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Datasheet for the decision of 25 June 2021

Case Number: T 2149/19 - 3.3.07

Application Number: 11732405.3

Publication Number: 2588090

IPC: A61K9/50

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL ORAL DOSAGE FORMS COMPRISING DABIGATRAN ETEXILATE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Patent Proprietor:
KRKA, tovarna zdravil, d.d., Novo mesto

Opponents:
Generics [UK] Ltd
Eder, Michael
Georg Kalhammer/Stephan Teipel

Headword:
Dabigatran etexilate/KRKA

Relevant legal provisions:
EPC Art. 56, 123(2)
RPBA Art. 12(4)

Keyword:

Inventive step - main request (no) - auxiliary request (yes)
Late-filed request - submitted with the statement of grounds of appeal
Amendments - allowable (yes)

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Beschwerdekammern

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Case Number: T 2149/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 25 June 2021

Appellant: (Patent Proprietor)	KRKA, tovarna zdravil, d.d., Novo mesto Smarjeska cesta 6 8501 Novo mesto (SI)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Appellant: (Opponent 1)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Party as of right: (Opponent 2)	Eder, Michael Marktstr. 4 80802 Munich (DE)
Representative:	Eder, Michael df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Party as of right: (Opponent 3)	Georg Kalhammer/Stephan Teipel Lederer & Keller Unsöldstrasse 2 80538 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 June 2019 concerning maintenance of the European Patent No. 2588090 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: M. Steendijk
A. Jimenez

Summary of Facts and Submissions

I. European patent 2 588 090 (hereinafter "the patent") was granted on the basis of ten claims.

The independent claim 1 as granted related to:

"Process for the preparation of a solid oral dosage form comprising dabigatran etexilate or a salt thereof as active substance and comprising a spherical core, wherein

(a) the spherical core is coated with a solution of tartaric acid and optionally a binder and/or further inert pharmaceutical excipients without powder layering of tartaric acid,

(b) the coated core of step (a) is coated with an isolating layer, and

(c) the core coated with an isolating layer of step (b) is coated with further layers wherein at least one of the further layers is a layer comprising the active substance."

II. Three oppositions had been filed against the grant of the patent on the grounds that its subject-matter lacked an inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

Appeals were filed by the patent proprietor and opponent 1 against the interlocutory decision of the

opposition division that the patent as amended in accordance with auxiliary request 6, filed during the oral proceedings held on 2 Mai 2019, was found to meet the requirements of the EPC.

The decision was based on the main request relating to the patent as granted, auxiliary request 1-5 filed on 2 March 2019 and auxiliary request 6 submitted during the oral proceedings of 2 Mai 2019.

III. The following documents were *inter alia* cited in the decision under appeal:

D1: WO 2009/097156
D2: WO 2010/007016
D3: DRUG INVENTION TODAY (DIT), vol. 2, no. 5, 2010, pages 233-237,XP003035614
D4: AAPS PHARMSCITECH, vol. 1, no. 2, 2000, pages 1-12, XP003035615
D5: INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND DRUG RESEARCH, 2009, pages 63-70, XP008159757
D7: TROPICAL JOURNAL OF PHARMACEUTICAL RESEARCH, vol. 7, no. 3, 2008, pages 1067-1075
D9: "British National Formulary 56", September 2008, BMJ Group/RPS Publishing page 129
D10: "CHMP Assessment report for Pradaxa", 2008, EMEA
D11: Experimental report filed 18 June 2018

IV. According to the decision under appeal the patent as granted met the requirements of Article 123(2) and sufficiently disclosed the claimed invention.

Document D2 represented the closest prior art. The claimed process for preparing a solid dosage form for dabigatran etexilate differed from this prior art in the preparation of the tartaric acid core by coating a

starting core with a solution of tartaric acid without powder layering of tartaric acid. In the absence of evidence of any particular effect, the problem to be solved was seen in the provision of an alternative process for preparing the dosage form. The claimed method was obvious as solution to this problem in view of the common general knowledge regarding solution/ suspension coating described in documents D3, D5 , D7 and the application of such type of coating for preparing tartaric acid cores as described in document D1.

The additional features in auxiliary requests 1-5, which more specifically defined the spherical core to be coated with the tartaric acid and the solvent mixture of the tartaric acid solution used for the coating, did not contribute to an inventive step in view of documents D1-D4 and D7.

Claim 1 of auxiliary request 6 required in addition to these specific features regarding the core and the solvent mixture that the solution of tartaric acid did not comprise a binder. As solution to the problem of providing an alternative process the defined subject-matter involved an inventive step, because no prior art suggested that binders could be dispensed with.

V. With its statement of grounds of appeal the appellant (patent proprietor) filed new auxiliary requests 1-8.

Claim 1 of auxiliary request 1 corresponded to claim 1 of the main request except that it defined under step (a):

"the spherical core is coated with a solution of tartaric acid without a binder and without powder layering of tartaric acid,"

Claim 1 of auxiliary request 2 corresponded to claim 1 of auxiliary request 1 except for the additional definition of the solvent mixture for the tartaric acid. Auxiliary requests 3-8 corresponded to auxiliary requests 1-6 on which the decision under appeal was based.

VI. The appellant (opponent 1) filed with its statement of grounds of appeal the following document:

D12: Handbook of Powder Technology, volume 11, 2007, page 779-811.

VII. In their replies to the appeal by the appellant (patent proprietor) the appellant (opponent 1) and opponent 3 objected against the admission of auxiliary requests 1-7.

VIII. In a communication pursuant to Article 15(1) RPBA issued on 19 January 2021 the Board expressed *inter alia* its preliminary opinion that auxiliary request 1 complied with the requirements of Article 123 (2) EPC and that the information in document D12 seemed relevant in the assessment of inventive step of the subject-matter of auxiliary request 1.

IX. The arguments of the appellant (patent proprietor) relevant to the present decision are summerized as follows:

(a) Document D2 described a laborious process for preparing tartaric acid cores by repeating the

steps of spraying a binding solution followed by sprinkling tartaric acid powder at least one hundred times to ensure the formation of uniform cores with quasi-spherical geometry. As corroborated by the experimental results in document D11 the process of claim 1 of the patent as granted provided with respect to the teaching of document D2 a simpler and more economic process for preparing stable oral dosage forms of dabigatran etexilate with suitable release properties by avoiding the use of tartaric acid in the form of a powder.

Document D2 itself did not suggest to spray a solution on the cores without subsequent powder sprinkling, as such process would increase the stickiness of the produced particles, which was contrary to the purpose of document D2. Moreover, the large-scale examples in document D2 indicated an already optimized process, which did not provide the skilled person with a motivation to further modify the process.

The mention of solution/suspension layering and powder layering in documents D3, D5 and D7 as commonly known layering techniques did not imply that these techniques could generally be exchanged one for another, let alone that the powder layering required for uniform geometry of the cores as described in document D2 could be replaced by solution coating.

Starting from document D2 the skilled person would not consider the teaching of document D1, because this document related to a dosage form for a different pharmaceutically active agent. Moreover,

document D1 described the use of non-organic solvents for dispersion coating of tartaric acid rather than solvent coating as defined in the claims of the patent as granted.

(b) The process of claim 1 of auxiliary request 1 additionally differed from the prior art in the feature that no binder was used in the tartaric acid coating.

Auxiliary request 1 represented an admissible response to the decision under appeal, which recognized an inventive step for a process in which the binder in the tartaric acid coating solution was omitted.

The application as originally filed explicitly disclosed the use of a binder as optional and thus implicitly disclosed the embodiment in which no binder was used.

As confirmed by the experimental results reported in document D11 stable oral dosage forms of dabigatran etexilate with suitable release properties could be prepared without the use of a binder in the tartaric acid coating solution. The teaching of documents D1 and D2 required the use of a binder and no prior art suggested that such binder could be dispensed with in an alternative process for preparing such dosage forms.

X. The arguments of the appellant (opponent 1) and opponent 3 relevant to the present decision are summerized as follows:

(a) The process of claim 1 of the main request did not define the nature of the spherical core to be coated nor the amount of tartaric acid resulting from the defined coating with the tartaric acid solution. The claim therefore included a process in which the procedure of document D2 was merely extended by an additional coating step without powder layering. Such process did not imply any simplification with respect to the prior art. Moreover, no unexpected effect from the defined solution coating on the resulting product had been demonstrated. Documents D9 and D10 indicated that the layered products from the prior art were stable and the experimental data from document D11 did not offer a comparison with the layered products form the prior art.

Merely as solution to the problem of providing an alternative process the claimed subject-matter did not involve an inventive step, because solution/ suspension layering was a commonly known technique for pellet formation, which was evident from documents D1, D3, D5 and D7.

The use of a dispersion involving a non-organic solvent for coating described in document D1 only concerned embodiments in which the starting core included a highly water soluble organic acid. Document D1 did therefore not generally dissuade from applying the well known technique of solution layering for preparing tartaric acid coated cores.

(b) Auxiliary request 1 should not be admitted into the appeal proceedings in view of Article 12(4) RPBA 2007, because this request introduced without justification only at the stage of the appeal the

feature of the absence of a binder in the tartaric acid coating solution irrespective of any additional restrictions regarding the nature of the core and the solvent mixture to be used. This request was furthermore not prima facie allowable under Article 123(2) EPC and resulted in non-convergence with the subsequent auxiliary requests 3-7.

Claim 1 of auxiliary request 1 did not comply with the requirement of Article 123(2) EPC, because it introduced an undisclosed disclaimer with relevance for the assessment of inventive step and because the remaining subject-matter was not directly and unambiguously disclosed in the application as filed.

The results reported in document D11 did not demonstrate that the absence of a binder in the tartaric acid solution allowed for preparing equivalent products with respect to the prior art or was otherwise associated with any unexpected effect. The underlying technical problem therefore merely concerned the provision of a process for preparing further dabigatran etexilate dosage forms in which reduced adhesion of the tartaric acid coating was simply accepted. As was evident from the common knowledge described in documents D5 and D12 the presence of a binder in the solvent was not indispensable for carrying out a solution layering process. The process of claim 1 of auxiliary request 1, which omitted the binder, was therefore obvious to the person skilled in the art.

XI. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent

be maintained as granted or on the basis of any of auxiliary requests 1-8 as filed with the grounds of appeal.

The appellant (opponent 1) requested that the decision under appeal be set aside and that the patent be revoked in its entirety. It further requested that auxiliary requests 1 to 7 be not admitted to the appeal proceedings.

Opponent 2 did not submit any substantive requests or observations during the appeal proceedings.

The opponent 3 requested that the appeal by the proprietor be dismissed and auxiliary requests 1 and 2 be not admitted into the proceedings.

Reasons for the Decision

Main request

1. Inventive step

1.1 Document D2 describes the preparation of dabigatran etexilate pellets involving the formation of uniform, quasi-spherical tartaric acid cores which are covered with an isolating coating on which a layer comprising the dabigatran etexilate is applied (see D2, page 2, lines 18-24).

The difference between the process of claim 1 as granted and this prior art concerns the preparation of the tartaric acid coated cores which are subsequently coated with an isolating layer. According to claim 1 of

the main request these tartaric acid coated cores are prepared starting from a spherical core, which is coated with a solution of tartaric acid without powder layering. In contrast, the process of document D2 for producing the tartaric acid coated cores involves powder layering by repeated alternating application of a tartaric acid solution and tartaric acid powder using tartaric acid particles as starting material (see D2, page 4, line 25 to page 5 line 3, see also page 13-14, example 1).

The identification of document D2 as closest prior art and the difference between this prior art and the process of claim 1 as granted were not in dispute during the appeal proceedings.

1.2 The appellant (patent proprietor) did not contest the finding in the decision under appeal (see section 15.5), that the available information, including the experimental results reported in document D11, did not demonstrate any advantageous properties of the dosage forms resulting from the process of claim 1 in comparison to the products of the prior art described in document D2. According to the appellant (patent proprietor) the claimed process should nevertheless not be regarded as mere alternative process for producing a dabigatran etexilate dosage form, because the claimed process involving solution layering of tartaric acid avoids with respect to the process of document D2 at least the powder layering step for providing the ultimate tartaric acid layer. The claimed process thereby provided a simplification irrespective of the origin of the spherical core to be coated with the tartaric acid solution and thus also in case an additional tartaric acid layer were to be provided on a

spherical core produced by a process according to document D2.

The Board observes that document D11 reports results indicating adequate stability and dissolution rates for pellets produced by a process involving the coating of spherical cores with a solution of tartaric acid as defined in claim 1 of the patent (see D11 tables and figure on pages 3-4). In the absence of evidence to the contrary the Board is therefore satisfied that the process involving solution coating with tartaric acid as defined in claim 1 indeed allows for the formation of adequate tartaric acid coated cores whilst conveniently avoiding a final powder layering step. The problem underlying the claimed subject-matter may therefore be seen in the provision of a convenient alternative method for preparing adequate solid oral dosage forms comprising dabigatran etexilate.

1.3 The Board agrees with the appellant (patent proprietor) that the powder layering technique described in document D2 itself, involving the repeated application of a binding solution followed by powder sprinkling, does not motivate the skilled person to leave out the final powder sprinkling, because such modification would result in particles with a binding solution layer on its surface, which in the context of powder layering as described in document D2 is only intended to accommodate a further powder layer.

However, when faced with the problem identified in section 1.2 above the skilled person may be presumed to apply the common general knowledge concerning the preparation of pellets for oral drug delivery as described in documents D3, D5 and D7.

Moreover, the skilled person would also consider the teaching in document D1. Although this document relates to formulations comprising a different drug (dipyridamole), this document is evidently relevant in the context of the above identified problem, because it describes in analogy with the teaching of document D2 the preparation of tartaric acid coated cores, which are to be coated with an isolating layer to accommodate a further coating comprising an acid sensitive drug (see D1, paragraph [0010]).

1.4 From the common general knowledge in documents D3, D5 and D7 (see D3 page 235, left column; D5 page 64 left column; D7, page 1073-1074) it is evident that

- solution/suspension layering on the one hand and powder layering on the other hand represent the two established techniques for preparing pellets with a layered structure for oral drug delivery, and

- solution/suspension layering conveniently avoids subsequent application of a powder.

The Board takes the view that on the basis of this common general knowledge the skilled person would in principle consider the modification of the process described in document D2 by providing the tartaric acid coating by way of solution/suspension layering in order to provide a convenient alternative. The argument by the appellant (patent proprietor), that document D2 concerned an already optimized process which the skilled person would not be inclined to modify, is in this context not convincing. The skilled person may be presumed to seek convenient alternatives, especially in case the relevant prior art involves a laborious

procedure, as maintained by the appellant (patent proprietor) with respect to the process of document D2.

The Board further acknowledges that the discussion of solution/suspension layering and powder layering in documents D3, D5 and D7 as commonly known coating techniques does not allow for the conclusion that these techniques can generally be exchanged one for another. However, document D7 specifically explains that layering techniques from solutions or suspensions produce homogeneous drug particles retaining approximately spherical shape and that these techniques are therefore particularly suitable for successive film coating (see page 1074, left column, first full paragraph). According to the teaching of document D2 a uniform, quasi-spherical geometry of the tartaric acid coated cores is required to allow effective coating with an isolating layer (see D2 page 2, lines 26-35). Document D7 thus indicates that solution and suspension layering are particularly suitable to achieve precisely the quality of the tartaric acid coating required according to document D2. In the Board's view the skilled person would therefore derive from the particular suitability of solution and suspension coating for successive film coating as described in document D7 a reasonable expectation that the powder layering of tartaric acid described in document D2 can indeed be successfully replaced by solution layering.

