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**Datasheet for the decision
of 15 April 2024**

Case Number: T 1994/22 - 3.3.02

Application Number: 17186415.0

Publication Number: 3275871

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.

Opponent:
Generics [UK] Limited

Headword:

Relevant legal provisions:
EPC 1973 Art. 56

Keyword:

Inventive step

Decisions cited:

G 0002/21, T 0777/08, T 0041/17, T 0116/18, T 1989/19

Catchword:

Inventive step: unexpected balance of beneficial properties - no (points 1.7 and 1.8 of the Reasons). In contrast: see parallel case T 672/21 (points 1.4.5 and 1.5 of the Reasons)

Purported technical effect not encompassed by the teaching of the application as filed in the sense of G 2/21 (point 1.3 of the Reasons)



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1994/22 - 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)

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Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted on 13 June 2022
rejecting the opposition filed against European
patent No. 3275871 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 the opponent ("appellant") lies from the opposition division's decision to reject the oppositions filed against European patent No. 3 275 871.
- II. Claim 1 of the patent as granted reads as follows:
- "1. A Form-II 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 : 9.0 degrees, 12.9 degrees, 20.7 degrees and 22.6 degrees, wherein the X-ray powder diffraction diagram is obtained by using Cu K α 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 |
| D32 | Test on the influence of Selexipag crystal Forms II and III on the photostability properties of Selexipag tablets |
| D34 | JP 2001-129765 |
| D34a | English translation of D34 |
| A036 | Certificate of experimental results |

- IV. In the impugned decision, the opposition division's conclusions included the fact that the subject-matter of the claims of the patent involved an inventive step starting from D1a/D34/D34a.
- 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 an 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 sets of claims according to auxiliary requests 1 to 5.
- VII. In further letters, the appellant filed further submissions regarding the inventive step of the claims of the main request and auxiliary requests 1 to 5.
- VIII. In further letters, the respondent filed further submissions with regard to inventive step and document A036 (denoted D36 by itself).
- IX. The board summoned the parties to oral proceedings as per their requests, and issued a communication under Article 15(1) RPBA.
- X. Oral proceedings before the board were held by videoconference on 15 April 2024, in the presence of the appellant and the respondent.
- XI. 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. Furthermore, it requested that document A036 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 5 filed with the reply to the appeal.

XII. The appellant's case and the respondent's case, insofar as they are relevant to the present decision, are summarised in the Reasons below.

Reasons for the Decision

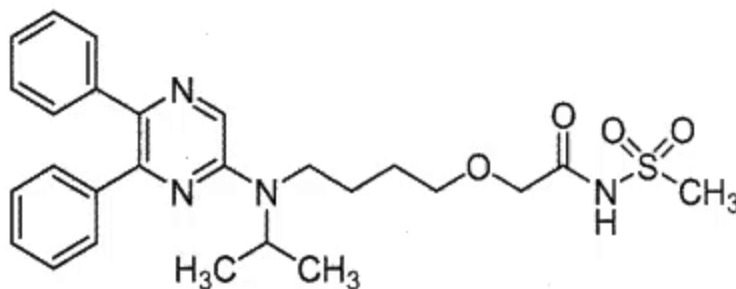
Main request

1. Inventive step - claim 1

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

2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methanesulfonyl)acetamide is known as selexipag. Selexipag is an agonist of the prostaglandin receptor PGI₂. PGI₂ is known for its roles in mediating inflammation and 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 objected to the inventive step of the subject-matter of claim 1 of the main request in view of D10 as the closest prior art.

The respondent *inter alia* relied on post-published data D32 and submitted that Form II as claimed had an improved photostability over Form III (comparative).

D32 is a post-published document filed by the respondent before the opposition division. D32 sets out the results of a light stability test of tablets comprising Form II (according to claim 1 of the main request) and Form III (comparative). After the stability test, the tablets comprising Form II exhibited a residual ratio of active pharmaceutical ingredient (API) of 89.3%, while the tablets comprising Form III showed a residual ratio of API of 73.4%. From this light stability test, it is concluded in D32 that Form II (according to claim 1 of the main request) is more photostable than Form III (comparative).

1.3 G 2/21 - taking into account the effect demonstrated in the post-published experimental data in D32

The appellant submitted that the application as filed made no mention of the photostability of Form II, let alone contained any evidence of it. Based on G 2/21, the respondent could not rely on the effect of improved photostability.

According to G 2/21 (headnote 2), *"a patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention."*

Considering order no. 2 of G 2/21, the question to be answered in the present case is thus whether the effect relied on by the respondent and demonstrated in the post-published experimental data (D32), namely that of improved photostability of Form II, can be derived by the skilled person, having the common general knowledge in mind, and based on the application as filed, as being encompassed by the technical teaching (requirement (i)) and embodied by the same originally disclosed invention (requirement (ii)).

The respondent relied on the statements made in T 116/18 as regards G 2/21 and submitted that, based on paragraphs [0006] and [0007] of the application as filed (A1 application), referring to the provision of a novel crystal of compound A (selexipag) and to a pharmaceutical product of *"high quality for which constant effect can always be shown and a form which is handled easily industrially"*, the skilled person would have understood that the effect of improved

photostability was implied by or at least related to the technical problem initially suggested in the originally filed application. Therefore, requirement (i), as encompassed by the technical teaching, was met. Furthermore, the skilled person would not have had any legitimate reason to doubt that the improved photostability could be achieved with the claimed polymorphic form of selexipag. Based on their common general knowledge the skilled person had been aware on the filing date that different polymorphic forms of APIs may have different, e.g. improved, photostability, and so the effect of improved photostability of selexipag Form II was not irreconcilable with the provision of a novel polymorphic form. Therefore, requirement (ii), as embodied by the same originally disclosed invention, was also met in the present case.

Before the board comments on the respondent's arguments, the relevant passages of decision T 116/18 will be reiterated here.

According to point 11.10 of the Reasons, the requirement that the purported technical effect be encompassed by the technical teaching (requirement (i)) means that this *"purported technical effect together with the claimed subject-matter need only be conceptually comprised by the broadest technical teaching of the application as filed. This in turn means that said effect need not be literally disclosed in it by way of a positive verbal statement (see also point 11.13.1 below). Instead, for example, it may also be sufficient that the skilled person, having the common general knowledge in mind, and based on the application as filed, recognises that said effect is necessarily relevant to the claimed subject-matter."*

In line with T 116/18 (point 11.14), in the present case the board acknowledges that the mere fact that photostability or improved photostability is not contained in terms of a positive verbal statement in the application as filed and that the application as filed does not contain any data as regards photostability, as such, does not imply that the effect of improved photostability cannot be relied on in terms of G 2/21 or T 116/18.

The board also agrees with T 116/18 (point 11.10) that the purported technical effect **together with the claimed subject-matter** need only be conceptually comprised by the broadest technical teaching of the application as filed and that it may also be sufficient for the skilled person, having the common general knowledge in mind, and based on the application as filed, to recognise that said effect is relevant to the claimed subject-matter; however, it is precisely this requirement that is not met in the present case.

All that is disclosed in paragraph [0005] of the application as filed (paragraph [0006] of the application as published), as relied on by the respondent, is a "*thing of a high quality for which constant effect can be always shown and of a form which is handled easily industrially*". The board does not consider such a sweeping statement regarding high quality and easy industrial handleability which covers a plethora of potential advantageous properties to encompass photostability, let alone improved photostability. If such a sweeping statement was sufficient, a reference to high quality would be sufficient to invoke whatever technical effect as being encompassed by an application as filed in the sense of G 2/21. This would essentially render the first criterion of order no. 2 of G 2/21 meaningless. In the

present case, in more concrete terms, the application as filed is in fact directed to particle size (table 1), residual solvent content (table 2) and amount of impurities (table 3). These properties are entirely unrelated to photostability. Therefore, based on these properties, having the common general knowledge in mind, the skilled person would by no means have recognised that (improved) photostability is relevant to the claimed subject-matter. Going from these specific properties to the effect of photostability would also clearly change the nature of the invention, contrary to what is required by T 116/18 (point 11.13.3 of the Reasons). Hence, the effect of photostability is not encompassed by the teaching of the application as filed.

Furthermore, even if it were wrongly concluded in the respondent's favour that the technical teaching of the application as filed were to encompass photostability in the sense of T 116/18, it would not do so "together with the claimed subject-matter", as required by this decision (point 11.10). More specifically, points (1) to (3) of paragraph [0006] of the application as filed (paragraph [0007] of the application as published), claims 1 and 2, and points [1] to [3] on page 37 of the application as filed, as relied on by the respondent, refer to Form I, Form II and Form III in equal terms. These passages do not teach that Form II, i.e. the form claimed in claim 1 of the main request, is the preferred polymorphic form of selexipag, let alone that it should exhibit a photostability that is improved compared with Form I and Form III. Hence, the effect of improved photostability together with Form II is not encompassed by the teaching of the application as filed.

