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Datasheet for the decision of 5 April 2016

Case Number: T 2152/12 - 3.3.07

Application Number: 00972083.0

Publication Number: 1242013

IPC: A61K9/20, A61K9/68

Language of the proceedings: EN

Title of invention:
ORAL TRANSMUCOSAL DRUG DOSAGE USING SOLID SOLUTION

Patent Proprietor:
Cephalon, Inc.

Opponent:
LTS LOHMANN Therapie-Systeme AG

Relevant legal provisions:
RPBA Art. 12(1), 12(4)
EPC Art. 56

Keyword:
Continuation of the appeal proceedings after withdrawal of the opposition (yes)
Late-filed evidence - admitted (yes)
Inventive step - (yes)

Decisions cited:
T 0629/90

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Case Number: T 2152/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 5 April 2016

Appellant: (Patent Proprietor)	Cephalon, Inc. 41 Moores Road P.O. Box 4011 Frazer, PA 19355 (US)
Representative:	Hallybone, Huw George Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	LTS LOHMANN Therapie-Systeme AG Lohmannstrasse 2 56626 Andernach (DE)
Representative:	Schweitzer, Klaus Plate Schweitzer Zounek Industriepark Kalle-Albert Rheingaustrasse 196 65203 Wiesbaden (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 July 2012 revoking European patent No. 1242013 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. European patent No. 1 242 013, based on European application 00972083.0, was granted on the basis of sixteen claims.

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC), it was not sufficiently disclosed (Article 100(b) EPC) and it extended beyond the content of the application as filed (Article 100(c) EPC). The following document was among those cited during the first-instance proceedings:

D1: US 2,698,822

III. By decision posted on 25 July 2012 the opposition division revoked the patent. The decision was based on a main request and an auxiliary request both filed during the oral proceedings held on 19 June 2012.

Independent claim 1 and 12 of the auxiliary request read respectively as follows:

"1. A solid dosage form for oral transmucosal delivery of a pharmaceutical agent comprising:
(a) a solid solution in the form of a compressible powder, said solid solution comprising a pharmaceutical agent mixed at the molecular level with a dissolution agent, said dissolution agent having a dissolution rate in the solvents found in the oral cavity, said dissolution rate of said dissolution agent being greater than said dissolution rate of said pharmaceutical agent; and
(b) a buffer system physically mixed with the compressible powder;

wherein said buffer system is selected from the group consisting of phosphate, carbonate, tris, tartrate, borate, acetate, and maleate buffers;
wherein said pharmaceutical agent is an organic acid or an organic base; and wherein said solid solution is created by wet granulation, co-melt, spray drying or freeze drying".

"12. A method of manufacturing a solid dosage form for oral transmucosal delivery of a pharmaceutical agent, the method comprising:
(a) forming a solid solution in the form of a compressible powder, said solid solution comprising a pharmaceutical agent mixed at the molecular level with a dissolution agent, said dissolution agent having a dissolution rate in the solvents found in the oral cavity, said dissolution rate of said dissolution agent being greater than said dissolution rate of said pharmaceutical agent; and
(b) physically mixing the powder with a buffering agent;
wherein said solid solution is created by wet granulation, co-melt, spray drying or freeze drying
wherein said buffering agent is selected from the group consisting of phosphate, carbonate, tris, tartrate, borate, acetate, and maleate buffers; and
wherein said pharmaceutical agent is an organic acid or an organic base".

IV. The decision of the opposition division can be summarized as follows:

(a) Claim 1 of the main request did not comply with the requirements of Article 123(2) EPC

(b) The subject-matter of the auxiliary request complied with the requirements of Articles 123(2) EPC. In particular, feature (b) of claim 1, objected to by the opponent, had a basis in original claim 2 and on page 7, lines 10 to 13, of the original application. The subject-matter of the auxiliary request complied also with the requirement of clarity.

(c) The description of the patent contained an example relating to the preparation of a composition according to claim 1. The subject-matter of the auxiliary request was therefore sufficiently disclosed.

(d) Starting from the disclosure of example 5 of D1 a two-fold selection of the active ingredient and of the buffer was to be made in order to arrive at the subject-matter of claim 1. The requirement of novelty was therefore met.

(e) Document D1 was the closest prior art for the assessment of inventive step. The subject-matter of claim 1 differed from the disclosure of D1 in that a buffer system was physically mixed with a solid solution in the form of a compressible powder. The experimental data included in the patent did not demonstrate that the distinguishing feature had a positive effect on the drug absorption, as claimed by the patent proprietor. The technical problem was therefore to be seen in the provision of an alternative transmucosal composition. Document D1 already taught the addition to the the solid solutions disclosed therein of various substances, including sodium bicarbonate which was a known

buffer. Accordingly, the subject-matter of the auxiliary request was not inventive.

V. The patent proprietor (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal filed on 4 December 2012 the appellant filed a main request consisting of thirteen claims.

Independent claim 1 of this request was identical to claim 1 of the auxiliary request forming part of the basis of the appealed decision (see point III above).

Independent claim 12 was based on the corresponding claim of the auxiliary request considered by the opposition division (see point III above) and it differed therefrom in replacing the feature "buffering agent" by "buffer system" and in moving the feature "wherein said solid solution is created by wet granulation, co-melt, spray drying or freeze drying" at the end of the claim.

With the statement setting out the grounds of appeal the appellant also submitted the following document:

D8: Confirmatory Experiment

VI. With letter dated 5 February 2016, the appellant submitted six sets of claims as auxiliary requests 1 to 6.

VII. The opponent replied to the proprietor's appeal by a letter dated 15 April 2013. Further submissions were filed by the opponent on 11 July 2014 and 3 February 2016.

VIII. In a communication sent in preparation of oral proceedings on 4 December 2015, the Board gave *inter alia* a positive opinion as to the novelty of the subject-matter of the main request and indicated that the objections raised by the respondent concerning the feature "compressible", in relation to Article 123(2) EPC and the requirement of sufficiency of disclosure, were not persuasive.

IX. With a letter dated 4 April 2016 the opponent withdrew the opposition.

X. Oral proceedings were held on 5 April 2016.

XI. With regard to the requirement of inventive step of the main request, the appellant essentially argued as follows:

The dosage form of claim 1 differed from the composition disclosed in the closest prior art D1 on account of the presence of a buffer system physically mixed with the solid solution. The pharmacokinetic study described in document D8, demonstrated the effectiveness of the formulation of claim 1 as oral transmucosal dosage form and showed its improved absorption over a formulation representing the teaching of D1. In the light of the data provided in D8 the technical problem was to be seen in the provision of an improved solid oral dosage form for oral transmucosal delivery of pharmaceutical agents that are organic acid or organic bases. None of the prior art documents suggested modifying the composition of D1 by adding a buffer, physically mixed with the solid solution, in order to increase the drug absorption. The requirements of Article 56 EPC were therefore met.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained according to the main request filed on 4 December 2012 with the grounds of appeal, or according to auxiliary requests 1 to 6 filed on 5 February 2016.

Reasons for the Decision

Procedural matters

1. Following the withdrawal of the opposition with letter of 4 April 2016, the opponent has ceased to be a party to the appeal proceedings as far as the substantive issues are concerned.

The competence of the Board for reviewing the first-instance decision to revoke the patent in suit is however not affected by the withdrawal of the opposition (cf. T629/90, OJ EPO 1992, 654).

Admissibility of document D8

2. Document D8 was submitted by the appellant with the statement setting out the grounds of appeal and forms therefore part of the basis of the appeal proceedings (Articles 12(1)(a) and 12(4) RPBA).

Pursuant to Article 12(4) RPBA the Board has the power to hold inadmissible evidence which could have been presented during the first-instance proceedings.

2.1 An essential aspect of the reasoning of the opposition division in its decision was the conclusion that the experimental data contained in the patent were not sufficient in order to substantiate an improved effect

for the formulation of the invention over the formulation of the closest prior art (see point IV (e) above).

2.2 Document D8 is an experimental report relating to the comparison of the drug absorption profiles of a formulation according to the invention and a formulation representing the teaching of the closest prior art. Thus, by filing document D8 the appellant addresses a key argument of the opposition division's reasoning.

The Board sees no reason for considering that the situation during the first instance proceedings was such that the appellant should have filed document D8 already at that stage.

2.3 In view of the above, the Board finds it appropriate to admit document D8 into the appeal proceedings.

Main request

3. The subject-matter of this request is substantially identical to the subject-matter of the auxiliary request refused by the opposition division (see point V above).

3.1 The opposition division decided that the amendments introduced in the then pending auxiliary request complied with the requirements of Article 123(2) EPC and that the amended claims were clear. Furthermore, the requirements of novelty and sufficiency of disclosure were also met (see point IV above).

3.2 The objections raised by the former opponent in appeal proceedings and the submissions on file, do not affect

the validity of the conclusions of the opposition division (see also points 4 to 6 of the notification sent by the Board on 4 December 2015). Hence, the requirements of Article 123(2), 84 and 54 EPC and the requirement of sufficiency of disclosure are met.

4. Inventive step

4.1 The invention addresses the problem of providing a solid oral transmucosal dosage form that provides higher absorption rates of the active substance (see [0001]).

4.2 Closest prior art

4.2.1 The Board agrees with the approach followed by the opposition division to consider document D1 as the closest prior art. This document relates to solid compositions suitable for use by administration and absorption through the mucosa of the buccal cavity (column 1, lines 15 to 35). Example IV relates *inter alia* to a composition containing a solid solution consisting of a mixture of polyoxyethylene glycol and bufotoxin, i.e. a drug which is an organic acid.

It was not disputed that the solid dosage form of claim 1 of the main request differs from the composition of example IV of D1 in that it comprises a buffer system which is physically mixed with the solid solution.

4.3 Technical problem

4.3.1 The experiments disclosed in document D8 relate to three different formulations containing droperidol as active ingredient.

The formulation CM, which is representative for the subject-matter of the request in suit, contains a solid solution of droperidol and polyethylene glycol physically mixed with a buffer consisting of a mixture of Na_2HPO_4 and citric acid. The second composition (CM-B), which represents the teaching of D1, differs from the composition CM in that it does not contain the buffer. The third composition (PM) is a physical mixture consisting of the same components of the composition CM.

Figure 1 shows that the composition CM provides the best result in terms of concentration of droperidol in the plasma.

The comparison of the results for the compositions CM and CM-B is of particular relevance in the context of defining the technical problem over document D1, in that it makes it possible to appreciate the positive effect on the absorption of the active ingredient of the distinguishing feature, i.e. the presence of a buffer, physically mixed with the solid solution,.

4.3.2 It follows that the technical problem over the disclosure of D1 is the provision of a formulation for oral transmucosal delivery comprising a drug in solid solution with an excipient, wherein said formulation provides a better absorption of the active ingredient.

4.4 Obviousness

4.4.1 Document D1 does not provide any indication on how to modify the compositions disclosed therein in order to enhance the absorption of the active ingredient.

In example V it is reported that various inert ingredients can be added to the solid solutions containing the drug before forming the final tablets. The list of suitable inert ingredients includes also sodium bicarbonate, i.e. a buffer substance. However, example V also indicates that these inert ingredients are optionally added to the composition "in order to adjust the hardness of the tablets and promote ease in the mechanical steps of tablet manufacture". Accordingly, this passage of D1 does not provide any relevant hint to the skilled person confronted with the problem of improving the absorption of the active ingredient.

4.4.2 None of the other prior art documents considered during the opposition and the appeal proceedings suggest to modify the composition of example IV of D1 by the addition of a buffer physically mixed with the solid solution in order to improve the absorption of the active ingredient.

4.5 It is therefore concluded that the solid dosage form defined in claim 1 of the main request is inventive.

4.6 Independent claim 12 relates to a process for preparing a solid dosage form for oral transmucosal delivery (see III above). Although this claim does not contain any reference to claim 1 in order to define the solid dosage form, it is evident, in view of the ingredients used and of the manufacturing process, that the formulation obtained by the method of claim 12 has the same features of the dosage form of claim 1.

Hence, also claim 12 meets the requirement of 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 main request filed with the grounds of appeal and a description to be adapted.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated