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Datasheet for the decision of 7 December 2021

Case Number: T 2401/16 - 3.3.02

Application Number: 11739338.9

Publication Number: 2535339

IPC: C07D417/12, A61K31/506, A61P35/00, A61P35/02

Language of the proceedings: EN

Title of invention:
POLYMORPHS OF DASATINIB, PREPARATION METHODS AND PHARMACEUTICAL COMPOSITIONS THEREOF

Applicant:
Nanjing Cavendish Bio-Engineering Technology Co., Ltd.
Yan, Rong

Headword:

Relevant legal provisions:
EPC Art. 54
RPBA Art. 12(4)
RPBA 2020 Art. 15(3), 25(2)

Keyword:
Novelty
Late-filed auxiliary requests

Decisions cited:
G 0007/93, T 1209/05, T 1652/08, T 1253/09

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2401/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 7 December 2021

Appellant: (Applicant 1)	Nanjing Cavendish Bio-Engineering Technology Co., Ltd. No. 6 Maiyue Road Maigaoqiao Pioneering Park Qixia District Nanjing Jiangsu 210028 (CN)
Appellant: (Applicant 2)	Yan, Rong Room 105, No9 Yijing Garden Gulou Digest Nanjing Jiangsu 210001 (CN)
Representative:	Rippel, Hans Christoph Patentanwälte Isenbruck Bösl Hörschler PartG mbB Eastsite One Seckenheimer Landstrasse 4 68163 Mannheim (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 28 April 2016 refusing European patent application No. 11739338.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	P. O'Sullivan
Members:	S. Bertrand
	E. Mille

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies from the decision of the examining division to refuse European patent application 11 739 338.9 on the basis of the main request.

II. The main request contains a set of six claims, independent claims 1 and 5 of which read as follows:

"*1. A Polymorph I of Dasatinib monohydrate, characterized by diffraction peaks at 9.1±0.2, 11.1±0.2, 13.7±0.2, 15.1±0.2, 17.8±0.2, 19.4±0.2, and 23.0±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation, obtainable from a solution of Dasatinib in dimethyl formamide or dimethyl sulfoxide by the method according to claim 5.*

5. A preparation method of the Polymorph I of any one of Claim 1 to 4 includes the following steps:

1) Dasatinib is added into dimethylformamide or dimethylsulfoxide;
2) dissolved by stirring and heating;
3) a mixed solvent system of water and an organic solvent is added; wherein, the organic solvent is one kind of solvent or a mixed solvent of several kinds, to which Dasatinib is insoluble or slightly soluble;
4) after finish adding, it is heat-preserved and then cooled down slowly to 0~5°C with stirring to make crystal precipitated completely and grow the grain;
5) after filtration, the solid is collected and dried."

Claim 1 of the auxiliary request is identical to claim 5 of the main request, with the exception that it includes the characterising data from claim 1 of the main request, namely "[a] *preparation method of a Polymorph I of Dasatinib monohydrate characterized by diffraction peaks at 9.1±0.2, 11.1±0.2, 13.7±0.2, 15.1±0.2, 17.8±0.2, 19.4±0.2, and 23.0±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation, ...*".

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

D1: US 2005/215795 A1

D7: WO 2009/053854 A2

IV. In the impugned decision, the examining division's conclusions included the following:

- the subject-matter of claims 1-4 according to the main request was not novel in view of D1 or D7;
- the subject-matter of process claim 5 of the main request lacked an inventive step, and
- the claim set of the auxiliary request was not admitted into the proceedings.

V. With the statement setting out the grounds of appeal, the appellant contested the reasoning of the examining division regarding the subject-matter of the claims according to the main request and the non-admittance of the auxiliary request. The appellant submitted a copy of the main request and the auxiliary request considered in the impugned decision.

VI. On 23 April 2021, the board issued a communication pursuant to Article 15(1) RPBA in preparation for the oral proceedings, scheduled as requested by the appellant. The board provided the preliminary view that the subject-matter of claim 1 of the main request lacked novelty over both D1 and D7. More specifically, the polymorph I disclosed in the application was identical to the polymorph of example 8 disclosed in D1 and polymorph "H 1-7" disclosed in D7 respectively. Furthermore, the view was provided that claim 5 of the main request lacked inventive step. Finally, the board stated that whether the auxiliary request should be admitted into proceedings would be addressed at oral proceedings before the board.

