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Case Number: T 2461/09 - 3.3.07

Application Number: 98305960.1

Publication Number: 901786

IPC: A61K9/14, A61K47/38

Language of the proceedings: EN

Title of invention:
Solid pharmaceutical dispersions with enhanced bioavailability

Patent Proprietor:
BEND RESEARCH, INC.

Opponent:
Shin-Etsu Chemical Co., Ltd.

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:

Catchword:

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Case Number: T 2461/09 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 December 2013

Appellant: (Patent Proprietor)	BEND RESEARCH, INC. 64550 Research Road Bend, OR 97701-8599 (US)
Representative:	Albrecht, Thomas Kraus & Weisert Patent- und Rechtsanwälte Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Opponent 4)	Shin-Etsu Chemical Co., Ltd. 6-1, Ohtemachi 2-chome Chiyoda-ku, Tokyo 100-0004 (JP)
Representative:	Scholz, Volker Boehmert & Boehmert Pettenkoferstrasse 20-22 80336 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 December 2009 revoking European patent No. 901786 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: J. Riolo
Members: D. Semino
P. Schmitz

Summary of Facts and Submissions

I. The appeal of the patent proprietor (appellant) lies against the decision of the opposition division announced at the oral proceedings on 26 November 2009 to revoke European Patent 0 901 786. Independent claims 1 and 21 of the patent as granted read as follows:

"1. A composition comprising a spray dried solid dispersion, which dispersion comprises 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 and amorphous 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 standardised

conditions, such as 500mL of MFD, paddle speed of 100rpm and 37°C."

"21. A process for making a spray dried solid dispersion as claimed in claim 1 comprising;
A. forming a solution comprising (i) HPMCAS, (ii) a sparingly water-soluble drug, and (iii) a solvent in which both (i) and (ii) are soluble; and
B. spray drying said solution, thereby forming spray dried particles having an average diameter less than 100 µm,
wherein the drug to HPMCAS weight ratio is from 1/0.4 to 1/20."

II. Four notices of opposition were filed against the granted patent requesting revocation of the patent in its entirety on the grounds of lack of novelty and lack of inventive step, insufficiency of disclosure and extension of the subject-matter beyond the content of the application as filed in accordance with Article 100(a), (b) and (c) EPC.

III. The oppositions of opponents 1, 2 and 3 were withdrawn during opposition proceedings.

IV. The decision was based on the patent as granted as main request and on four set of claims filed as auxiliary requests I to III with letter of 24 September 2009 and as auxiliary request IV A during oral proceedings on 26 November 2009.

Claim 1 of auxiliary request I corresponded to claim 1 as granted with the specification in tests (a) and (b) that the comparison is relative to "the equilibrium drug concentration of a control composition". In claim 1 of auxiliary request II it was additionally indicated

that the dispersion "consists of" the drug and HPMCAS. Claim 1 of auxiliary request III included in addition the specification that "said dispersion is in the form of particles less than 100 µm in diameter". Auxiliary request IV A comprised only process claims wherein claim 1 read as follows:

"1. A process for making a solid dispersion consisting of a sparingly water-soluble drug and hydroxypropyl methyl cellulose acetate succinate (HPMCAS), said drug being molecularly dispersed and amorphous in said dispersion, said process comprising 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 the drug and HPMCAS are mutually soluble, said solution having a ratio of said drug to HPMCAS of from 1 to 0.4 to 1 to 20, and the concentration of said drug in said solvent is less than 20 g/100 g of solvent with a total solids content less than 25 weight %;
(b) breaking up said solution into small droplets, wherein said droplets range in size from 1 to 500 µm;
(c) directing said droplets and a drying gas into a drying chamber to cause evaporation of a sufficient amount of said solvent from said droplets to cause solidification of said droplets in less than 5 seconds to form said solid dispersion;
thereby forming spray dried particles having an average diameter less than 100 µm, 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 the equilibrium drug concentration of 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 the equilibrium drug concentration of 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 standardised conditions, such as 500mL of MFD, paddle speed of 100rpm and 37°C."

V. In the decision the following documents were cited *inter alia*:

E2: Yamaguchi et al., Yakuzaigaku, 53(4), 1993, pages 221-228
E2a: translation into English of E2
E37: "Evaluation of Dispersions using Differential Scanning Calorimetry (DSC)", report filed by the patent proprietor with letter of 24 September 2009

VI. As far as relevant to the present decision, the decision under appeal can be summarised as follows:

a) Article 100(c) EPC prejudiced claim 1 of the patent as granted as far as the definition of the control composition for the functional criteria (a) and (b) was concerned.

b) By means of the addition of the expression "the equilibrium drug concentration of" with reference to the control composition for the functional criteria (a) and (b) in claim 1 according to auxiliary request I the issue under Article 100(c) was made moot.

c) There was no lack of sufficiency related to the term "molecularly dispersed and amorphous", as the skilled person could assess by DSC technology the molecular state of a dispersion and by conducting spray drying one would inevitably arrive at a drug/polymer dispersion having at least part of the drug amount in a "molecularly dispersed and amorphous" state. In that respect the claim was understood as implying that at least a part of the drug was present as molecularly dispersed, i.e. as separate drug molecules surrounded only by polymer, the rest of the drug being present as amorphous domains.

d) Novelty of the product of claim 1 of auxiliary request I was acknowledged.

e) Taking the embodiment of E2 (with reference to its translation into English E2a) with a dispersion comprising CMEC in a 1/0.5 drug to polymer ratio as the closest prior art, the subject-matter of the independent claims of the auxiliary requests was found not to be inventive.

VII. The appellant lodged an appeal against that decision. With the statement setting out the grounds of Appeal 14 set of claims were filed as main request and auxiliary requests I to XIII.

The main request corresponded to auxiliary request 1 on which the decision was based. Claim 1 of auxiliary requests I to V corresponded to claim 1 of the main request in which the dispersion was specified to be "homogeneous" (auxiliary request I) or "a solid solution" (auxiliary request II) or in which the drug was specified to be molecularly dispersed and amorphous in said dispersion "such that there is little or no drug present as separate amorphous domains" (auxiliary request III) or "such that there is no drug present as separate amorphous domains" (auxiliary request IV) or simply "molecularly dispersed" without the specification of being "amorphous" (auxiliary request V). Auxiliary requests VI, VII and VIII corresponded to auxiliary requests II, III and IV A on which the appealed decision was based. Claim 1 of auxiliary requests IX to XIII was a process claim corresponding to claim 1 of auxiliary request VIII with the amendments of auxiliary requests I to V respectively.

VIII. In the reply to the statement setting out the grounds of appeal opponent 4 (respondent) maintained the objections of extension beyond the content of the application as filed, insufficiency of disclosure, lack of novelty and lack of inventive step.

IX. In a communication sent in preparation of oral proceedings the Board addressed *inter alia* the issues of sufficiency of disclosure expressing concerns with regard to the term "molecularly dispersed" (paragraph 2.1 of the communication).

X. Oral proceedings were held on 3 December 2013.

XI. The arguments of the appellant can be summarised as follows:

Sufficiency of disclosure

Contrary to the understanding of the opposition division, the expression "molecularly dispersed and amorphous" with reference to the state of the drug in the dispersion meant undoubtedly that the drug molecules were isolated from each other, i.e. scattered in the dispersion down to the molecular level, and could not mean that only part of the drug was present in the molecularly dispersed form and the rest was present as amorphous domains. Indeed the word "amorphous" (i.e. non-crystalline) in the context of the claim was redundant. It was true that in the patent several alternatives were possible, including having the drug present in small crystals or in amorphous drug-rich domains, and that there was no information whether in the examples the drug was effectively "molecularly dispersed", which meant that there was a theoretical possibility that it was not. However, this was not the crucial issue for establishing sufficiency of disclosure, which related instead to the questions whether the skilled person had sufficient information about how to obtain a product according to the claim and how to verify that such a product had effectively been obtained. The answer to both question was affirmative. As to the first issue, paragraph [0047] in the patent indicated how to obtain a drug in the "molecularly dispersed" state and underlined the step of rapid drying as the key feature for the method of manufacture of the product. As to the measurement, differential scanning calorimetry, even if not mentioned in the patent, was known to the skilled person and made it possible to verify whether the drug was actually "molecularly dispersed", as shown in document E37.

XII. The arguments of the respondent can be summarised as follows:

Sufficiency of disclosure

There was lack of sufficiency due to the presence of the expression "molecularly dispersed and amorphous" with reference to the state of the drug in the dispersion. The general teaching in the patent was very broad and there was no specific teaching about how to obtain a product with the drug in the "molecularly dispersed" state. In this respect it was not convincing that a rapid spray drying automatically resulted in the dispersion of the drug at the molecular level. On the contrary it was to be expected that the result depended on the conditions of the process which were not specified. In addition, it was not specified in the patent how to assess whether the desired result had been obtained and there were doubts that differential scanning calorimetry, which was in any case not mentioned in the patent, was suitable for that. The examples in the patent were completely silent in this respect, i.e. they did not provide any information whether the drug was molecularly dispersed in the compositions obtained therein.

XIII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or of one of auxiliary requests I to XIII filed with the statement of grounds of appeal.

XIV. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Sufficiency of disclosure

1. The question of sufficiency of disclosure in the present case boils down to the issue whether the patent discloses a spray dried solid dispersion comprising a drug which is "molecularly dispersed and amorphous in said dispersion" and a process for making such a dispersion in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

1.1 The Board concurs with the appellant in the understanding of the expression "molecularly dispersed and amorphous", namely that the drug must be both "molecularly dispersed" and "amorphous" as indicated by the use of the word "and", which specifies that both conditions must be met, that "molecularly dispersed" means that the drug molecules are isolated from each other in the dispersion, i.e. scattered in the dispersion down to the molecular level, and that the further specification of "amorphous", which is a synonym of non-crystalline, is superfluous in the present context, as a molecularly dispersed drug cannot be in crystalline form.

1.2 The question to be answered is therefore whether the skilled person is given sufficient information as to how to obtain a product with the whole drug (or a large part of it) dispersed at molecular level.

1.3 As far as the status of the drug in the dispersion is concerned, the general teaching in the patent is to be found in paragraph [0023], whose last three sentences read: "In general, the drug is dispersed in the HPMCAS

such that most of the drug is not present in crystalline form greater than about 0.1 µ in diameter. The drug may be present in amorphous drug-rich domains as long as the drug will dissolve to form supersaturated solutions in *in vitro* tests disclosed hereinafter. However, it is generally preferred for the drug to be molecularly dispersed such that there is little or no drug present as separate amorphous domains."

1.4 The general teaching in the patent is therefore very broad, including in the broadest form the presence of crystals of any dimension, as long as most of them are not greater than 0.1 µm in diameter, in the intermediate form the presence of amorphous drug-rich domains with no limitation on the quantity of drug present in those domains and only in the most specific one a dispersion at molecular level, which corresponds to what is claimed.

1.5 In spite of that there is a single disclosure of a process for making the spray dried dispersion, namely in paragraph [0047] where it is underlined that the spray drying should be a rapid one, in particular in the first and in the fourth sentences, which read: "Generally, the temperature and flow rate of the drying gas is chosen so that the HPMCAS/drug-solution droplets are dry enough by the time they reach the wall of the apparatus that they are essentially solid, so that they form a fine powder and do not stick to the apparatus wall" and "This rapid drying is critical to the particles maintaining a uniform, homogeneous composition instead of separating into drug-rich and polymer-rich phases". Following that, some indications are given about reasonable solidification times and droplet sizes (last three sentences in the paragraph).

1.6 That single disclosure of a process does not specify, however, the conditions under which the skilled person should carry out the manufacture of the product in order to specifically obtain a molecularly dispersed drug.

1.7 Indeed the term "molecularly dispersed" is only mentioned once in paragraph [0023] (see citation in point 1.3) in the whole patent and nowhere a clear guidance for the skilled person is to be found about how the desired dispersion is to be obtained. Actually in the whole patent there is not even an indication whether the desired molecular dispersion was at all obtained.

1.8 The fact that a method of verification as to whether the drug is molecularly dispersed is not present in the patent is particularly relevant because it confirms that the skilled person, while reading the patent, is left at loss as to whether the desired result (a molecularly dispersed drug) has indeed been obtained. In this context it is relevant to note that the examples (paragraph [0076] and following) not only lack details about the method of production (the apparatuses are mentioned with reference to the figures, but the conditions are not given), but also do not give any information about whether the obtained products contain a molecularly dispersed drug, neither by means of a measurement, nor even as a plain statement. The only general information in this respect is that the whole powder is "substantially amorphous" (see e.g. the last sentence of paragraph [0076] for example 1). On top of that, in view of the fact that the general disclosure is very broad, as far as the status of the drug in the dispersion is concerned, it can by no means be implied

that a molecularly dispersed drug is necessarily meant to be obtained in the examples. The appellant has indeed not denied that it is not known whether the examples fall under the claim.

1.9 In this respect the fact that a method of measurement known to the skilled person, such as differential scanning calorimetry, may exist does not change the fact that such a method is not mentioned in the present patent, nor applied to the products obtained in the examples disclosed therein, so that the skilled person has no guidance in the general part of the description, nor in the specific examples about how to obtain the desired molecular dispersion of the drug. Indeed not even a single embodiment of the claimed dispersion is disclosed in the patent.

1.10 On this basis the Board can only come to the conclusion that, due to the specification in the claims that the drug is "molecularly dispersed" in the spray dried dispersion, the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Conclusions

2. As the specification that the drug is "molecularly dispersed" is present in all independent product and process claims of all requests on file, the grounds of opposition under Article 100(b) EPC stays against all requests on file.

3. In view of the fact that all requests on file fall for the ground of opposition under Article 100(b) EPC, there is no need for the Board to decide on any other ground.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Hampe J. Riolo

Decision electronically authenticated