged stability of Form I was not a surprising technical effect because the skilled person always looked for the most thermodynamically stable polymorph in order to avoid the problem of interconversion within the dosage form.

The board disagrees. In T 41/17 (point 1.3 of the Reasons) it was concluded that the skilled person would have performed screening of the different polymorphs of the pharmaceutically active compound disclosed in the closest prior art, which could exist in order to isolate and identify the most thermodynamically stable form thereof. By doing so, he would have arrived at the claimed polymorph, which was the most thermodynamically stable form and which, for this reason, was expected

not to convert to other forms under mechanical stress. However, unlike in T 41/17, in the present case the stability is not the only property, but rather part of a balance of beneficial properties. Hence, even if the stability of Form I (which is at an intermediate level) had been expected, the same would not apply to the balance of various beneficial properties discussed above.

The board also notes that the mere fact that the skilled person would have carried out routine screening for polymorphs as such does not render the claimed Form I obvious. As set out in T 1684/16 (point 4.3.4 of the Reasons), the fact that the skilled person is taught in the prior art to investigate polymorphs in order to isolate the crystalline form having the most desirable properties is in itself not necessarily sufficient to consider a specific polymorphic form having a certain desired property or, as in the present case, balance of properties obvious (see point 4.3.4 of the Reasons).

Thus the subject-matter of claim 1 of the main request, and by the same token of claims 2 to 13, which include the subject-matter of claim 1, involves an inventive step in view of D10 as the closest prior art.

2. The objection of lack of inventive step of the subject-matter of claim 1 of the main request in view of D10 as the closest prior art was the only objection raised by the appellant.

3. It follows that the main request is allowable.

4. Admittance of A034

During the oral proceedings, the board decided not to admit A034 into the proceedings. A034 was filed by the respondent with its letter dated 5 March 2024. A034 comprises experimental data on the particle size distribution of Form I, Form II and Form III crystallised under conditions different from those used in the patent. Since the decision is in the respondent's favour, there is no need to give any reason for the non-admittance of A034.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

H. Jenney M. O. Müller

Decision electronically authenticated