VII. With a letter dated 6 December 2021, the appellant informed the board that it would not attend the oral proceedings, scheduled for the following day.

VIII. Oral proceedings before the board were held on 7 December 2021 by videoconference in the absence of the appellant pursuant to Rule 115(2) EPC and Article 15(3) RPBA 2020.

IX. The appellant's arguments, where relevant to the present decision, may be summarised as follows:

Main request - Novelty

- The polymorph of dasatinib monohydrate of claim 1 obtainable by the method of claim 5 as recited therein, was different from the polymorphs disclosed in D1 (the form of example 8) and D7 (form H 1-7), since:

  - it lacked a characteristic peak at 4.6 (2-theta), and displayed XRPD peaks having a different intensity,

- it had a DSC of 122 and 281°C, while the polymorphic form disclosed in D1 had a DSC of 125 and 288°C.

- it displayed differences in stability compared to the polymorph of example 8 of D1, as demonstrated by the comparative tests in the description of the patent.

Auxiliary request - Admittance

- The decision of the examining division not to admit the auxiliary request was incorrect.

- It could not be concluded that the auxiliary request was not allowable, since the subject-matter of claim 1 was inventive. Specifically, since the comparative tests in the description (table 16, pages 33-34) showed unexpected effects at least in terms of oxidative-, alkali-, light- and heat deterioration, the process of the invention led to a product with higher stability comprising less impurities.

- For this reason, the auxiliary request was clearly allowable and should be admitted into the proceedings.

X. The appellant requested that:

- the decision under appeal be set aside and a patent be granted on the basis of the main request, which was identical to the main request considered by the examining division in its decision, or

- alternatively, a patent be granted on the basis of the auxiliary request filed with the statement of grounds of appeal, which was identical to the

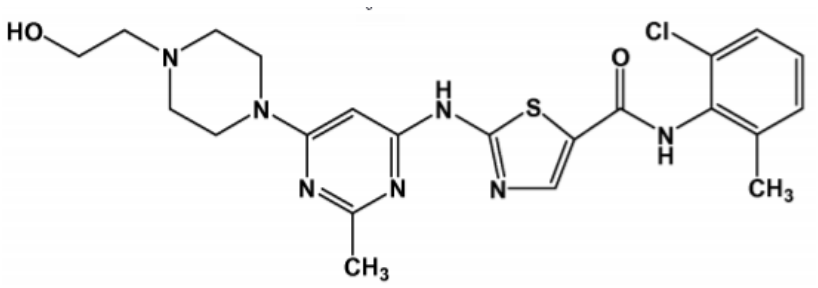
auxiliary request not admitted into the proceedings by the examining division.

Reasons for the Decision

1. The appellant did not attend oral proceedings before the board. In accordance with Article 15(3) RPBA 2020, it is treated as relying on its written case.

Main request - claims 1 to 6 filed with the statement of grounds of appeal

2. Claim 1 relates to a crystalline form of Dasatinib monohydrate denoted polymorph I. Dasanitib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidyl]amino]-5-thiazolformamide. Its chemical structure is as follows:



3. Article 54 EPC

3.1 According to claim 1, the polymorph I is characterized by diffraction peaks at 9.1±0.2, 11.1±0.2, 13.7±0.2, 15.1±0.2, 17.8±0.2, 19.4±0.2, and 23.0±0.2 of 2θ.