The appellant (patent proprietor) argued that document D1 would only teach the skilled person to perform the tartaric acid coating with a dispersion and not with a solution as defined in claim 1 of the patent as granted. The Board acknowledges that document D1 explains in paragraph [0065] that in some embodiments, due to the high aqueous solubility of an organic acid

present in the core, the first coating layer is applied using a non-aqueous organic solvent in the coating dispersion/solvent system. However, document D1 refers in the same paragraph [0065] also to embodiments in which "the first coating layer can be achieved by powder layering, and solution or dispersion coating in a fluid-bed or high shear mixer/granulator". In line with this teaching, the document shows in its experimental section that a dispersion of tartaric acid with METHOCEL ® in a mixture of ethanol and water can indeed be effectively applied to provide a first coating to for instance tartaric acid crystals as initial core material (see D1 example 1A and example 2 in paragraphs [0073] and [0078]). The Board therefore considers the teaching in document D1 to confirm the skilled person's expectation that the powder layering in document D2 may be successfully replaced by solution or dispersion layering.

1.5 Accordingly, the Board concludes that the process defined in claim 1 of the main request would be obvious to the skilled person in view of the prior art and hence does not involve an inventive step.

Auxiliary request 1

2. Admission of the request

Claim 1 of auxiliary request 1 differs from claim 1 as granted by the requirement that in the defined step (a) the spherical core is coated with a solution of tartaric acid without a binder.

The feature regarding the absence of a binder from the tartaric acid solution had been defined in claim 1 of auxiliary request 6 which was found allowable by the

opposition division, but only in combination with the more specific definitions of the solid dosage form as a pellet comprising less than 45% by weight of tartaric acid, of the core as a sugar sphere and of the solution of tartaric acid in a mixture of ethanol and water.

In its decision the opposition division recognized an inventive step for this process in view of the absence of a binder in the tartaric acid solution without any particular further considerations regarding the other limitations introduced with the relevant request. The Board therefore takes the view that the filing of auxiliary request 1 with the statement of grounds of appeal may be regarded as a fair response to the decision under appeal, which did not present the parties to the appeal proceedings with a fresh case to respond to.

The Board does furthermore not recognize any ground for not admitting auxiliary request 1 in the alleged violation of Article 123(2) EPC or in the circumstance that lower ranked auxiliary requests define amendments which are not convergent with respect to the amendments of auxiliary request 1. Under Article 12(4) RPBA 2007, the only criterion that the board can apply when exercising its discretion not to admit a request presented by a party with its statement of appeal which meets the requirements of Article 12(2) RPBA is whether this request could have been presented in the first-instance proceedings. Its prima-facie allowability is not a criterion at this stage nor is its convergency with lower ranked requests.

The Board has therefore in accordance with Article 12(4) RPBA 2007 decided not to exercise its discretion

not to admit auxiliary request 1 into the appeal procedure.

3. Article 123(2) EPC

The Board expressed in the communication pursuant Article 15(1) RPBA 2020 its preliminary opinion that the amendment in accordance with auxiliary request 1 does not violate the provision of Article 123(2) EPC.

No substantive arguments were submitted by the appellant in response to the preliminary opinion expressed by the Board in its communication.

The Board finds therefore no reason to deviate in this decision from the expressed preliminary opinion that auxiliary request 1 complies with the requirement of Article 123(2) EPC having regard to the explicitly disclosed optional presence of a binder and the mention of a preferred embodiment in which the solution does not include binder in the application as originally filed (see original page 10, lines 9-10 and claim 7).

4. Inventive step

4.1 The process defined in claim 1 of auxiliary request 1 differs from the process of document D2 not only in the feature that the tartaric acid coated cores are prepared starting from a spherical core which is coated with a solution of tartaric acid without powder layering, but also in the feature that the solution of tartaric acid does not comprise a binder.

The identification of the differences between the claimed subject-matter and the closest prior art was not in dispute.

4.2 According to the appellant (patent proprietor) the problem to be solved associated with the further distinguishing feature of the omitted binder was the provision of an alternative process for preparing stable oral dosage forms of dabigatran etexilate with suitable release properties.

The appellant (opponent 1) and opponent 3 argued that the results reported in document D11 did not demonstrate that the problem of providing an alternative process was actually solved, because the experiments did not include any comparison showing that the claimed process resulted in pellets which are equivalent to those of the prior art. The claimed process should therefore be considered to merely accept the inferior adhesion resulting from the omission of the binder from the coating solution.

The Board notes that the experiments described in document D11 concerned a process for preparing dabigatran etexilate pellets using a tartaric acid solution in a mixture of ethanol and water without any further binder in line with the definition in claim 1 of auxiliary request 1. As observed in section 1.2 above the results reported in document D11 show adequate stability and dissolution rates for the resulting pellets. In the absence of evidence to the contrary the Board is therefore satisfied that the process of claim 1 of auxiliary request 1 indeed solves the problem of providing an alternative process for preparing stable oral dosage forms of dabigatran etexilate with suitable release properties.

4.3 It is not in dispute that the powder layering process described in document D2 as well as the dispersion

coating described in document D1 involve the use of a binder for applying the tartaric acid coating to the starting core (see D2 page 3 line 37 to page 3 line 3; see D1 paragraph [0064]).

Documents D3, D5, D7 also specifically refer to the use of a binder in solution/suspension layering (see D3 page 235 Figure 4, see D5 page 67 Figure 1, see D7 pages 1073-1074 bridging paragraph) and do not provide any indication that such binder could be dispensed with.

In this context the Board recognizes that according to document D5 in solution/suspension layering the spraying of the solution or suspension followed by the drying phase "allows dissolved material to crystallize and form solid bridges between the cores and the initial layer of the drug substance" (see D5 page 64 left column second paragraph). However, this passage in document D5 is preceded in the same paragraph by an introduction according to which in solution/suspension layering drug particles **and other components** (emphasis by the Board) are dissolved or suspended in the application medium. The cited passage from document D5 does therefore not suggest that upon drying of the dissolved material the drug substance sufficiently adheres to the cores without the aid of other components, in particular without a binder.

The Board further acknowledges that document D12 mentions that "Usually, water can be used alone as binding liquid, if a suitable pelletization aid like MCC is included in the dry formulation" (see D12 page 799 last paragraph). This passage in document D12 was relied upon by the appellant (opponent 1) and opponent 3 to argue that it was common knowledge that in

solution layering the presence of a binder in the coating solution was not essential. However, in the preceding section headed "DIRECT PELLETIZATION VS. LAYERING OF SEEDS" document D12 explicitly informs that in the relevant chapter "only direct pelletization processes are discussed but not layering processes" (see D12 page 784 final sentence of section 3). The passage in document D12 indicating the use of water alone as binding liquid does therefore not suggest that in solution layering the binder in the coating solution can be dispensed with.

The Board therefore takes the view that having regard to the prior art it would not have been obvious for the skilled person to omit a binder from the coating solution with the tartaric acid in order to solve the problem of providing an alternative process for preparing stable oral dosage forms of dabigatran etexilate with suitable release properties.

4.4 Accordingly, the Board concludes that the process defined in claim 1 of the auxiliary request 1 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the set of claims filed as auxiliary request 1 with the statement of grounds of appeal on 28 October 2019 and a description to be adapted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated