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Datasheet for the decision of 28 November 2017

Case Number: T 1895/15 - 3.3.07

Application Number: 06019789.4

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Title of invention:
Solid pharmaceutical dispersions with enhanced bioavailabilty

Applicant:
Pfizer Products Inc.

Headword:
Solid pharmaceutical dispersions with enhanced bioavailabilty/ Pfizer Products Inc.

Relevant legal provisions:
EPC Art. 54, 84, 56, 111(1)

Keyword:
Main request - Novelty (no)
Auxiliary request 1 - Clarity (no)
Auxiliary request 2 - Inventive step (yes)
Remittal

Decisions cited:

Catchword:

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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 1895/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 November 2017

Appellant: (Applicant)	Pfizer Products Inc. Eastern Point Road Groton, CT 06340-5146 (US)
Representative:	Beckmann, Claus Kraus & Weisert Patentanwälte PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 28 April 2015 refusing European patent application No. 06019789.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application n° 06 019 789.4, which is a divisional application of the earlier application EP 98 305 960.1.
The decision was based on 3 sets of claims filed with letter of 30 July 2014 as main request and with letter of 18 December 2014 as auxiliary requests 1 and 2.

a) Claim 1 of the main request read as follows:

"1. A composition comprising a spray dried solid dispersion, which dispersion consists essentially of a sparingly water-soluble drug and HPMCAS wherein the drug to HPMCAS weight ratio is from 1/0.4 to 1/20; said drug being molecularly dispersed in said dispersion; said dispersion satisfying either of the following tests:

(a) providing a maximum concentration of said drug in MFD (model fasted duodenal fluid) that is higher by a factor of at least 1.5 relative to a control composition;
wherein MFD is water which is 82 mM in NaCl, 20 mM in Na_2HPO_4 , 47 mM in KH_2PO_4 , 14.7 mM in sodium taurocholate and 2.8 mM in 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine to yield a solution pH of about 6.5 and osmotic pressure of about 290 mOsm/kg, or
(b) effecting, in vivo, a maximal observed blood drug concentration (C_{max}), that is higher by a factor of at least 1.25 relative to a control composition,

wherein the control composition is identical to the test composition except that it comprises pure drug in its equilibrium form and does not comprise HPMCAS, or

the HPMCAS is replaced by an equal amount of inert, non-adsorbing solid diluent such as microcrystalline cellulose, and the test composition and control composition are tested under like or standardized conditions, such as 500mL of MFD, paddle speed of 100 rpm and 37°C."

b) The subject-matter of claim 1 of auxiliary request 1 differed from claim 1 of the main request by the following specification and suppression brought to the preamble as indicated in bold:

"1. A composition comprising a spray dried **homogeneous amorphous solid solution**, which **solid solution** consists essentially of a sparingly water-soluble drug and HPMCAS wherein the drug to HPMCAS weight ratio is from 1/0.4 to 1/20; ~~**said drug being molecularly dispersed in said dispersion**~~; said solid solution satisfying either of the following tests:
.... paddle speed of 100 rpm and 37°C."

c) Claim 1 of auxiliary request 2 was restricted to the process of preparation as follows:

"1. A process for making a homogeneous amorphous solid solution, which solid solution consists essentially of a sparingly water-soluble drug and HPMCAS;
wherein the process consists of the steps of

a) providing a solution consisting of a sparingly water-soluble drug, HPMCAS, and a solvent, said solvent being an organic compound in which said drug and HPMCAS are mutually soluble, said solution having a drug to HPMCAS weight ratio from 1/0.4 to 1/20,

b) breaking up said solution into small droplets, wherein said droplets range in size from 5 to 100 µm,

c) directing said droplets into a spray drying apparatus, wherein a strong driving force for solvent evaporation is provided by maintaining the pressure in the spray-drying apparatus at a partial vacuum and/or mixing the liquid droplets with a warm drying gas;

said solution satisfying either of the following tests:

(i) providing a maximum concentration of said drug in MFD (model fasted duodenal fluid) that is higher by a factor of at least 1.5 relative to a control composition;

wherein MFD is water which is 82 mM in NaCl, 20 mM in Na_2HPO_4 , 47 mM in KH_2PO_4 , 14.7 mM in sodium taurocholate and 2.8 mM in 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine to yield a solution pH of about 6.5 and osmotic pressure of about 290 mOsm/kg, or

(ii) effecting, in vivo, a maximal observed blood drug concentration (C_{max}), that is higher by a factor of at least 1.25 relative to a control composition,

wherein the control composition is identical to the test composition except that it comprises pure drug in its equilibrium form and does not comprise HPMCAS, or the HPMCAS is replaced by an equal amount of inert, non-adsorbing solid diluent such as microcrystalline cellulose, and the test composition and control composition are tested under like or standardized conditions, such as 500mL of MFD, paddle speed of 100 rpm and 37°C."

II. The documents cited during the examination proceedings included the following:

E2: Yamaguchi etal., Yakuzaigaku, 53(4), pg 221-228, (1993)
E2a: English translation of E2 (provided by Pfizer)
E3: US 4,983,593 (family member of E5)
D4 : Experimental data filed by proprietor on 24th September 2009 ("E37" in parent opposition proceedings)
D5: Experimental report filed by the applicant on 30 July 2014.
E5: EP-A-0344603 (family-member of E3)
E6: EP-A-0784974
E9: EP-A-0413299
E10: WO 96/19239
E10c: English translation of E10 (provided by Shin-Etsu Chemical Co., Ltd.)
E11: JP 61-227524
E11 b: English translation of E11 (provided by Janssen Pharmaceutica N.V.)
E14: Exhibit A submitted by Patentee 19th October 2006
E24: EP-B-0 901 786
E38: Reports filed by proprietor on 18th November 2009

III. According to the decision under appeal, the main request did not meet the requirements of Article 83 EPC, in view of the term “molecularly dispersed”, for the same reason as the parent patent EP 901 786 in decision T 2461/09.

As regards auxiliary request 1, the term "molecularly dispersed" was replaced by the term "homogeneous amorphous solid solution". The examining division did not see a reason to deviate from the decision taken in opposition of the parent patent (EP 901 786) in view of inventive step. E2a was considered as closest prior art and disclosed spray dried dispersions of a sparingly water soluble drug within the claimed drug to polymer ratio prepared with carboxymethylcellulse (CMC). No

technical effect was associated with this difference, since both polymers performed very good in terms of increased bioavailability (E2a, Fig. 2 and page 5, point 7, last line). The objective technical problem was to provide an alternative for preparing spray dried dispersions in the claimed range. Since E2a taught the use of HPMCAS for the purpose of increasing bioavailability of sparingly water-soluble drugs, it did not require inventive skills to replace CMC by HPMCAS.

The same conclusions as regards inventive step applied to the subject-matter of auxiliary request 2, which was a process-type claim.

The examining division indicated furthermore in its decision that examination of the requirements of Article 76(1), 123(2) 83, 84 and 54 EPC of auxiliary request 2 was not discussed during oral proceedings.

IV. The applicant (hereafter called appellant) filed an appeal against that decision. With the statement setting out the grounds of appeal dated 3 September 2015, the appellant filed a main request and 6 auxiliary requests.

Claim 1 of the main request corresponded to claim 1 of auxiliary request 1 which was the subject of the decision of the examining division.

Claim 1 of auxiliary request 1 was restricted by a further parameter, namely "and wherein the average particle size of said spray dried homogeneous amorphous solution is less than 100 µm in diameter".

Claim 1 of auxiliary request 2 corresponded to claim 1 of auxiliary request 2 which was the subject of the decision of the examining division with the following amendments in bold:
- "A process for making a **spray dried** homogeneous solid solution",
- "said **solid solution** satisfying either of the following tests".

V. A communication in preparation for oral proceedings was sent by the Board expressing its preliminary view. The Board's opinion was that the main request was not novel over E3 and that auxiliary request 1 did not meet the requirements of Article 84 EPC in view of the parameter of "average particle size". As regards auxiliary request 2, E3 was seen as the closest prior art.

VI. With the letter of 27 October 2017 the appellant submitted further auxiliary requests 7-13.

VII. Oral proceedings before the board of appeal took place on 28 November 2017.

VIII. The appellant's arguments can be summarised as follows:

E3 could not be relevant for the novelty of the main request, since this document did not describe an amorphous solid solution fulfilling all tests as claimed. There were a lot of compounds that could not form an amorphous solid solution as claimed.

As regards the clarity of the parameter of "average particle size" in claim 1 of auxiliary request 1, the skilled person knew that spray drying formed spherical particles and that their diameter was thus easy to

measure. Moreover, for the same reason, the mention of the type of diameter to be used was not necessary.

As regards the inventive step of claim 1 of auxiliary request 2, said subject-matter differed from the disclosure of E3, as well as from E2A, in the droplet size range and in step c) of the claimed process. E3 did also not disclose the amorphous state of the composition. The effect obtained was the improvement of the bioavailability. In E2A, the amount of polymer was also less than the claimed ratio of drug to polymer of 1/0.4 to 1/20. The evaporation process with an higher amount of polymer had a different effect, such as a faster evaopration, a prevention of phase separation and resulted in a more homogenous amorphous solid solution. Documents E2A or E3 did not give any process conditions in the disclosed spray drying processes, and the claimed process was inventive over both documents.

IX. Requests

The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or auxiliary requests 1-6, filed with the grounds of appeal, or on the basis of auxiliary requests 7-13, filed with letter dated 27 October 2017.

Reasons for the Decision

1. Main request - Article 54 EPC

Document E3 mentions in columns 3 and 4 the following: "An NZ-105 composition of this invention can be prepared by dissolving NZ-105 and HPMCAS in an organic solvent, removing the solvent by means of vacuum-drying, spray-drying, freeze-drying, or the like to

produce powder or particles of NZ-105 and HPMCAS....A desirable result can be obtained by formulating an amount of 1-7 parts by weight, especially 3-5 parts by weight of HPMCAS per unit weight of NZ-105."

Said document discloses thus explicitly the preparation of a composition comprising a sparingly soluble drug and HPMCAS, by dissolving NZ-105 and HPMCAS in a NZ-105/HPMCAS ratio comprised between 1/1 and 1/7, into an organic solvent and removing the solvent by evaporation, so as to improve the solubility of the drug and to promote its bioavailability (see E3, col. 2, l. 18-40). The solvent removal process may be a spray-drying process, which constitutes a selection from an unique list of possibilities, namely from "vacuum-drying, spray-drying, freeze-drying". E3 discloses thus directly and unambiguously a spray-dried powder consisting of a sparingly-soluble drug and HPMCAS in a weight ratio comprised within the range of claim 1 of the main request.

As to the state of "homogenous amorphous solid solution" of the claimed composition, as well as the claimed C_{max} tests that the composition has to fulfill, the Board came to the conclusion that any composition obtained by spray-drying a sparingly soluble drug and HPMCAS will necessarily and inevitably possess all properties of the composition claimed in claim 1 of the main request. This conclusion is reached in view of the absence of any specific process feature or setting in claim 1 of the main request or in the description of the application, allowing specifically the preparation of a spray-dried composition being a "homogenous amorphous solid solution" fulfilling the claimed C_{max} tests. The description of the application describes indeed very general spray-drying process conditions and

settings (see par. [0048]-[0050] and examples) and does not put forward any process parameter or setting which could appear as essential or responsible for the particular properties of the finally obtained composition.

Moreover, as regards the "amorphous" nature of the claimed composition, the claimed composition does not require to be in a 100% amorphous state, as confirmed by several examples of the present application which achieve the preparation of only a "substantially amorphous powder" (see for instance, examples 1 and 4). Consequently, the spray-dried composition of E3 is inevitably an homogenous amorphous solid solution presenting the same pharmacokinetics as the compositions claimed in claim 1 of the main request, and said spray-dried compositions of document E3 fall under the claimed subject-matter of claim 1 of the main request.

The main request does not meet the requirements of Article 54 EPC.

2. Auxiliary request 1 - Article 84 EPC

Claim 1 of this request has been amended by the specification of the particle size, namely "wherein the average particle size of said spray dried homogeneous amorphous solution is less than 100 µm in diameter".

However, there is no definition in the claims, or more generally in the application as a whole, as to what this term refers to, nor how said average particle size has to be determined. The Board concurs with decisions of the jurisprudence, according to which the generic parameter "average particle size" renders the claims

unclear as neither the type of average (volume, surface, number) nor a method for determining it is indicated in the claims (see T 1819/07 point 3; T 45/10, point 4.3 of the reasons).

The Board could in particular not follow the argument of the appellant that the claimed spray-dried composition comprised almost perfect spherical particles and that the mention of the type of average particle size to be used was thus not necessary. Said argument is indeed not only unsubstantiated, but also is technically not credible, since it is obvious that at least the process conditions and the properties of the starting products have an influence on the final particle morphology. Moreover, even in the case of perfect spherical particles, the type of average size has nevertheless to be given, since the different methods of determining the different average particle sizes give different results.

Consequently, auxiliary request 1 does not meet the requirements of Article 84 EPC.

3. Auxiliary request 2

The subject-matter of claim 1 of auxiliary request 2 has been reformulated as a process-type claim, comprising three steps a)-c), with essentially the specification of the drug to HPMCAS weight ratio of 1/0,4 to 1/20 in step a), the droplets size of "5 to 100 µm" in step (b), and the use of a partial vacuum and/or drying gas in step c).

This request is similar to auxiliary request 2 which was the subject of the decision of the examining division as regards only its inventive step.

Inventive step

3.1 The claimed invention relates to a process for making spray-dried compositions of sparingly-soluble drugs in hydroxypropylmethylcellulose acetate succinate, that have increased aqueous concentration and bioavailability.

3.2 In its decision, the examining division mentioned that the inventive step objections raised against auxiliary request 1, corresponding now to the main request of the appeal proceedings, were upheld *mutatis mutandis* for auxiliary request 2. Said auxiliary request 2 was thus found to lack inventive step over document E2a, since this document was considered to have the largest number of technical features in common with the claimed subject-matter, at the detriment of document E3 which was considered as less close by the examining division.

3.2.1 E2a discloses the spray drying process of a drug and carboxy methyl cellulose (CMEC) or HPMCAS, for improving the properties and bioavailability of the drug. A solution of the drug and CMEC was provided and further spray-dried, without further indication of the droplets size; the solid dispersion of drug with HPMCAS at the drug/polymer ratio of 10:1 was prepared in similar fashion.
The Board notes however that E2a focuses mainly on solid dispersions of a drug in CMEC, and HPMCAS is used in E2a only as a reference composition at a unique drug/HPMCAS weight ratio of 10/1 (thus higher than the claimed 1/0,4). The drug/CMEC ratios tested in E2a are 10/5, 10/2, 10/1 and 10/0,1, among which the ratio 10/5 is the only comprised between the claimed range of 1/0,4- 1/20. In this context, E2 highlights furthermore that the solubility properties of the drug decreased

with increasing amounts of CMEC, such as in particular at the ratio 2/1, and the ratio offering the best solubility was 10/1 (see Fig. 3 and 4 and par. 3). This document does thus neither disclose the drug/ HPMCAS weight ratio of step a), nor the specific claimed claimed droplet size of step b), nor explicitly step c).

3.2.2 Document E3 discloses the preparation of a composition comprising a sparingly soluble drug and HPMCAS, by dissolving NZ-105 and HPMCAS in a NZ-105/HPMCAS ratio comprised between 1/1 and 1/7, into an organic solvent and removing the solvent by evaporation, i.e by spray-drying, so as to improve the solubility of the drug and to promote its bioavailability (see E3, col. 2, l. 18-40). This document does therefore neither disclose the specific claimed claimed droplet size of step b), nor explicitly step c).

3.2.3 The Board notes that both documents E2a and E3 relate to the same purpose as the claimed invention. The technical teaching of document E3 shows however undeniably the largest number of similarities with the claimed subject-matter and this document should represent the closest state of the art.

3.2.4 Document E2a mentions furthermore a process involving HPMCAS only in the frame of a reference, and teaches, in the case of the concurrent polymer CMEC, to use a composition comprising a drug and a polymer preferably with lower amounts of polymers, preferably at the ratio 10/1 in the case of CMEC. Said document not only fails to suggest substituting HPMCAS for CMEC, but does not provide any incentive to make a composition of drug and polymer at a weight ratio of 1/0,4 to 1/20 as claimed in claim 1 of auxiliary request 2. It implies that,

independently from the technical problem that the claimed process intends to solve over document E2a, at least a part of the claimed solution, i.e. "a) providing a solution consisting of a sparingly water-soluble drug, HPMCAS, and a solvent, said solvent being an organic compound in which said drug and HPMCAS are mutually soluble, said solution having a drug to HPMCAS weight ratio from 1/0.4 to 1/20", is, in any case, not obvious in view of the teaching of E2a, and the claimed subject-matter is inventive over E2a.

3.3 The decision of the examining division does therefore not hold good. It remains necessary to assess the inventive step of the claimed subject-matter over the document which is considered by the Board as the closest prior art, namely E3. This assessment constitutes a substantial amendment to the case considered by the examining division, and necessitates a new full examination, especially as regards the technical features absent from the disclosure of E3.

Remittal to the examining division

Although Article 111(1) EPC does not guarantee a party an absolute right to have all the issues in the case considered by two instances, it is well recognised that any party should, whenever possible, be given the opportunity to said consideration by two instances of the important elements of the case. The essential function of an appeal proceedings is to consider whether the decision under appeal is correct. Hence, a case is normally remitted if further criteria of patentability have not yet been examined and decided in the proceedings leading to the decision under appeal. This is the situation here, since an examination as regards Articles 76(1), 123(2), 84, 83 or 54 EPC, as

well as Article 56 EPC over E3 has not yet been performed on the subject-matter of auxiliary request 2. Hence, the Board considers it appropriate to remit the case to the examining division for further prosecution on the basis of auxiliary request 2.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated