Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 23 April 2021

Case Number: T 0134/18 - 3.3.07

Application Number: 06769997.5

Publication Number: 1885339

IPC: A61K9/16, A61K9/20, A61K9/28, A61K31/506

Language of the proceedings: EN

Title of invention:
FORMULATIONS OF A SRC/ABL INHIBITOR

Patent Proprietor:
Bristol-Myers Squibb Holdings Ireland

Opponents:
Aechter, Bernd
Fresenius Kabi Deutschland GmbH
Generics [UK] Limited

Headword:
Formulations of a SRC/ABL inhibitor / BRISTOL-MYERS SQUIBB

Relevant legal provisions:
EPC Art. 113(1), 56, 100(a)

Keyword:
Right to be heard - substantial procedural violation (no)
Inventive step - (no)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0134/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 23 April 2021

Appellant: (Opponent 1)	Aechter, Bernd Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburgerstrasse 4 80335 München (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Appellant: (Opponent 2)	Fresenius Kabi Deutschland GmbH Else-Kröner-Stasse 1 61352 Bad-Homburg v.d.H. (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Borkenberg 14 61440 Oberursel (DE)
Appellant: (Opponent 3)	Generics [UK] Limited Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Bristol-Myers Squibb Holdings Ireland Hinterbergstrasse 16 6312 Steinhausen (CH)
Representative:	Dehns St. Bride's House

10 Salisbury Square
London EC4Y 8JD (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 13 December 2017 rejecting the opposition filed against European patent No. 1885339 pursuant to Article 101(2) EPC.**

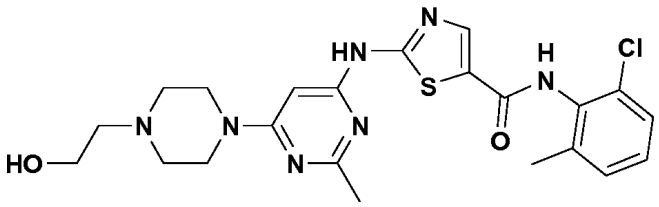
Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
A. Jimenez

Summary of Facts and Submissions

I. European patent 1 885 339 ("the patent") was granted on the basis of 5 claims. Claim 1 of the patent read as follows:

"A pharmaceutical composition for oral administration comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) solvate, hydrate, or pharmaceutically acceptable salt thereof



(I)

and a non-reactive coating wherein the non-reactive coating is a coating having polyethylene glycol as plasticizer."

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

III. The opposition division rejected the oppositions filed against the patent.

IV. The decision of the opposition division referred, among others, to the following documents:

D1: US 6 596 746
D22: Aulton, Pharmaceutics: The Science of Dosage Form Design, 2002, pages 441-446

D23: Prescribing information for Sprycel
D24: Declaration of Julia Gao dated 12 October 2016.
D25: Hovorka et al, Journal of Pharmaceutical Sciences, 90(3), 2001, pages 253-269.
D26: McGinity et al, Drug Development Communications, 2(6), 1976, pages 505-519.
D27: Johnson et al, Journal of Pharmaceutical Sciences, 73(10), 1984, pages 1414-1417.
D28: Schulz et al, Acta Pharm. Technol. 32(2), 1986, pages 78-81.
D29: Handbook of pharmaceutical excipients - 1994; pages 84-87, 141-142, 223-229, 252-261 and 280-282.

V. With respect to inventive step, the opposition division found that D1 was the closest prior art. D1 disclosed dasatinib, i.e. the compound of formula (I) according to claim 1. The subject-matter of claim 1 differed in that a pharmaceutical composition comprising dasatinib and a non-reactive coating which was a coating having PEG as plasticizer was provided. The problem was the provision of a suitable pharmaceutical formulation for dasatinib. The claimed solution was inventive because the skilled person was not led by D1 to consider a tablet coated with a coating having PEG. The criteria of inventive step were thus fulfilled.

VI. Each of the three opponents (appellants) lodged an appeal against the decision of the opposition division.

With its statement setting out the grounds of appeal, appellant 1 filed the following document A030:

A030: Aulton, Pharmaceutics: The science of Dosage Form Design, 2002, chapter 27, pages 397-440.

Furthermore, appellant 3 expressed the view that the opposition division had committed a procedural violation justifying a reimbursement of the appeal fee.

VII. In its reply to the appeals, the patent proprietor (respondent) defended its case on the basis of the patent as granted as main request (see I. above), and on the basis of auxiliary requests I-VII filed on 12 October 2016 (and re-submitted with the reply to the grounds of appeal).

Claim 1 of each of the auxiliary requests I-VII differed from granted claim 1 by the following additional features:

- the composition was "in the form of a tablet" (auxiliary requests I, III, V, VII),

- "the pharmaceutically acceptable carrier comprises lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate" (auxiliary requests II, III, VI, VII), and

- "the non-reactive coating does not react with the compound of formula (I)" (auxiliary requests IV, V, VI, VII).

VIII. The Board summoned the parties to oral proceedings, and set out its preliminary opinion in a communication under Article 15(1) RPBA issued on 11 January 2021. In this communication, the Board indicated that the criteria of inventive step did not appear to be met by the any of the respondent's requests. The Board also expressed the preliminary view that the opposition division had not committed a procedural violation, so

that appellant 3's request for a refund of the appeal fee was not justified.

IX. By letter dated 25 March 2021, the respondent announced that it would not be represented at the oral proceedings.

By letter dated 29 March 2021, in reply to a communication from the Board, appellant 3 withdrew its request for oral proceedings to discuss the reimbursement of the appeal fee.

The Board cancelled the oral proceedings.

X. The appellants' arguments can be summarised as follows:

(a) Procedural violation and reimbursement of the appeal fee

In its notice of opposition, appellant 3 had argued that the patent lacked an inventive step over D1 in combination with the common general knowledge regarding the well-known use of PEG as plasticizers in coatings (as reflected in D22). Contrary to Article 113(1) EPC, the appealed decision did not address this central argument.

Although the opposition division noted the argument in the decision (see point 4.4), the subsequent reasoning (see point 4.5) had no relevance to this argument, and the opposition division's conclusion was explicitly limited to obviousness in view of D1 alone.

Therefore, appellant 3’s right to be heard had not been respected and a refund of its appeal fee was justified.

(b) Main request, inventive step

The closest prior art D1 disclosed pharmaceutical compositions comprising dasatinib and a pharmaceutically acceptable vehicle or diluent (see see example 455 and claim 46). D1 also mentioned that the compounds of formula I disclosed therein, *inter alia* dasatinib, could be administered orally by any suitable means, such as in the form of tablets (see column 25, lines 35-39).

The only distinguishing feature was the coating comprising PEG.

The opposed patent neither showed that the claimed pharmaceutical composition exhibited any advantages as compared to the non-coated pharmaceutical composition of D1, nor that it was stable.

The objective technical problem was the provision of a suitable dasatinib composition.

The claimed solution was just a matter of applying common general knowledge to the disclosure of D1. As outlined in the textbook D30 (see page 398, left column), the oral route was the most common way of administering drugs, and among oral dosage forms tablets were the most common. In addition, as outlined in the textbook D22 (see page 441), film coatings of tablets were known to confer benefits and properties to the dosage form over the uncoated variety. In this respect, D22 disclosed that plasticizers were generally added to film coating formulations, and mentioned PEGs as first example for such plasticizers (see page 444). Therefore, the skilled person starting from D1 would have solved the problem by providing a commonly known

pharmaceutical composition for oral administration comprising a coating having PEG as plasticizer.

Furthermore, the skilled person would have had no reason to expect that a PEG-containing coating would oxidise the active ingredient. D24 was a mere allegation by the patentee's employee that oxidation would have been expected, and D25-D28 did not relate to oxidation caused by PEG-containing tablet coatings.

The respondent's data regarding stability of dasatinib in tablets having a PEG-containing film coating *versus* tablets having a triacetin-containing film coating offered no relevant comparison with the closest state of the art.

Thus, the main request did not meet the requirements of inventive step.

(c) Auxiliary requests, inventive step

Regarding claim 1 of auxiliary request I, the requirement for the composition to be a tablet was not associated with any technical effect. Tablets for oral administration were disclosed in D1 (see column 25, lines 36-38) and were known from common general knowledge.

The pharmaceutically acceptable carriers defined in claim 1 of auxiliary request II, namely lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate, were commonly known excipients (see D29 and D1, column 25, lines 60-62).

Regarding claim 1 of auxiliary request IV, the feature that the non-reactive coating did not react with dasatinib did not modify the assessment of inventive step.

Claim 1 of each of auxiliary requests III, V, VI and VII combined the features of claim 1 of auxiliary requests I, II and IV.

Hence, none of the auxiliary requests I-VII satisfied the criteria of inventive step.

XI. The respondent's arguments can be summarised as follows:

(a) Main request, inventive step

The closest prior art D1 did not disclose any specific pharmaceutical compositions for oral administration comprising dasatinib and a pharmaceutically acceptable vehicle or diluent. The discussion in D1 pertaining to various pharmaceutical formulations was general and not specific to dasatinib.

Starting from D1, the problem underlying the invention was the provision of a suitable pharmaceutical formulation for dasatinib.

D1 disclosed that the compounds shown therein could be administered by any suitable means, for example orally, and listed PEGs as possible excipients for some formulations. However, D1 did not clearly and unambiguously disclose that PEGs could be used as plasticizers in coatings for compositions of dasatinib for oral administration.

A skilled person, starting from D1 and looking to formulate dasatinib, would not have considered the claimed formulations with any expectation that they would be stable. As explained in D24, dasatinib was prone to oxidation by oxidizing agents to form an N-oxide. As evidenced by D25-D28, it was known at the priority date of the opposed patent that PEG contained peroxide impurities, which might be expected to react with dasatinib to form the N-oxide thereof. Yet, it had unexpectedly been found that when a tablet containing dasatinib was prepared using a film coating containing PEG as the plasticizer, additional N-oxide degradant was not formed. This was shown experimentally in a comparison with tablets where triacetin was used as plasticizer: contrary to what the skilled person would have expected, the overall stability of dasatinib in the formulation was better in the PEG tablet. Thus, the claimed invention was associated with a surprising technical effect.

Accordingly, the main request met the requirements of inventive step.

(b) Auxiliary requests, inventive step

Auxiliary requests I-VII fulfilled the criteria of inventive step for the same reasons as the main request.

XII. Appellants 1, 2 and 3 each request that the decision under appeal be set aside and that the patent be revoked. Appellant 3 additionally requests that the appeal fee be refunded because the opposition division committed a substantial procedural violation.

XIII. The patent proprietor (respondent) requests that the appeals be dismissed, or, alternatively, that the patent be maintained on the basis of one of the auxiliary requests I-VII filed on 12 October 2016.

Reasons for the Decision

1. Cancellation of the oral proceedings

By letter dated 25 March 2021, the respondent announced that it would not be represented at the oral proceedings. Following established case law (see the Case Law of the Boards of Appeal, 9th edition 2019, III.C.4.3.2), such a statement should normally be treated as equivalent to a withdrawal of the request for oral proceedings.

Furthermore, by letter dated 29 March 2021, appellant 3 withdrew its request for oral proceedings to discuss the reimbursement of the appeal fee.

The oral proceedings were accordingly cancelled, and the present decision can be issued in writing.

2. Procedural violation and refund of the appeal fee

2.1 According to appellant 3, the opposition division failed to take into account its argumentation that the patent lacked an inventive step over D1 in view of the common general knowledge reflected in D22, and therefore disregarded facts and arguments which were central to the case, in contravention of Article 113(1) EPC.

2.2 The right to be heard under Article 113(1) EPC requires that those involved be given an opportunity not only to present comments (on the facts and considerations pertinent to the decision) but also to have those comments considered, that is, reviewed with respect to their relevance for the decision on the matter (see the Case Law of the Boards of Appeal, 9th edition 2019, III.B.2.4.1).

2.3 In the present case, the appealed decision summarizes the opponents' objections at point 4.4 (last paragraph), including appellant 3's argumentation based on common general knowledge as reflected in D22 (using the numbering D7 given by appellant 3 with its notice of opposition). Then, at point 4.5, the decision explains why the opposition division did not follow the opponents' argumentation, and states in particular in the second paragraph:

"Furthermore, the opposition division is of the opinion that the argumentation by the opponents is based on hindsight, for the following reasons: An excipient can be included in a composition for a number of reasons, and in a number of ways. The reference to PEG as a suitable excipient in D1 cannot therefore be considered as a clear and unambiguous disclosure that polyethylene glycols can be used as plasticizers in coatings for compositions of dasatinib for oral administration."

Although D22 is not specifically cited again at point 4.5, it can be inferred from this paragraph, which follows the summary of the opponents' attacks, that the opposition division considered the opponents' attacks based on common general knowledge, including appellant 3's argumentation.

2.4 According to appellant 3, the opposition division's conclusion is explicitly limited to obviousness in view of D1 alone, and could not as a matter of logic apply to appellant 3's attack, since this attack was based on common general knowledge regarding the known use of PEG as a common plasticizer specifically for use in coatings. However, in the Board's view, the decision does not suffer from a lack of logic such that it would demonstrate that the opposition division did not consider appellant 3's argumentation. In particular, appellant 3's argumentation neither contradicts that PEG could be included in a composition for a number of reasons, and in a number of ways, nor that PEG was not known as plasticizers in coatings for compositions of dasatinib for oral administration, as argued by the opposition division in the passage quoted above. In other words, the decision of the opposition division shows that the substance of the appellant 3's argumentation based on D1 in view of common general knowledge was considered and found not convincing. The correctness of the decision in this respect is the subject of the substantive review by the Board, but is not relevant to the issue of compliance with Article 113(1) EPC.

2.5 Thus, the opposition division did not commit a substantial procedural violation, and a refund of the appeal fee is not justified.

3. Main request (patent as granted), inventive step

3.1 The invention pertains to pharmaceutical compositions of dasatinib. The composition comprises a pharmaceutically acceptable carrier, a therapeutically effective amount of dasatinib, and a non-reactive coating which does not cause decomposition of dasatinib

(see paragraphs [0004]-[0006] of the patent). The patent mentions that some coatings contain plasticizers which may react with dasatinib and produce unwanted impurities in the compositions (see paragraph [0019]). The compositions of the invention utilise coatings having the non-reactive plasticizer PEG. The examples comprise the coating Opadry® White, containing hydroxypropylmethylcellulose, titanium dioxide, and PEG.

3.2 D1 represents the closest prior art. This is not contested.

D1 discloses dasatinib (see example 455 and claim 43) and pharmaceutical compositions thereof, further comprising a pharmaceutically acceptable vehicle or carrier (see claim 46).

D1 also makes a general reference to pharmaceutical compositions for e.g. oral, parenteral, nasal, topical or rectal administration (see column 25, line 36 and following). Compositions for oral administration may be, among other forms, provided as tablets, and may include excipients such as PEG (see column 25, line 55 to column 26, line 14). However, these general references do not pertain specifically to dasatinib but rather to any of the numerous compounds disclosed in D1. D1 does not show a dasatinib composition for oral administration.

3.3 The subject-matter of claim 1 differs from the dasatinib compositions of D1 in that the composition is for oral administration and comprises a non-reactive coating which is a coating having PEG as plasticizer.

3.4 The Board agrees with the respondent's proposed objective technical problem, namely the provision of a suitable pharmaceutical formulation for dasatinib.

3.5 D1 generally teaches that the pharmaceutical composition comprising the compounds disclosed therein, which include dasatanib, may be formulated for oral administration (see column 25, lines 36-39), such as in the form of tablets. Tablets for oral administration were also generally known to be the most common option (see A030, page 398, left column). The skilled person is furthermore generally aware that tablets may be coated (see for instance D22, page 441), and that the coating generally contains plasticizers such as PEG (see D22, page 444). The choice of PEG is all the more obvious considering that D1 mentions PEG as possible excipient for oral dosage forms (see column 26, lines 5-7).

3.6 According to the respondent, the claimed invention is characterised by a surprising technical effect, in the sense that despite the sensitivity of dasatinib to oxidation (see D24) and the known presence of oxidising peroxide impurities in PEG (as evidenced by D25-D28), no N-oxide degradant was formed in a dasatinib tablet with a PEG-containing film coating. As evidence of this unexpected stability, the respondent refers to the data submitted on 15 January 2010 and on 12 October 2016. This data would show a better overall stability under stress conditions of dasatinib in tablets coated with a PEG-containing film as compared with a triacetin-containing film.

However, in the Board's view, none of D25-D28 show or state that PEG, when used as a plasticiser in a coating, can be expected to oxidise any drug in a solid

formulation. No evidence of such an expectation is given in the inventor's declaration D24 either. Rather, D25-D28 discuss stability issues in unrelated formulations, such as solutions (see D25, page 256, left column; D27, page 1417), ointments (see D26, paragraph bridging pages 506-507), or suppositories (see D28). In contrast, the use of PEG as plasticizer in tablet coatings is part of the common general knowledge as discussed above (see 3.5). Accordingly, it is not credible that the skilled person would expect any stability issue when formulating dasatinib with a PEG-containing film.

Consequently, the respondent's data comparing PEG and triacetin as plasticizers show at best the absence of a stability issue which the skilled person would have no reason to expect. Moreover, the quantitative comparison offered with triacetin is not relevant to the assessment of inventive step over D1, since compositions comprising triacetin as plasticiser do not represent the closest prior art.

3.6.1 Accordingly, the Board agrees with the appellants that the skilled person would expect that a dasatinib composition for oral administration, having a PEG-containing coating, would solve the problem of providing a suitable composition.

Thus the main request does not meet the requirements of inventive step.

4. Auxiliary requests I-VII, inventive step

4.1 The respondent did not provide any substantive arguments regarding the relevance of the amendments

carried out in auxiliary requests I-VII to inventive step.

Regarding claim 1 of auxiliary request I, no technical effect is shown to be associated with the limitation of the dosage form to a tablet. Tablets for oral administration are not only considered in D1 (see column 25, lines 36-38) but also known from common general knowledge (see 3.5 above with reference to A030).

Likewise, the presence of the pharmaceutically acceptable carriers defined in claim 1 of auxiliary request II, namely lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate, is not shown to lead to any further effect. These carriers are all known from common general knowledge (see D29), and are for the most part also considered in D1 (see column 25, lines 60-62).

Regarding claim 1 of auxiliary request IV, the feature that the non-reactive coating does not react with dasatinib merely defines explicitly the term "non-reactive coating" of granted claim 1. This feature does not modify the assessment of inventive step provided above.

Claim 1 of each of auxiliary requests III, V, VI and VII combine the features of claim 1 of auxiliary requests I, II and IV. Accordingly the same conclusions apply to each of these requests.

Hence, none of the auxiliary requests I-VII overcome the lack of inventive step found for the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

3. Appellant's 3 request for a refund of the appeal fee is refused.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated