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**Datasheet for the decision  
of 14 January 2020**

**Case Number:** T 0041/17 - 3.3.02

**Application Number:** 05797740.7

**Publication Number:** 1797038

**IPC:** C07D213/81, A61K31/44,  
A61P35/00

**Language of the proceedings:** EN

**Title of invention:**

THERMODYNAMICALLY STABLE FORM OF BAY 43-9006 TOSYLATE

**Patent Proprietor:**

Bayer HealthCare LLC

**Opponents:**

Fresenius Kabi Deutschland GmbH  
Biofer S.p.A.

**Headword:**

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

Inventive step

**Decisions cited:**

T 0777/08, T 2114/13, T 0517/14

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

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Case Number: T 0041/17 - 3.3.02

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.02**  
**of 14 January 2020**

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**Decision under appeal:** **Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
7 November 2016 concerning maintenance of the  
European Patent No. 1797038 in amended form**

**Composition of the Board:**

<b>Chairman</b>	M. O. Müller
<b>Members:</b>	S. Bertrand
	M. Blasi
	P. O'Sullivan
	L. Bühler

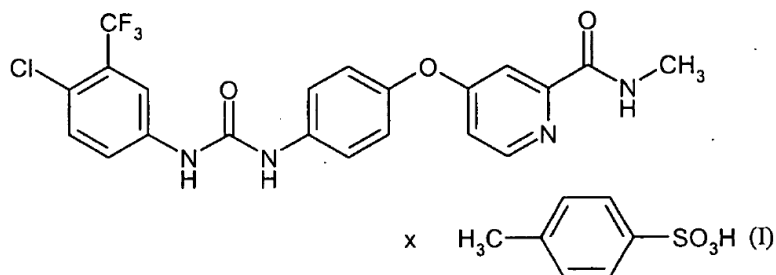
## Summary of Facts and Submissions

- I. European Patent No. 1 797 038 was opposed under Article 100(a) (lack of novelty and inventive step), (b) and (c) EPC.
- II. The appeal by opponent 1 (hereinafter "appellant") lies from the interlocutory decision of the opposition division that the European patent in amended form according to the main request then on file met the requirements of the EPC.
- III. The opposition division came, *inter alia*, to the following conclusions:
- The subject-matter of the claims according to the main request involved an inventive step in view of D1 as the closest prior art.
- IV. The following documents are referred to in the present decision:
- |      |  |
|------|--|
| D1   | WO 03/068228 A1  |
| D24  | S. Byrn, et al., Pharmaceutical Research 1995, vol 12(7), p. 945-954                       |
| D25  | M. Bavin, Chemistry & Industry 1989, vol 21, p. 527-529                                    |
| D32  | Submission dated 27 September 2010 in the examination proceedings of the patent in dispute |
| D40a | DSC thermograms of untreated and pestled polymorph II                                      |

- D40b DSC thermograms of untreated and pestled polymorph I
- D41 Affidavit by Dr. Britta Olenik, 26 April 2016
- D42 Affidavit by Dr. Roland Boese, 10 May 2016
- D50 A. Grunenberg, Pharmazie in unserer Zeit 1997, Nr. 5, p. 224-231

V. The main request found allowable by the opposition division contains fourteen claims, with independent claim 1 reading as follows:

"A compound of the formula (I)



in the polymorph I which shows in the X-ray diffractometry peak maxima of the 2 Theta angle [sic] including 4.4, 10.7, 11.1, 11.4, 11.6, 12.2, 12.8, 13.2, 14.8, 16.5, 16.7, 17.7, 17.9, 18.8, 19.3, 19.6, 20.1, 20.5, 20.8, 21.5, 21.7, 22.3, 22.5, 22.9, 23.4, 23.7, 24.0, 24.5, 25.1, 25.4, 26.0, 26.4, 26.6, 27.0, 27.6, 28.2, 28.6, 28.8, 29.3, 29.6, 29.9, 30.8, 31.2, 31.6, 31.8, 32.1, 32.4, 32.7, 33.1, 33.8, 34.2, 34.6, 35.4, 35.7, 37.1."

VI. In its statement setting out the grounds of appeal, the appellant contested the reasoning of the opposition division and submitted, *inter alia*, that the subject-matter of the claims of the main request considered by

the opposition division did not involve an inventive step considering D1 as the closest prior art.

- VII. In its reply to the statement setting out the grounds of appeal, the patent proprietor (hereinafter "respondent") provided counter-arguments regarding, *inter alia*, inventive step. It submitted sets of claims of a main request, and auxiliary requests I and II. The set of claims of the main request is identical to that of the main request underlying the decision under appeal.
- VIII. By letter of 25 February 2019, opponent 2 informed the board that it would not be attending any oral proceedings which may be scheduled.
- IX. Oral proceedings before the board were scheduled in view of corresponding requests of the parties and held on 14 January 2020. Oral proceedings took place in the absence of duly summoned opponent 2 pursuant to Rule 115(2) EPC and Article 15(3) RPBA 2020.
- X. The appellant's arguments, where relevant to the present decision, may be summarised as follows:
- D1 disclosed sorafenib tosylate without characterising the solid form thereof and without describing the synthesis thereof.
  - The distinguishing feature was the specific crystalline form of sorafenib tosylate, namely polymorph I.
  - The data provided by D32 and D41 only evidenced thermodynamic stability and not mechanical stability, since the tests therein concerned only

the conversion or not of one polymorph of sorafenib tosylate to another solid form.

- The objective technical problem was the provision a stable form of sorafenib tosylate.
- The solution was obvious in view of the teaching of D25 (page 528, right column, second paragraph), D24 (page 948, right column, first paragraph) and D50 (page 225, left column, first paragraph). These documents taught routine methods of screening in the field of pharmaceutical drug development. The skilled person was aware that polymorphism was known in molecules useful in the pharmaceutical industry. It would have found forms I, II and III and considered the thermodynamically most stable form as the most likely successful candidate. Consequently, in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of the thermodynamically most stable crystalline form of a known pharmaceutically active compound did not involve an inventive step. This was in line with T 777/08.

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

- D1 was the closest prior art. It disclosed sorafenib tosylate in claim 22 without describing the physical form thereof and was silent about any crystalline form. The distinguishing feature was thus the specific crystalline form of sorafenib tosylate, namely polymorph I.
- D32 and D41 showed that polymorph I of sorafenib tosylate was stable under mechanical stress



conditions, while polymorphs II and III of sorafenib tosylate were unstable and partially transformed to an amorphous state under the same stress conditions.

- The objective technical problem was the provision of a mechanically stable crystalline form of sorafenib tosylate suitable for the preparation of a pharmaceutical tablet.
- The prior art did not give any hint as to whether a crystalline form of sorafenib tosylate could be obtained and, if so, how it could be prepared. The cited prior art did not even mention the possibility of modifying mechanical stress resistance by certain crystalline forms.
- The provision of a thermodynamically stable crystalline form required two steps and was not a routine experiment, the process of crystallisation and the appearance of individual polymorphs depending from various factors, as mentioned in D25 (page 527, right column, first full paragraph).
- It was in no way certain that the thermodynamically most stable form also was the mechanically stress resistant form. As shown in the experiments of D32, D40a and D41, sorafenib tosylate polymorphs II and III at least partially transformed to amorphous products under mechanical stress conditions. If mechanical stress stability was equal to thermodynamic stability, the skilled person would have expected that polymorphs II and III interconverted to the energetically more stable, i.e. thermodynamically stable, polymorph I under stress conditions.

- The stability to mechanical stress of polymorph I was an unexpected effect in accordance with T 777/08 (headnote 1), T 517/14 (reasons 5.4) and T 2114/13. The claimed subject-matter involved an inventive step.

XII. The parties' final requests were the following:

- The appellant requested that the decision under appeal be set aside and that the patent be revoked.
- The respondent requested that the appeal be dismissed, or alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests I or II submitted with the reply to the statement setting out the grounds of appeal.

## **Reasons for the Decision**

Main request

Inventive step - Article 56 EPC

1. The invention

The invention as defined in granted claim 1 concerns a specific crystalline form of sorafenib tosylate (polymorph I).

Polymorph I according to the invention was found to be thermodynamically stable at room temperature and storage-stable and particularly suitable for preparations that are prepared via granulation or grinding (patent, paragraph [0007]).

1.1 The closest prior art

Both parties considered the disclosure of D1 as the closest prior art.

In the same way as the patent, D1 aims at providing aryl ureas which are used for the treatment of disorders mediated by the vascular endothelial growth factor (VEGF) in which angiogenesis plays an important role, for example in tumor growth (abstract of D1). Claim 22 of D1 relates to a method of therapeutic treatment comprising administering N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate. This compound is known as sorafenib tosylate.

The distinguishing feature in view of D1 is the crystalline form of sorafenib tosylate ("polymorph I") as defined in claim 1. D1 discloses sorafenib tosylate without characterising the form thereof.

1.2 Formulation of the technical problem

D32 shows in conjunction with D40b that polymorph I of sorafenib tosylate as claimed is thermodynamically stable under mechanical stress conditions. The mechanical stress test consists of grinding for about 30 seconds 100 mg of polymorph I in a mortar and comparing it with the untreated sample by differential scanning calorimetry (DSC). D40b shows that the DSC thermograms of ground polymorph I ("pestled") and of the initial sample ("untreated") are the same.

Polymorph II of sorafenib tosylate was also tested under the same conditions in D32. D40a shows a difference in the DSC thermograms of ground polymorph II and of the initial sample. The DSC thermogram of the ground polymorph II exhibits an

additional peak at about 150°C, which is characteristic for a phase change from a crystalline form to an amorphous form, showing that this polymorph, contrary to polymorph I, at least partially transforms to an amorphous form when subjected to mechanical stress.

Polymorph III of sorafenib tosylate was tested in D41. In test B, polymorph III was crushed in a mortar for 10 seconds. Thereafter, an X-Ray powder diffraction (XRPD) was measured (enclosure 3 of D41) and compared to the XRPD diagram of polymorph I (enclosure 4 of D41). In comparison to the XRPD diagram of polymorph I, the XRPD diagram of polymorph III shows a decrease of peak intensity and an increase of noise signals which demonstrate a change into the amorphous form of sorafenib tosylate.

Considering the above, D32, D40a, D40b and D41 show that polymorph I of sorafenib tosylate is more thermodynamically stable than polymorph II and polymorph III, which partially convert to the amorphous form when the polymorph is ground in a mortar. As submitted by the respondent with reference to D42 (bottom of page 2 to the top of page 3), during tablet pressing, an active ingredient is subjected to mechanical stress. By using a stable form of the active ingredient, the risk that it is converted to another form is reduced and helps to ensure the manufacture of a pharmaceutical product with consistent properties.

In view of these results, the objective technical problem is the provision of a stable crystalline form of sorafenib tosylate suitable for the preparation of a pharmaceutical tablet.

### 1.3 Obviousness of the solution

As regards the preparation of a pharmaceutical product, D50 (paragraph 2.2 bridging pages 224 and 225) discloses the following:

*"Die Modifikationen einer polymorphen Verbindung können sich in zahlreichen chemisch-physikalischen Eigenschaften unterscheiden... Besonders hervorzuheben sind die unterschiedlichen Löslichkeiten der Modifikationen, weil dadurch die Bioverfügbarkeit von Arzneimitteln beeinflusst werden kann. Andere Eigenschaften wirken sich auf die Herstellung von Zubereitungen aus. Dazu zählen der Kristallhabitus (Fließfähigkeit), Härte und Dichte der Kristalle (Mahlung), Schmelzpunkt (Schmelzcharakteristik von Suppositorien), Löslichkeit (i.v.-Lösungen), **thermodynamische Stabilität** (Kristallwachstum und Entmischung von Suspensionsformulierungen). Aus diesem Grund ist es unerlässlich, die chemisch-physikalischen Eigenschaften der polymorphen Formen eines Wirkstoffs in der präklinischen Phase zu bestimmen. **Zur Vermeidung von Unterschieden in der Bioverfügbarkeit und in der Verarbeitung zu Arzneimitteln ist dann die Modifikation mit günstigen Eigenschaften zu definieren. Dies ist in der Regel die bei Raumtemperatur thermodynamisch stabile Form des Wirkstoffs.**" (emphasis added by the board)*

D50 thus teaches that thermodynamic stability of a polymorphic form affects its suitability for the preparation of pharmaceutical compositions. D50 continues that for avoiding changes during the manufacture of the pharmaceutical preparation, it is essential to define the polymorph with the most

favourable properties, which is, as a general rule, the thermodynamically stable form. Those "favourable properties" include the avoidance of changes in the processing to a medicament, and thus implicitly include a step such as milling or grinding of the solid polymorph.

The above passage lastly discloses that, because inter alia the thermodynamic stability of a polymorphic form affects its suitability for preparing a pharmaceutical formulation, a screening of the different polymorphic forms is needed to determine their physico-chemical properties.

The need for screening and isolating the thermodynamically most stable form is confirmed by D25, which teaches that "*The thermodynamically stable polymorph needs to be identified ... These can be identified by simple techniques, for example by stirring or shaking excess solid with solid at different temperatures*" (first full paragraph of the right column on page 528).

The same follows from the review article D24 (first paragraph of the right column on page 948), disclosing that "*Selection of the most stable form [sic] would, of course, insure that it there [sic] would be no conversion into other forms*".

Faced with the objective technical problem and starting from the sorafenib tosylate of D1, the skilled person would therefore have performed a screening of the different polymorphs of sorafenib tosylate which could exist in order to isolate and identify the thermodynamically most stable form thereof. By doing so, he would have arrived at polymorph I of sorafenib tosylate, which is the thermodynamically most stable

form and which is, for this reason, expected not to convert to other forms under mechanical stress. It is to be noted in this context that none of the parties disputed that polymorph I of sorafenib tosylate is the thermodynamically most stable form and does not convert to other forms.

The subject-matter of claim 1 being directed to polymorph I of sorafenib tosylate, is thus obvious. Consequently the solution of claim 1 to the technical problem identified above (1.2, *supra*) does not involve an inventive step.

1.4 This finding is in line with decisions T 777/08 (OJ EPO 2011, 633), T 517/14 and T 2114/13, cited by the respondent.

1.4.1 According to decision T 777/08 (headnote I), the skilled person "*would be familiar with routine methods of screening. Consequently, 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*".

Since the property of polymorph I of sorafenib tosylate not to convert to other forms is expected by virtue of it being the thermodynamically most stable form, it does not represent an unexpected property as referred to in decision T 777/08. Consequently, the board's finding above is in line with decision T 777/08.

1.4.2 The board notes that the facts of the present case differ from those that led to decision T 517/14 relied on by the respondent. In that decision (reasons, 5), the starting point was different, namely a monohydrate form of a certain salt of an active ingredient, the

objective technical problem was different, namely the provision of a form of an active ingredient that was stable against degradation, and the situation with regard to obviousness was a different one in that in view of the available prior art, the solution the skilled person would have chosen in the case underlying T 517/14 was different from the claimed one. For this reason, decision T 517/14 is not relevant to the present case.

- 1.4.3 In decision T 2114/13 (reasons, 5), inventive step was acknowledged on the basis that the closest prior art disclosed a mixture of two polymorphic forms of febuxostat and that the technical problem was the provision of a pharmaceutical composition of febuxostat with improved polymorphic stability, in particular during formulation.

Also this decision concerns a case that is different from the present one. The effect in case T 2114/13, i.e. polymorphic stability against "solvent-mediated conversion" of a slurry in acetone and water (second paragraph of point 5.4 of the reasons) is different from the effect in the present case (stability under mechanical stress) and the closest prior art in case T 2114/13 was a document disclosing a polymorphic mixture while the closest prior art in the present case relates to a compound whose form is not specified.

- 1.5 The respondent also referred to D24 (pages 947, 948 and 952) and D25 (page 527, right column first full paragraph). It essentially argued that the process of crystallisation was poorly understood and was not a matter of routine experimentation, the process of crystallisation depending on various factors. The prior art did not teach a crystalline form of sorafenib tosylate. The skilled person had to take two steps to



arrive at the invention starting from the amorphous form of sorafenib tosylate disclosed in D1, namely the provision of a crystalline form and the provision of the thermodynamically stable crystalline form.

The board is not convinced. Each of D24, D25 and D50 teaches to perform a screening of any pharmaceutical solids in order to isolate the thermodynamically most stable crystalline form, as set out above (1.3, *supra*). Therefore, the two-steps approach referred to by the respondent or the absence of any teaching in the prior art for a crystalline form of sorafenib tosylate did not represent a hindrance for the skilled person.

1.6 The respondent further argued that D25 would have dissuaded the skilled person to use the thermodynamically most stable crystalline form of sorafenib tosylate for the preparation of a tablet in view of the last sentence of the second full paragraph in the left column on page 948 of the document, which reads:

*"A metastable polymorph can be used in capsules or for tableting, and the thermodynamically stable one for suspensions"*.

The board notes that this general statement is conditional, due to the use of the term "**can be used**" in the sentence, so that the skilled person would not have mandatorily followed the teaching of this passage. Furthermore, the skilled person would have deduced from this sentence only that the metastable form of a polymorph is not stable enough to be used in suspensions. This does however not allow the reverse conclusion that the thermodynamically stable form cannot be used in capsules or for tableting. For both reasons, the passage referred to by the respondent did

not dissuade the skilled person from using the thermodynamically most stable crystalline form of sorafenib tosylate for the preparation of a tablet. Lastly, even if the passages were taken into consideration, the skilled person faced with the objective technical problem, would, as set out above, have carried out a screening in view of the general teaching of each of D24, D25 and D50, and would have isolated the thermodynamically most stable crystalline form of sorafenib tosylate which was expected not to convert to other forms.

- 1.7 The respondent also argued that, if mechanical stress stability was equal to thermodynamic stability, the skilled person would have expected that polymorphs II and III interconverted to the energetically more stable, i.e. thermodynamically stable, polymorph I under stress conditions. The opposite had however been observed in D32, D40a, D40b and D41. Mechanical stress stability was thus not equivalent to thermodynamic stability. Document D42 (last four paragraphs on page 2) confirmed that mechanical stability and thermodynamic stability of a polymorph did not necessarily correlate and that the relationship between mechanical stability and thermodynamics was unpredictable. The prior art did not teach the possibility of modifying mechanical stress resistance.

The board does not agree. The present case is concerned with stability against a change of the polymorphic structure under mechanical stress. D42 however discusses "mechanical stability", which, as set out by the appellant, is rather the stability against mechanical disintegration. More specifically, D42 discusses which forces are "decisive for keeping a crystal together" (last line of page 1) and states that metastable forms have "intermolecular interactions,

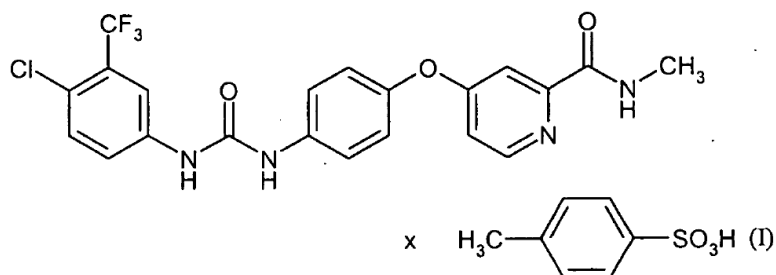
which can be easier disrupted" and continues that "However, the assumption that they are mechanically less stable is wrong" (fifth paragraph on page 2). Hence, D42 does not concern stability under mechanical stress. For this reason alone, the respondent's argument must fail. Furthermore, as established above (1.3, *supra*), the skilled person aiming at providing a stable crystalline form of sorafenib tosylate suitable for the preparation of a pharmaceutical tablet would have screened for the thermodynamically most stable crystalline form of sorafenib tosylate and would thus have arrived at polymorph I, irrespective of whether thermodynamic stability is identical to stability under mechanical stress and whether the prior art teaches the possibility of modifying mechanical stress resistance.

1.8 Therefore, the respondent's reasoning does not hold good. Accordingly, the board's finding above that the subject-matter of claim 1 does not involve an inventive step can be confirmed.

2. Auxiliary request I

2.1 Claim 1 of auxiliary request I reads :

"A compound of the formula (I)



*in the polymorph I which shows an X-ray diffraction pattern as shown in Figure 2".*

2.2 Claim 1 of auxiliary request I relates to the same compound of formula (I) as claim 1 of the main request. Therefore the same reasoning for lack of inventive step of the subject-matter of the main request applies *mutatis mutandis* to claim 1 of auxiliary request I.

2.3 Auxiliary request I is thus not allowable.

3. Auxiliary request II

3.1 Claim 1 of auxiliary request II relates to "**a pharmaceutical composition for oral administration**" comprising the compound of sorafenib tosylate" in the polymorph I [sic!] which shows in the X-ray diffractometry peak maxima of the 2 Theta angle including 4.4, 10.7, 11.1, 11.4, 11.6, 12.2, 12.8, 13.2, 14.8, 16.5, 16.7, 17.7, 17.9, 18.8, 19.3, 19.6, 20.1, 20.5, 20.8, 21.5, 21.7, 22.3, 22.5, 22.9, 23.4, 23.7, 24.0, 24.5, 25.1, 25.4, 26.0, 26.4, 26.6, 27.0, 27.6, 28.2, 28.6, 28.8, 29.3, 29.6, 29.9, 30.8, 31.2, 31.6, 31.8, 32.1, 32.4, 32.7, 33.1, 33.8, 34.2, 34.6, 35.4, 35.7, 37.1, **which is a tablet**" (emphasis added by the board).

3.2 The board notes that claim 1 of auxiliary request II only differs from claim 1 of the main request in that it concerns a pharmaceutical composition for oral administration in the form of a tablet. These differences have no impact on the choice of closest prior art, the distinguishing feature and the objective technical problem. More specifically, D1 is still the closest prior art, the distinguishing feature is still the specific crystalline form of sorafenib tosylate ("polymorph I") and the objective technical problem remains the provision of a stable crystalline form of sorafenib tosylate suitable for the preparation of a pharmaceutical tablet. Also the reasoning above with

regard to the obviousness of the subject-matter of the main request still applies to this request. More specifically, for the same reasons as given for the main request, the skilled person would, in view of D24, D25 and D50, have applied a screening for isolating the thermodynamically most stable form and would thereby have arrived at the subject-matter of claim 1 in an obvious manner.

- 3.3 For this reason, the same reasoning for lack of inventive step of the subject-matter of the main request applies *mutatis mutandis* to claim 1 of auxiliary request II.
- 3.4 Auxiliary request II is thus not allowable.
4. The board concludes that none of the claim requests of the appellant is allowable under Article 52(1) in combination with Article 56 EPC.

**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:



N. Maslin

M. O. Müller

Decision electronically authenticated