3.2 The board is of the view that the subject-matter of claim 1 lacks novelty in view of D1 or D7.

3.3 D1 (example 8, paragraphs [0356] - [0402]) discloses the preparation of a crystalline monohydrate of a compound of formula (IV). The formula of the compound of formula (IV) in D1 (paragraph [0339]) corresponds to the chemical formula for Dasatinib referred to in point 2 above. The crystalline form disclosed in this example is thus a polymorph of Dasatinib monohydrate. Paragraph [0381] of D1 lists the diffraction peaks of the X-ray powder diffraction (XRPD) pattern of the crystalline Dasatinib monohydrate: 4.6±0.2, **11.2±0.2**, **13.8±0.2**, **15.2±0.2**, **17.9±0.2**, 18.0±0.2, 18.4±0.2, 19.1±0.2, 19.2±0.2, **19.6±0.2**, 21.2±0.2, **23.2±0.2**, 23.6±0.2. 24.5±0.2, 25.9±0.2, and 28.0±0.2 (emphasis added by the board to show the peaks corresponding to those of claim 1 of the main request). The whole XRPD spectrum of the polymorph of example 8 is disclosed in figure 1 (paragraphs [0379] and [0381]).

The board notes that paragraph [0381] of D1 does not disclose the peak at 9.1±0.2 required by claim 1 of the main request. However figure 1 of D1 discloses all XRPD peaks identified in paragraph [0381] as well as *inter alia* a peak at approximately **9.1**. For these reasons, figure 1 in combination with paragraph [0381] of D1 discloses all the features of claim 1 of the main request.

D7 (paragraph [0210]) also discloses a crystalline polymorph of Dasatinib monohydrate having the following XRPD peaks: 4.6±0.2, **9.2±0.2**, **11.2±0.2**, **13.8±0.2**, **15.2±0.2**, **17.9±0.2**, **19.5±0.2**, **23.1±0.2**, 23.6±0.2, 25.9±0.2, 28.0±0.2 (emphasis added by the board to show the peaks corresponding to those of claim 1 of the main request).

The board notes that paragraph [0210] of D7 discloses **all** the peaks listed in claim 1 of the main request.

Therefore, the XRPD peaks listed in claim 1 do not distinguish the subject-matter thereof from D1 or D7.

3.4 Claim 1 also comprises the feature that the claimed polymorph is "*obtainable from a solution of Dasatinib in dimethyl formamide or dimethyl sulfoxide by the method according to claim 5*".

According to established case law, claim 1 is to be construed as a claim to the product as such, and is not rendered novel merely by the fact that it is produced by means of a new process. As set out above, the XRPD peaks of claim 1 coincide with those of the polymorphic forms disclosed in D1 and D7.

3.4.1 The appellant submitted that by virtue of its process of preparation ("*obtainable from a solution of Dasatinib in dimethyl formamide or dimethyl sulfoxide by the method according to claim 5*"), the polymorph I of claim 1 constituted a different crystalline form to that of example 8 of D1 as set out above, based on three features, as set out in the following.

Although the appellant's arguments in this regard concerned a comparison of the claimed polymorph with that of D1, it can be presumed, to the appellant's advantage, that the relevant polymorphic forms disclosed in D1 and D7 are identical, and that the appellant's arguments apply also with regard to establishing novelty over D7.

3.4.2 First, the appellant's argument regarding the alleged lack of a peak at 4.6 for the claimed polymorph is without merit, since as mentioned in the contested decision (point 3.2) as well as the statement of grounds of appeal (point 1.1), the corresponding peak of the claimed polymorph I differs from that of D1 in its intensity (14% for the claimed polymorph according

to the appellant). The diffraction peaks at positions 4.6 and 9.1 were thus different from those of D1 because of their intensity. The appellant cited the standard, "1995 USP 23/NF", according to which "*relative intensities may vary considerably from that of the reference standard*", and argued that "*the fact that relative intensities may vary does not mean that they do vary*" (emphasis by the appellant).

The board does not accept the appellant's argument. The fact that the relative intensities of the peaks may not be indicative of a different crystalline form (and this is not challenged by the appellant) is sufficient to conclude that differences in intensities are not sufficient proof of the presence of a different polymorphic form.

3.4.3 Second, the appellant submitted that the DSC values of the respective polymorphs were different and therefore indicative of the formation of a different polymorphic form. Specifically, the process of preparation referred to in claim 1 of the main request led to a polymorphic form having a DSC of 122 and 281°C, while the polymorphic form disclosed in example 8 of D1 had a DSC of 125 and 288°C.

The board does not agree. It is part of the common general knowledge that DSC measurements depend significantly on a number of factors including but not limited to sample preparation, sample size, particle size, heating rate and the instruments employed. For example, the measurements in the patent were obtained using a "US Perkin Elmer Diamond DSC" instrument (page 13, lines 11-13) while in D1 the measurement was performed using a "TA Instruments model Q1000" instrument (D1, paragraph [0352]). Given the only minor difference in the DSC value reported in D1 and those in

the present application, the board does not accept that the measurements provided serve as evidence that polymorph I is different from the forms disclosed in D1 (polymorph A) and D7 (H 1-7), rather than resulting merely from differences in the way in which the respective measurements were taken.

3.4.4 Third, the appellant argued as a further basis for acknowledging the novelty of claim 1, that the comparative tests in the description showed that a difference in stability was observed between the polymorph of claim 1 of the main request and that of CN200580011916.6, a patent family member of D1.

According to the appellant, at least for the tests on oxidative, alkali, light and heat deterioration (table 16 of the patent), the process of the invention led to a product with higher stability, producing less impurities. Since the method was included in the claim, the effects would have their origin in the method of preparation and would prove that the polymorph of claim 1 was different from that of example 8 of D1.

This argument is not accepted by the board for the following reasons. There is no explanation in the application as filed regarding the accuracy of the tests of table 16. In the absence of the experimental error and the repeatability for each test, it cannot be concluded that improved stability is achieved. Additionally, the specific nature of the initial impurities present in each sample ("before destruction") is not clarified in table 16. The different nature of the initial impurities can explain the difference of stability. In the absence of information on the initial impurities in the samples, no conclusion can be drawn that the difference of

stability originates in the alleged distinguishing feature (polymorphic form).

Furthermore, even if the difference of values in table 16 were to be considered relevant, the board notes that, in the acid deterioration test, the same stability is obtained for the polymorph of the invention compared to that of example 8 of D1. Furthermore, before the test on light and heat deterioration, the polymorphs are dissolved and thus not present as such in the solution. Consequently, the alleged effect regarding light and heat deterioration cannot be achieved by the alleged distinguishing feature (polymorphic form). With regard to the oxidative and alkali deterioration test, there is no mention of the exact conditions for the preparation of the samples. For instance, there is no information on the particle size of the polymorphic forms. If the particle size were not the same in both samples, it could not be concluded that the effect was convincingly achieved by the alleged distinguishing feature.

3.5 The appellant had the opportunity to explain the technical results of table 16 as requested by the examining division in the summons to attend oral proceedings. Additionally, in its communication (point 5.6, penultimate paragraph), the board gave an explanation as to why it shared the examining division's opinion. The appellant however neither replied to the issues raised in the communication, nor attended the oral proceedings before the board. In the absence of a convincing explanation of the results of table 16, and none was provided in the written submissions of the appellant, it cannot be accepted that polymorph I is different from the polymorph of example 8 of D1, or form H 1-7 of D7 on this basis.

It follows that none of the data referred to by the appellant demonstrates that the method of preparation in claim 1 of the main request allows the preparation of a polymorph different from the polymorph of example 8 of D1 or H1-7 of D7.

3.6 Consequently, in the absence of evidence to the contrary, the polymorph I disclosed in the application is identical to the polymorph disclosed in example 8 of D1 and polymorph H 1-7 disclosed in D7. Therefore, the subject-matter of claim 1 lacks novelty in view of D1 or D7.

4. For these reasons, the main request is not allowable.

Auxiliary request

5. Claim 1 of the auxiliary request is essentially identical to claim 5 of the main request and is concerned with a process of preparing Polymorph I of Dasatinib monohydrate comprising the following steps:

> 1) Dasatinib is added into dimethylformamide or dimethylsulfoxide;
> 2) dissolved by stirring and heating;
> 3) a mixed solvent system of water and an organic solvent is added; wherein, the organic solvent is one kind of solvent or a mixed solvent of several kinds, to which Dasatinib is insoluble or slightly soluble;
> 4) after finish adding, it is heat-preserved and then cooled down slowly to 0-5°C with stirring to make crystal precipitated completely and grow the grain;
> 5) after filtration, the solid is collected and dried.

6. Admittance of the auxiliary request

6.1 The auxiliary request was filed on 29 February 2016, i.e. one day before the oral proceedings before the examining division. In the impugned decision (point 2), the examining division did not admit the auxiliary request. In the statement of grounds of appeal the appellant requested that a patent be granted on the basis of the auxiliary request, thereby implicitly requesting that it be admitted into the appeal proceedings.

6.2 Under Article 12(4) RPBA 2007 (which applies in the present case, the statement of grounds of appeal being filed before 1 January 2020, see the transitional provisions of Article 25(2) RPBA 2020), the board has the power not to admit *inter alia* requests into the proceedings that were not admitted at the first instance stage. According to e.g. G 7/93, T 1209/05, T 1652/08 and T 1253/09, the board shall overrule the way in which an examining division has exercised its discretion when deciding not to admit an auxiliary request only if it concludes that the first-instance department did so based on the wrong principles or in an unreasonable way. Thus, in the present case, it must be determined whether the examining division applied the wrong principle or applied the right principle but in an unreasonable way.

6.3 In point 2 of its decision, the examining division summarised the facts about the submission of the auxiliary request and came to the conclusion that the auxiliary request was late filed and clearly non-allowable. In particular, the examining division pointed out that the auxiliary request was filed one day before the oral proceedings, i.e. after the final

date for making further submission and/or amendment according to Rule 116(1) EPC, and that the subject-matter of claim 1 was clearly not inventive for the same reasons as claim 5 of the main request, which was identical (by reference to point 4 of the decision).

6.4 *Prima facie* allowability is the correct principle to be applied by a first-instance department in deciding on the admittance of late filed auxiliary requests. Therefore when deciding not to admit the auxiliary request, the examining division exercised its discretion based on the right principle.

6.5 Furthermore, the examining division did not apply the above principle in an unreasonable way for the following reasons:

The examining division concluded in its decision that claim 5 of the main request did not involve an inventive step in view of D1 as the closest prior art (point 4 of the decision). More specifically, the examining division considered that the claimed polymorph I was identical to the crystalline form disclosed in D1 (point 3.5 of the decision). This also applied to the polymorph obtained by the process of claim 5 of the main request, which was the same as the crystalline form disclosed in D1. The examining division considered that the distinguishing feature of claim 5 of the main request was the solvent (dimethylformamide or dimethylsulfoxide). No improvement was seen in this process, there being no reason that the compound obtained by the claimed process would exhibit different properties such an increased stability. Consequently, the technical problem underlying the subject-matter of claim 5 of the main request was formulated as the provision of an

alternative process for the preparation of polymorph I of Dasatinib. The examining division was of the view that it was routine practice to try different solvents in an attempt to crystallise a known active compound. It concluded that the subject-matter of claim 5 of the main request was not inventive. Since claim 1 of the auxiliary request corresponds to claim 5 of the main request, the lack of inventive step applied to claim 1 of the auxiliary request. Thus the examining division concluded that the auxiliary request was *prima facie* not allowable.

6.6 The appellant argued that the decision of the examining division was incorrect since the comparative tests in the description (table 16) showed unexpected effects. For this reason, the auxiliary request was clearly allowable.

The board does not agree.

As set out above (point 3.6), the board sees no unexpected effects in the results of table 16.

6.7 Thus, the board has no reason to doubt that the examining division's conclusion regarding the *prima facie* non-allowability of the auxiliary request was reached in a reasonable manner.

6.8 Furthermore, the examining division also decided not the admit this request due to it being late-filed. Indeed, with the letter dated 29 February 2016, the appellant both filed the auxiliary request and withdrew the request for oral proceedings, scheduled for the morning of the following day. As noted by the examining division, the final date for further submissions pursuant to Rule 116(1) EPC was 1 February 2016. Since

at most one day elapsed between the filing of the new request and the start of the scheduled oral proceedings, the examining division were provided with practically no time to study and prepare for this new request. It can only be concluded therefore that it was clearly reasonable for the examining division not to admit this request into the proceedings.

6.9 For these reasons, the board decided not to overturn the decision of the examining division not to admit the auxiliary request into the proceedings.

7. Since there are no allowable requests on file, the appeal is to be dismissed.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin P. O'Sullivan

Decision electronically authenticated