During the oral proceedings, the parties discussed decision T 1989/19. The respondent submitted that the present case was in line with T 1989/19 and that it was not a requirement that the application as filed disclosed improved photostability, so that the effect proven by the technical data in D32 could be taken into account in the formulation of the objective technical problem.

The board does not agree.

In T 1989/19 (points 3.3.15 and 3.3.16 of the Reasons), the board recognised that the technical effect derivable from the application as originally filed in the sense of G 2/21 was storage stability of the claimed compound, while the effect demonstrated by the post-published documents was the improvement in this storage stability over the cited closest prior art. In that case, the board held that once the criterion of the derivability of a technical effect in the sense of G 2/21 was fulfilled, this applied equally to the improvement in this effect.

The board agrees with the view expressed in T 1989/19; however, the situation in the present case is different from that in this decision. In the present case, as set out above, photostability is not encompassed and thus not derivable from the teaching of the application as filed in the sense of G 2/21. Furthermore, unlike in the case underlying T 1989/19, the application as filed in the present case refers to three polymorphic forms in equal terms, and the present case is not one in which the purported improvement is asserted to be present for the subject-matter of the application as filed over the subject-matter disclosed in the prior art. On the contrary, in the present case the improvement is asserted for part of the subject-matter

disclosed in the application as filed over other parts of this subject-matter in equal terms.

It follows that improved photostability of Form II as demonstrated in D32 cannot be taken into account in the assessment of the technical effects achieved by the distinguishing feature.

1.4 Hereinbelow, inventive step starting from D10 will be discussed.

It was common ground between the parties that example 84 can be regarded as the starting point for the assessment of 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 which type of solid form of selexipag is obtained, if any.

1.5 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 II, of selexipag. This was common ground between the parties.

1.6 Technical effects achieved by the distinguishing feature

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

- stability,

- particle size distribution, and linked to this, industrial processability,
- concentration of residual solvents,
- level of residual impurities, and
- improved photostability.

In view of the above conclusion under point 1.3, improved photostability cannot be taken into account. Consequently, only the first four properties will be discussed below.

1.6.1 Stability

The respondent relied on D21 and submitted that Form II as claimed had improved stability over Form I and Form III (both comparative).

D21 is a document filed by the respondent, discussing a stability test. More specifically, D21 demonstrates the relative stability of crystal Form I to Form III in a mixture of ethanol and methyl ethyl ketone. From this stability test, it follows that Form II (according to claim 1 of the main request) is more thermodynamically stable than Form I (comparative) and Form III (comparative). Form II thus has the highest thermodynamic stability.

This was common ground between the parties.

1.6.2 Particle size distribution

The respondent relied on table 1 of the patent. Table 1 of the patent compares the particle size distribution of the three forms, Form I to Form III (see below).

[Table 1]

	Crystal Form	D10	D50	D90
1	Form-I Crystal	5.6	12.8	25.8
2	Form-II Crystal of the Invention	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]				

From table 1, it can be concluded that the particle size of Form II (according to claim 1 of the main request) is larger than that of Form III (comparative), but smaller than that of Form I (comparative). Based on its intermediate position in terms of particle size, Form II thus has an intermediate industrial processability. As submitted by the respondent, the particle size of the crystals is inherent to Form II, in the absence of any evidence that it would be linked to its process of preparation.

1.6.3 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.

[Table 2]

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

As submitted by the respondent, the lower concentration of residual solvent observed for the claimed Form II (2169 + 246 = 2415 ppm) as set out in table 2 of the

patent facilitates more exhaustive removal of the solvent in comparison with the concentration for comparative Form III (93 + 2781 = 2874 ppm), but not in comparison with the concentration for comparative Form I (371 + 82 = 453 ppm). Form II thus has an intermediate level of residual solvent. As submitted by the respondent, the level of residual solvent is inherent to Form II, in the absence of any evidence that it would be linked to its process of preparation.

1.6.4 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 II (according to claim 1 of the main request), Form I (comparative) and Form III (comparative).

[Table 3]

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

As is apparent from the third column of the above table, the effectiveness of removing impurities for Form II (according to claim 1 of the main request) is higher than that for Form III (comparative), but lower than that for Form I (comparative). In the same vein, the purity level of Form II is higher than that of Form III but lower than that of Form I (second column). Form II thus also has an intermediate position as regards the level of residual impurity. As submitted by the respondent, the level of residual impurity is inherent to Form II, in the absence of any evidence that it would be linked to its process of preparation.

1.7 Objective technical problem

In view of the above experimental result, it can be concluded that Form II exhibits the best stability but only intermediate industrial processability, intermediate residual solvent content and an intermediate amount of residual impurities. As set out by the chairman during the oral proceedings, contrary to the situation in T 672/21 there is no balance of beneficial properties for Form II according to the main request. The objective technical problem may only be considered that of providing a crystalline form of selexipag which is the best for one property, but only intermediate for all other tested properties.

1.8 Obviousness

The respondent submitted that, in line with T 1684/16 (point 4.3.4 of the Reasons), there was no reasonable expectation based on the prior art that a suggested investigation in terms of polymorph screening would be successful in finding a form of selexipag having a balance of beneficial properties in terms of stability, industrial processability, solvent content and purity.

The board disagrees. Based on T 1684/16 and in line with T 777/08, an inventive step can be acknowledged if the claimed polymorph has an unexpected property meaning that its selection is non-arbitrary. In the present case, the board sees nothing unexpected in finding a polymorph that is optimum for one property but only intermediate for several other properties. If this were unexpected and thus gave rise to an inventive step being acknowledged, an applicant or proprietor having identified a new polymorph would simply need to carry out tests for long enough to find one single property for which the identified polymorph performs

best. As pointed out by the chairman during oral proceedings, this might result in a situation in which almost any polymorph in the world becomes inventive, which would render Article 56 EPC meaningless.

Therefore, the selection of Form II is an arbitrary selection from the host of alternatives covered by the closest prior art. Such an arbitrary selection without any unexpected balance of properties being produced cannot contribute to inventive step. The subject-matter of claim 1 of the main request therefore does not involve an inventive step in view of D10 as the closest prior art.

2. The main request is not allowable.

Auxiliary requests 1 to 5 (claims filed with the statement of grounds of appeal)

3. Claim 1 of auxiliary request 1 comprises the product-by-process feature "*and wherein said Form-II crystal of selexipag is obtainable by a process ... for 1 hour to 48 hours*".

Claim 1 of auxiliary request 2 comprises the product-by-process features of example 4 of the application as filed.

Claim 1 of auxiliary request 3 comprises the product-by-process features of examples 3 and 4 of the application as filed.

Claim 1 of auxiliary request 4 comprises the results of the measurements of the particle size distribution of example 1 of the application as filed.

Auxiliary request 5 is based on auxiliary request 4. In claim 1 of auxiliary request 4, the apparatus "*(HORIBA LA-910)*" was replaced with "*using HORIBA LA-910*".

4. The respondent submitted that auxiliary requests 1 to 5 were filed to address the issue that, according to the appellant, the properties demonstrated by the respondent were not inherent to the claimed Form II, but linked to its process of preparation.
5. When announcing its conclusion during oral proceedings that the subject-matter of claim 1 of the main request did not involve an inventive step, the board expressed the view that this conclusion applied to claim 1 of any of auxiliary requests 1 to 5. This was not contested by the respondent during the oral proceedings. In fact, in arriving at its conclusion for the main request, the board agrees with the respondent that the properties relied on by it (see points 1.6.2 to 1.6.4 above) are inherent to the claimed Form II rather than being linked to its process of preparation, but nevertheless denied inventive step.
6. Therefore, the subject-matter of claim 1 of auxiliary requests 1 to 5 does not involve an inventive step for the same reasons as those given for the main request.
7. Auxiliary requests 1 to 5 are not allowable.

Admittance of A036

8. During the oral proceedings, the board decided not to admit A036 into the proceedings. A036 was filed by the respondent with its letter dated 5 March 2024. A036 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. It served to demonstrate that the particle size of Form II is an inherent property of this form rather than being dependent on the process conditions applied during its preparation. As already set out above, the board agrees with the respondent

that the properties relied on by it are inherent to the claimed Form II rather than being linked to its process of preparation. Therefore, the experimental data in A036 are not relevant to the present decision. There is thus no need to give any reason for A036 not being admitted.

9. None of the claim requests is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



H. Jenney

M. O. Müller

Decision electronically authenticated