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Datasheet for the decision of 4 April 2023

Case Number: T 0186/21 - 3.3.07

Application Number: 13792149.0

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Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CFTR MEDIATED DISEASES

Patent Proprietor:
Vertex Pharmaceuticals Incorporated

Opponent:
Generics (U.K.) Limited

Headword:
Pharmaceutical compositions for the treatment of CFTR mediated diseases / VERTEX

Relevant legal provisions:
RPBA 2020 Art. 12(2), 12(4), 12(6)
EPC Art. 123(2), 56

Keyword:

Late-filed objection - admitted (no)
Late-filed evidence - admitted (yes)
Amendments - added subject-matter (no)
Inventive step - (yes)

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Case Number: T 0186/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 April 2023

Appellant: (Opponent)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 December 2020 concerning maintenance of the European Patent No. 2914248 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	L. Basterreix

Summary of Facts and Submissions

I. The appeal was filed by the opponent (appellant) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed during the oral proceedings on 16 November 2020, the patent met the requirements of the EPC.

II. Claim 1 of this main request read as follows:

"A solid oral pharmaceutical composition comprising:
200 mg of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl) benzoic acid (Compound 1) Form I and
a solid dispersion comprising substantially amorphous N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide (Compound 2) and a polymer,
wherein the substantially amorphous Compound 2 is present in the solid oral pharmaceutical composition in an amount of 125 mg,
wherein Compound 1 Form I is characterized by one or more peaks at 15.4, 16.3, and 14.5 degrees in an X-ray powder diffraction pattern,
wherein substantially amorphous Compound 2 has less than 15% crystallinity, and
wherein the solid oral pharmaceutical composition is a tablet comprising 25 to 50 percent by weight Compound 1 Form 1, and 15 to 35 percent weight of a solid dispersion comprising Compound 2."

III. The following terms are used in this decision:
- Compound 1 refers to lumacaftor, i.e. 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane carboxamido)-3-methylpyridin-2-yl) benzoic acid;

- Compound 2 refers to ivacaftor, i.e. N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide.

IV. The decision under appeal cited, among others, the following documents:

D2: Rowe et al. Progress in cystic fibrosis and the CF Therapeutics Development Network, Thorax, 67, 889-890, September 18, 2019
D3: Merk und Schubert-Zsilavecz, Neue Ansatz bei Mukoviszidose, Pharmazcutischc Zeitung, 13.09.2011
D5: US 2011/0256220 A1
D6: WO 2010/019239 A2
D7: Vertex, Press-Release, Data from Phase 2 Combination Study of VX-809 and Ivacaftor in People with Cystic Fibrosis Who Have the Most Common Genetic Mutation (F508del) Presented at North American Cystic Fibrosis Conference, October 11, 2012
D16: Harry G. Brittain "Polymorphism in pharmaceutical solids", Marcel Dekker, Inc., 2008

V. According to the appealed decision,

(a) The main request complied with the requirements of Article 123 (2) EPC.

(b) Regarding inventive step, starting from the Compound 1 compositions of the closest prior art D5, the subject-matter of claim 1 of the main request differed in that (i) Compound 2 was present in an amount of 125 mg in substantially amorphous form in a solid dispersion (with a polymer) with less than 15% crystallinity, (ii) the weight percentages of Compounds 1 and 2, (iii) the presence of compounds 1 and 2 in the same tablet

and (iv) the combination of the claimed amounts of compounds 1 and 2. The problem to be solved was the provision of an alternative medicament for the treatment of cystic fibrosis which is present in a stable formulation and which has good patient compliance. The claimed solution involved an inventive step.

VI. In their statement setting out the grounds of appeal, the appellant raised objections, regarding the main request, of added subject-matter against claims 1, 2, 5 and 8 and lack of inventive step.

VII. With the reply dated 17 September 2021, the patent proprietor (respondent) defended their case on the basis of the main request upheld by the opposition division, and on the basis of auxiliary requests 1-51 submitted in the first instance proceedings and auxiliary requests 52-86 filed with said reply. The respondent additionally filed the following documents with said reply:

D22: WO 2009/038683 A2
D23: Serajuddin et al. "Solid Dispersion of Poorly Water-Soluble Drugs", Journal of Pharmaceutical Sciences, 88(10), 1999, pages 1058-1066

VIII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

IX. Oral proceedings were held before the Board.

X. The parties' requests are the following:

(a) The appellant requests that the decision under appeal be set aside and that the patent be revoked

in its entirety. The appellant further requests that documents D22 and D23 not be admitted into the appeal proceedings.

(b) The respondent requests that the appeal be dismissed, i.e. that the patent be maintained on the basis of the main request upheld by the opposition division or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-51 as pending during the opposition division hearing, or on the basis of one of auxiliary requests 52-86 filed with the reply to the appeal.

The respondent further requests that the appellant's new attacks not be admitted into the proceedings, namely:
- the objection of added matter against the feature "25 to 50 % w/w of Compound 1 and 15 to 35 % w/w of Compound 2" of claim 1 and claim 2 of the main request,
- the objection of added matter against the feature "30 to 50% w/w Compound 1 Form 1" of claim 5 of the main request,
- the objection that the list of compositions in claim 8 of the main request represents a selection from a list,
- and the objection of added matter against the tablet weights in claim 1 of auxiliary requests 7 and 8.

XI. The appellant's arguments may be summarised as follows:

(a) Claims 1, 2, 5 and 8 of the main request infringed Article 123(2) EPC.

In claim 1, the dosage "200 mg of Compound 1 and 125 mg of Compound 2" represented a first selection out of two equal alternative dosages. The feature "25 to 50 % w/w of Compound 1 and 15 to 35 % w/w of Compound 2" of claims 1 and 2 represented an unallowable intermediate generalization from its combination with the feature of the pharmaceutical composition PC-III, or a further selection out of two equal alternatives.

The feature "30 to 50 % w/w Compound 1 Form I" of claim 5 lacked a direct and unambiguous disclosure in the application as filed.

Lastly, compositions "PC-VIII, PC-IX, PX-XI, PC-XIV, PC-XV and PC-XVII" of claim 8 represented a selection of a range of equal alternative compositions.

In as far as these objections were raised for the first time in appeal proceedings, they were not complex and were to be admitted because the respondent had to be able to address the negative decision of the opposition division.

(b) D22 and D23 had been filed with the reply to the appeal, without justification for this late filing, and merely confirmed information already present in D16. Thus D22 and D23 were not to be admitted into the proceedings.

(c) Regarding inventive step, starting from the formulations of paragraphs [0360] and [0361] of D5 as closest prior art, the differentiating features were:

i. the additional presence of Compound 2 in form of a solid dispersion comprising 125 mg of substantially amorphous Compound 2 having less than 15% crystallinity and a polymer, and
ii. the weight percentage of Compound 2.
The technical problem was the provision of an alternative medicament for the treatment of cystic fibrosis.
The claimed solution did not involve an inventive step because the skilled person would have combined 200 mg of Compound 1 Form I with 125 mg of substantially amorphous Compound 2 in a single composition as suggested in D5, wherein Compound 2 is present as a solid dispersion according to D6.

XII. The respondent's arguments may be summarised as follows:

(a) In appeal, the appellant raised for the first time objections of added subject-matter against the feature "25 to 50 % w/w of Compound 1 and 15 to 35 % w/w of Compound 2" of claim 1 of the main request, against claim 2 and claim 5, and against the selection of the list of compositions in claim 8. These amendments to the opponent’s case contravened Article 12(2) RPBA and the requirements for procedural economy, and were therefore not to be admitted into proceedings under Article 12(4) RPBA.

(b) D22 and D23 had been filed in response to the grounds of appeal and the appellant's argument disputing the incompatibility of amorphous Compound 2 with water. These documents expanded on D16 and were to be admitted into the proceedings.

(c) The main request did not introduce added subject-matter.

In claim 1, the combination of 200 mg of Compound 1 and 125 mg of Compound 2 was described in the application as filed as being preferred, and was the only combination specified in the experimental methods for preparing tablets of the invention (see paragraphs [00367] and [00389]). The feature "25 to 50% w/w of Compound 1 and 15 to 35 % w/w of a solid dispersion comprising Compound 2" of claims 1 and 2 was disclosed in paragraph [0024] in the context of the composition of the invention, without any indication that it was limited to the composition PC-III of paragraph [0022]. The loading feature of claim 5 (30 to 50 % w/w of Compound 1 Form I) was disclosed in paragraph [0016] in conjunction with paragraph [0024] of the application as filed. Lastly, the list of formulations in claim 8 was not a selection but resulted from the deletion of the formulations of original claims 20-37 which were incompatible with claim 1.

(d) As to inventive step, to the extent that D5 could qualify as closest prior art, the differentiating features were that:
(i) Compounds 1 and 2 were in the same vehicle;
(ii) That vehicle was a tablet;
(iii) Compound 1 was present in an amount of 200 mg and Compound 2 was present in an amount of 125 mg;
(iv) Compound 2 was present in a substantially amorphous form in a solid dispersion; and
(v) The loading of 25 to 50 weight percent Compound 1 and 15 to 35 weight percent solid dispersion comprising Compound 2.

The technical problem was the provision of an alternative medicament for the treatment of cystic fibrosis which was present in a stable formulation and which had good patient compliance.
Additionally, the amorphous ivacaftor led to improved biovailability and thus improvement in efficacy and compliance.
The skilled person would not have considered the claimed solution because both the dosage regimen and the coformulation were not obvious in view of the prior art.

Reasons for the Decision

1. Admittance of the appellant's new objections

1.1 Under Article 12(2) and (4) RPBA 2020, a party's appeal case shall be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based. Any part of a party's appeal case which does not meet these requirements is to be regarded as an amendment, unless the party demonstrates that this part was admissibly raised and maintained in the proceedings leading to the decision under appeal. Any such amendment may be admitted only at the discretion of the Board.

Article 12(6) RPBA 2020 further provides that the Board shall not admit objections which should have been submitted in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

1.2 In appeal, the appellant's objections of added subject-matter against claims 1 and 2 of the main request are based on the feature "25 to 50 percent by weight Compound 1 Form 1, and 15 to 35 percent weight of a solid dispersion comprising Compound 2" (see sections 2.3 and 2.4 of the grounds of appeal). With respect to claim 1, the appellant objects that this feature represents:
- a selection from paragraphs [0016] and [0024], whose combination with the selection of the amounts 200 mg / 125 mg would infringe Article 123(2) EPC, or
- an unallowable intermediate generalisation from paragraph [0024], read in the context of paragraph [0022], or claim 10, dependent on claim 5, where it would only be shown in combination with the composition (PC-III).
The appellant's objection to claim 2 is likewise based on the alleged unallowable intermediate generalisation of the same feature.

However, these objections were never put forward by the appellant in the proceedings before the opposition division. The appealed decision does not discuss the feature above in the context of added matter of claims 1 or 2. These objections thus represent an amendment to the appellant's case, whose admission in the appeal proceedings is subject to the Board's discretion.

The Board does not share the appellant's view that the raising of these new objections is in reaction to the appealed decision, considering that a main request with the same claim 1 as the present main request was filed already with the reply to the opposition. The sole fact that the opposition division took a decision contrary to the appellant's request for revocation does not allow the appellant to bring a fresh case in appeal.

Under these circumstances, the Board concludes that these objections should have been submitted in the opposition proceedings and are not to be admitted under Article 12(6) RPBA 2020.

In addition, the Board does not consider the appellant's argument of intermediate generalisation to be *prima facie* convincing. The feature relating to the 25-50 wt% Compound 1 Form I and 15-35 wt% solid dispersion comprising Compound 2 is presented in paragraph [0024] generally as one embodiment of the invention, without any reference to paragraph [0022] or a combination with composition (PC-III).

Accordingly, the Board did not admit the corresponding objections presented in sections 2.3 and 2.4 of the grounds of appeal.

1.3 In contrast, and contrary to the respondent's view, the appellant had already objected, in the proceedings before the opposition division, to added matter in claims 5 and 8 of the main request. The issues of the combination of the ranges shown in paragraphs [0016] and [0024] regarding claim 5, and of selection of the formulae in claim 8, are addressed respectively in sections 2.5.1 and 2.7 of the appealed decision. The corresponding parts of the appellant's case, set out in sections 2.5 and 2.6 of the grounds of appeal, are thus not seen as an amendment but as part of the objections on which the decision under appeal is based (Article 12(2) RPBA 2020), and are considered in the appeal proceedings.

2. Admittance of D22 and D23

The respondent filed D22 and D23 with their reply to the appeal, as part of their defence regarding inventive step and in response to the appellant's argument disputing the incompatibility of amorphous Compound 2 with water.

During the oral proceedings before the Board, the appellant contested the admittance of D22 and D23 .

The Board considers D22 and D23 as evidence further supporting facts which the respondent had already put forward, namely that the skilled person would have expected that wet granulation would not be compatible with use of an amorphous form of Compound 2 because the water would be expected to cause the amorphous form to crystallize (see the reply dated 17 September 2022, sections 4.19 and 4.20). The respondent had previously relied on D16 in this respect. Considering that D22 and D23 were thus filed as additional evidence supporting already submitted facts, and in response to the contrary argument put forward by the appellant in their grounds of appeal (see the top of page 12), the Board concluded that Article 12, paragraphs (4) and (6) RPBA 2020, was not a bar to their admittance.

Accordingly, D22 and D23 were admitted into the proceedings.

3. Main request

3.1 Article 123(2) EPC

3.1.1 Regarding claim 1, as a result of the non-admission of the arguments of sections 2.3 relating to the feature

"25 to 50 percent by weight Compound 1 Form 1, and 15 to 35 percent weight of a solid dispersion comprising Compound 2" (see 1.2 above), the appellant's case rests solely on an alleged single selection of the dosage "200 mg of Compound 1 and 125 mg of Compound 2". This single selection could however not lead to a finding of added subject-matter.

The Board nonetheless notes that this dosage of 200 mg of Compound 1 Form I / 125 mg of Compound 2 is presented as preferred in the application as filed, because it is the only combination specified in the experimental methods for preparing tablets of the invention (see paragraphs [00367] and [00389]). Accordingly, the appellant's objection is in any case not convincing.

3.1.2 The appellant's objection of added subject-matter against claim 2 is not admitted (see 1.2 above) and thus does not need to be considered.

3.1.3 Claim 5 pertains to the composition of claim 1 comprising 30-50 wt% Compound 1 Form I. The Board shares the respondent's opinion that this feature is disclosed in paragraph [0016] in conjunction with paragraph [0024] of the application as filed, i.e. it results from the combination of the range 30-55 wt% with the range 25-50 wt% for Compound 1.

The appellant considers that paragraphs [0016] and [0024] pertain to different embodiments, namely those of compositions PC-I and PC-III of paragraphs [0015] and [0022] respectively. However, the Board considers that the wording of each of paragraphs [0016] and [0025] pertains generally to the invention, and neither refers to compositions PC-I and PC-III nor to

paragraphs [0015] and [0022]. The claims as filed do not justify either such a narrow reading of these paragraphs of the description in the context of compositions PC-I and PC-III only. This is firstly because claim 3, disclosing the first range of 30-55 wt% Compound 1, is dependent on claim 1 and does not mandate that the composition be PC-I. Secondly, while claim 10, showing the range 25-50 wt% Compound 1, is dependent on claim 5 which pertains to composition PC-III, the same is not true for the separate disclosure in paragraph [0024] of the description.

3.1.4 Lastly, claim 8 does not involve the selection of a single composition, but recites a list of 6 different compositions, which differs from e.g. paragraphs [0036]-[0050] of the application as filed only in that the list is shortened.

3.1.5 Accordingly, the main request complies with the requirements of Article 123(2) EPC.

3.2 Inventive step

3.2.1 The closest prior art D5 discloses pharmaceutical compositions comprising Compound 1 in Form I for the treatment of a CFTR-mediated disease such as cystic fibrosis (see the abstract). In paragraphs [0360] and [0361], as well as paragraphs [0029], [0030] and [0033], D5 describes tablet formulations comprising Compound 1 Form I in doses of 100 mg or 200 mg, amounting to 48.5 wt% of the tablet. Compound 1 Form I of D5 is characterised by the same XRPD peaks as in claim 1 of the main request (see paragraph [0228]).

3.2.2 The subject-matter of claim 1 of the main request differs from these specific compositions of D5 in that

the tablet comprises 15-35 wt% of a solid dispersion comprising substantially amorphous Compound 2 and a polymer, wherein the substantially amorphous Compound 2 has less than 15% crystallinity and is present in an amount of 125 mg.

3.2.3 It is for the purposes of the present decision not necessary to assess whether the above differences are associated with any additional technical effect in comparison with D5, such as regarding stability or improved bioavailability. The technical problem may thus be formulated, as submitted by the appellant, as the provision of an alternative medicament for the treatment of cystic fibrosis.

3.2.4 Obviousness

The appellant contends that the claimed solution is obvious in light of D6. D6 discloses pharmaceutical compositions comprising a solid dispersion of substantially amorphous Compound 2 (referred to as Compound 1 in D6) having less that 15% crystallinity and a polymer (see the abstract and paragraphs [0039], [0042], [0045] and [0047]), which may be in the form of a tablet comprising 125 mg Compound 2, for administration twice daily (see paragraph [0241]).

The relevant question is whether the skilled person would consider co-formulating crystalline Compound 1 Form I and the solid dispersion of amorphous Compound 2 in the same tablet in the amounts defined in claim 1.

As submitted by the appellant, the prior art suggests the combination as a co-administration of Compound 1 and Compound 2. Thus D5 teaches that Compound 1 can be employed in combination therapies (see paragraph

[0277]), and that the additional therapeutic agent may be Compound 2 (see paragraph [0279]). D5 further describes the co-administration of 400 mg Compound 1 and 250 mg of Compound 2 once a day, and that these dosage amounts may be achieved by administration of one or more tablets, for instance Compound 1 may be administered as two tablets of 200 mg each (see paragraphs [0290]-[0293]). Likewise, paragraphs [0243] and [0250] of D6 mention Compound 1 as an additional agent for co-administration with Compound 2.

However the above passages do not refer to a co-formulation, i.e. to formulating both Compounds 1 and 2 in the same tablet. The combination therapies mentioned in D7 (see page 2, 4th paragraph relating to Part 3 study), D2 (page 884, 1st paragraph on the left and table 2) and D3 (see page 6/11, 1st paragraph) do not clearly refer to co-formulation either.

The sole mention of a co-formulation is to be found in D5, which indicates that the composition may comprise Compound 1 and Compound 2 together with a further additional agent (see paragraph [0280]). However, this passage is unspecific as to which of the forms of Compound 1 considered in D5 should be used, which form of Compound 2, and how to co-formulate these agents together. D5 contains no example of such a co-formulation.

3.2.5 For the following reasons, the Board shares the opposition division's opinion that the skilled person would not have combined the crystalline form of Compound 1 of D5 with a substantially amorphous form of Compound 2 of D6 in the same tablet, in view of the different manufacturing techniques used in D5 and D6.

In D5, the core tablet composition comprising Compound 1 form I and excipients is prepared using a wet granulation process (see paragraphs [0360] and [0361]).

In contrast, in D6, the tablets are prepared by direct compression of a blend of the solid suspension of amorphous Compound 2 and the excipients, where the ingredients are substantially free of water (see paragraph [0186]). The intermediate solid dispersion of amorphous Compound 2 of D6 is prepared by spray-drying a water-containing mixture (see pages 66-70), but the resulting intermediate is dried and is not subjected to any wet process during preparation of the tablet (see pages 70-72). There is therefore no indication in D6 that the solid dispersion of amorphous Compound 2, once prepared, could be exposed to any wet processes in the preparation of the tablet, and paragraph [0186] suggests the contrary.

Furthermore, from common general knowledge, the skilled person would have expected stability issues to arise when subjecting the solid dispersion of amorphous Compound 2 to the wet granulation process of D5. This is substantiated in D16, which indicates that amorphous materials must be considered as thermodynamically metastable and susceptible to back-conversion to a crystalline form, and that one should not expect to be able to wet-granulate the metastable phase of a particular compound if that metastable phase is capable of transforming into a more stable form (see pages 334 and 340). Likewise, D23 indicates that the crystallization of amorphous materials is facilitated by moisture (see page 1061, right column, last paragraph). The Board sees no ground to expect that the issues to be expected when wet-granulating amorphous form would not arise when wet-granulating a solid

suspension of an amorphous form in a water-soluble polymer. This is all the more so since D23 reports unsuccessful attempts to wet granulate a solid dispersion of amorphous drug (see page 1060, left column, lines 20-24 of the final paragraph).

The skilled person would therefore not consider combining the teachings of D5 and D6, i.e. would not subject the solid suspension of amorphous Compound 2 to the wet granulation process of D5 or otherwise combine the wet granules of D5 with the materials of D6, because they would expect such a combination to be incompatible with the amorphous state of compound 2.

The appellant also referred to the possibility of using other granulation techniques, such as the moisture activated dry granulation method mentioned in D15 (see page 150). There is however no evidence that the use of such methods would allow the preparation of tablet compositions meeting the loading requirements of claim 1. Lastly, as pointed out by the respondent, there is no evidence that any co-formulation of an amorphous drug and a crystalline drug had been approved at the priority date.

3.2.6 Accordingly, the subject-matter of the main request involves an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Stridde A. Usuelli

Decision electronically authenticated