

Internal distribution code:

- (A) [] Publication in OJ
(B) [] To Chairmen and Members
(C) [X] To Chairmen
(D) [] No distribution

**Datasheet for the decision
of 9 February 2010**

Case Number: T 0360/07 - 3.3.01

Application Number: 00952815.9

Publication Number: 1230237

IPC: C07D 401/12

Language of the proceedings: EN

Title of invention:
Magnesium omeprazole

Patentee:
SHERMAN, Bernard Charles

Opponent:
Hexal AG

Headword:
Magnesium omeprazole/SHERMAN

Relevant legal provisions:
EPC Art. 54, 84, 100(a)

Keyword:
"Main request: Novelty (no) - low solvent content cannot
render the product novel"
"First to fourth auxiliary requests: Clarity (no)"
"Fifth auxiliary request: inventive step (yes) - non obvious
solution"

Decisions cited:
T 0990/96, T 0142/06

Catchword:
-



Case Number: T 0360/07 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 9 February 2010

Appellant: SHERMAN, Bernard Charles
(Patent Proprietor) 50 Old Colony Road
Willowdale
Ontario M2L 2K1 (CA)

Representative: Howard, Paul Nicholas
Carpmaels & Ransford
43-45, Bloomsbury Square
London WC1A 2RA (GB)

Respondent: Hexal AG
(Opponent) Industriestrasse 25
D-83607 Holzkirchen (DE)

Representative: Hamm, Volker
Maiwald Patentanwalts GmbH
Jungfernstieg 38
D-20354 Hamburg (DE)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 20 December 2006
revoking European patent No. 1230237 pursuant
to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: P. Ranguis
Members: C. M. Radke
C.-P. Brandt

Summary of Facts and Submissions

I. The Proprietor of the patent appealed against the decision of the opposition division to revoke European patent no. 1 230 237.

II. The opponent had requested to revoke the patent in its entirety based on grounds under Article 100(a) EPC (lack of novelty, inventive step and industrial applicability).

III. The following documents were *inter alia* cited during the opposition proceedings:

(D3) WO-A-00/30 612

(D4) Swedish patent application no. 9 804 003-3 filed on 23 November 1998 (priority document of (D3))

(D7) EP-A-0 124 495

(D8) U. Schöffling, *Arzneiformenlehre*, 2nd edn. 1993, Deutscher Apotheker Verlag, Stuttgart/DE, page 76

IV. The opposition division decided

- that the subject-matter of the claims was industrially applicable as the products could be made and used in any kind of industry;
- that the subject-matter of the claims was novel;
- that example 6 of document (D7) was considered to represent the closest prior art.

The problem to be solved was to provide an alternative form of magnesium omeprazole with a reduced solvent content. Knowing that crystals can trap solvents, the person skilled in the art would have tried to produce an amorphous product, namely by evaporating the solvent

fast, particularly by spray drying. The opposition division concluded that the subject-matter of claims 1 and 4 as granted was not based on an inventive step.

V. The decision under appeal was based on claims 1 to 13 as granted, the independent claims 1, 4 and 11 reading as follows:

- "1. A process of producing magnesium omeprazole, said process comprising the steps of:
- i) reacting magnesium with a lower alcohol to produce magnesium alkoxide in solution in the lower alcohol as solvent,
 - ii) adding omeprazole to the solution, the amount of omeprazole being about 2 moles per mole of magnesium, and
 - iii) flash-evaporating the solvent."
- "4. Magnesium omeprazole having a degree of crystallinity of under 67% and a residual organic solvent content of less than 7% by weight."
- "11. A solid pharmaceutical composition for oral administration comprising magnesium omeprazole of any of claims 4 to 10."

VI. The following additional documents were *inter alia* cited during the appeal proceedings:

- (D19)O. I. Corrigan, *Thermochimica Acta*, vol. 248
(1995), 245-258
(D20)US-A-5 013 833

(D22) C. Witschi and E. Doelker, *European Journal of
Pharmaceutics and Biopharmaceutics*, vol. 43
(1997), 215-242

(D28) Expert Opinion ("Gutachten") of Mr. K.-J. Steffens
dated 4 January 2010, 7 pages including cv

VII. The claims on file are

- claims 1-13 as granted (Main Request);
 - claims 1-13 of the First Auxiliary Request;
 - claims 1-10 of the Second Auxiliary Request;
 - claims 1-9 of the Third Auxiliary Request;
 - claims 1-8 of the Fourth Auxiliary Request; and
 - claims 1-3 of the Fifth Auxiliary Request;
- all auxiliary requests being submitted during the oral proceedings before the Board.

(a) The independent claims of the Main Request are cited under point V above.

(b) Claim 4 of the First Auxiliary Request reads as follows:

"4. Magnesium omeprazole having an equilibrium water content of 5% to 8% depending on the relative humidity of the air, a degree of crystallinity of under 67% and a residual organic solvent content of less than 7% by weight."

(c) Claim 4 of the Second and Fourth Auxiliary Requests and claim 3 of the Third Auxiliary Request differ from claim 4 of the First Auxiliary Request in that they require that

- the degree of crystallinity is under **25%**, where claim 4 of the Fourth Auxiliary Request additionally requires that
- the residual organic solvent content is less than **2%** by weight.

(d) The claims of the Fifth Auxiliary Request are identical with claims 1 to 3 of the Main Request. Its only independent claim 1 is cited under point V above.

VIII. The arguments of the Appellant as far as relevant for this decision may be summarised as follows:

- (a) The subject-matter of the claims is novel as example 2 of document (D3) neither discloses the flash evaporation of the solvent, nor a magnesium omeprazole having a residual organic solvent content of less than 7% by weight. Decision T 0142/06 applied to the present case rather than T 0990/96. The Appellant contended during the oral proceedings before the Board that the patent application (D3) enjoyed the priority of patent application (D4).
- (b) The expression "having an equilibrium water content of 5% to 8% depending on the relative humidity of the air" in the independent claims of the First to Fourth Auxiliary Requests was clear. It was well within the ability of the person skilled of the art to determine whether or not the equilibrium water content lies in the given range by equilibrating the product in air.

- (c) Example 6 of document (D7) was considered to represent the closest prior art.

The problem to be solved was the provision of an alternative form of magnesium omeprazole with reduced levels of residual solvent, as well as the provision of an alternative method of producing magnesium omeprazole having a lower content of organic solvent. This problem was solved as was evident from examples 2 and 3 of the patent in suit.

The method of claim 1 was not obvious because document (D7) did not teach to flash evaporate the solvent, whereas document (D8) which related to spray drying, was silent on the issue of residual solvent and did not teach to spray dry final products, whereas document (D22) only mentioned that microspheres might be spray dried. The examples of document (D20) did not show a considerable decrease of residual solvent when spray drying. The expert opinion (D28) was not based on any evidence filed.

IX. The arguments of the Respondent which are relevant for this decision may be summarised as follows:

- (a) The subject-matter of the product claims lack novelty in view of example 2 of document (D3). On the one hand document (D3) mentioned that the use of supercritical techniques such as in example 2 reduced the residual solvent in the product, on the other, decision T 0990/96 showed that the degree of purity of the product cannot render the

claimed subject-matter novel. Decision T 0142/06 dealt with a case where the purification of the product led to a new use. As this was not the case for magnesium omeprazole, this decision did not apply.

- (b) The expression "having an equilibrium water content of 5% to 8% depending on the relative humidity of the air" in the independent claims of the First to Fourth Auxiliary Requests was vague and rendered these claims unclear. The equilibrium water content of an amorphous sample was zero in anhydrous air and increased continuously with increasing humidity of the surrounding air. Therefore, such a sample might be considered to fall within the claim if the equivalent water content was measured at a place of high humidity while it might be deemed not to be covered by the claims when its equilibrium water content was determined in a less humid climate.
- (c) It also considered example 6 of document (D7) to be the closest prior art. The problem to be solved was to provide an alternative form of magnesium omeprazole and a process for preparing magnesium omeprazole having less residual solvent. The subject-matter of claim 1 was not inventive because spray drying was a method well known in the pharmaceutical industry, and often formed amorphous products, as was evident from documents (D8), (D19), (D20), (D22) and (D28). The contents of residual solvent achieved by spray drying in document (D20) were always within the range given in the present claims. Hence, the subject-matter

of claim 1 of the Main Request did not involve an inventive step.

X. The Board issued a communication as an annex to the summons. There it announced that it might be discussed whether or not a lower content of residual solvent rendered the subject-matter of claim 4 of the Main Request novel with reference to decision T 0990/96 (OJ EPO 1998, 489).

XI. The Appellant requested that the decision under appeal be set aside and the patent be maintained as granted or on the basis of one of the First to Fifth Auxiliary Requests submitted during the oral proceedings on 9 February 2010.

The Respondent requested that the appeal be dismissed.

XII. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Article 123 EPC

2.1 Neither were the present claims objected to under Article 123 EPC, nor was the opposition based on grounds under Article 100(c) EPC.

2.2 Main Request / Fifth Auxiliary Request

Claims 1 to 13 of the Main Request, namely the claims as granted, are based on claims 1-3 and 5-14 as originally filed.

Claims 1 to 3 of the Main Request are identical to the claims of the Fifth Auxiliary Request.

2.3 First Auxiliary Request

Claims 1 to 13 as granted are based on claims 1-3 and 5-14 as originally filed, with amendments in claims 1 and 4 which are based on page 10, lines 18-21 of the application as filed.

2.4 Second Auxiliary Request

Claim 1 is based on original claim 1 and page 10, lines 9-10 ("having a degree of crystallinity of under 25%") and page 10, lines 18-21 of the application as filed. Claim 4 is based on original claim 5 and page 10, lines 9-10 and 18-21 of the application as filed. Claims 2, 3, and 5-10 are based on original claims 2, 3, 6-8 and 12-14.

2.5 Third Auxiliary Request

Claim 1 is based on original claims 1 and 3 and page 10, lines 9-10 ("having a degree of crystallinity of under 25%") and page 10, lines 18-21 of the application as filed. Claim 3 is based on original claim 5 and page 10, lines 9-10 and page 10, lines 18-

21 of the application as filed. Claims 2 and 4-9 are based on original claims 2, 6-8 and 12-14.

2.6 Fourth Auxiliary Request

Claim 1 is based on original claim 1 and page 10, lines 9-10 ("having a degree of crystallinity of under 25%") and page 10, lines 18-21 of the application as filed. Claim 4 is based on original claim 7 and page 10, lines 9-10 and 18-21 of the application as filed. Claims 2, 3, and 5-8 are based on original claims 2, 3, 8 and 12-14.

2.7 All the amendments limit the scope of the claims.

2.8 Hence, the claims satisfy the requirements of Article 123 EPC.

3. Main Request / Novelty

3.1 The Respondent deemed the subject-matter of claim 4 not to be novel in view of document (D3). This document is a patent application published after the priority date of the patent in suit. Therefore, it has to be assessed to which extent document (D3) forms part of the prior art.

The patent in suit is based on an application filed on 04 August 2000, claiming the priority of an application filed on 16 November 1999. The validity of this priority was not disputed. It is based on the fact that the wording of the specification and the claims of the priority document is identical with the one of the application as originally filed.

Document (D3) was published on 02 June 2000. It is based on an application filed on 22 November 1999, claiming the priority of application (D4) filed on 23 November 1998.

The Appellant contended that the priority claimed in document (D3) was valid (see above under point VIII(a)). The Board is satisfied that the wording of document (D3) relevant for this decision, including the examples and claims of (D3), is identical with the one of the priority document (D4).

For these reasons, the relevant parts of document (D3) have a valid priority date prior to the one of the patent in suit and thus form part of the state of the art under Article 54(3).

In this context Article 54(3) EPC 2000 and Article 54(4) EPC 1973 apply (see the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000, special edition no. 1 OJ EPO 2007, 197, Article 1, paragraph 1).

- 3.2 Document (D3) discloses in example 2, experiment 2-1a the production of amorphous (S)-omeprazole magnesium salt by dissolving (S)-omeprazole magnesium salt in ethanol and introducing the solution into CO₂ as an antisolvent.
- 3.3 Whereas claim 4 of the Main Request requires that the magnesium omeprazole has "a residual organic solvent

content of less than 7% by weight", document (D3) does not specify the organic solvent content of the products disclosed therein.

Therefore, it is to be assessed whether or not this feature of claim 4 renders its subject-matter novel.

3.4 The Appellant considered decision T 0142/06 of 11 March 2008 to apply to this case rather than T 0990/96 (OJ EPO 1998, 489)(see under point VIII(a) above).

3.4.1 Decision T 0990/96 states that "... a document disclosing a low molecular chemical compound and its manufacture makes available this compound to the public in the sense of Article 54 EPC in all grades of purity as desired by a person skilled in the art" if "Conventional methods for the purification ... such as recrystallisation, distillation, chromatography, etc., which normally can be successfully applied in purification steps, are within the common general knowledge of those skilled in the art." (see point 7 of the reasons).

This statement is preceded by the following:

"It is common general knowledge that any chemical compound obtained by a chemical reaction will normally contain impurities for various reasons, such as side-reactions, incomplete conversion of starting materials, etc., and that it is not possible for thermodynamical reasons to obtain a compound, which is - in the strict sense - completely pure, i.e. totally free of any impurity." (see point 6 of the reasons).

This clearly indicates that the conclusion drawn in point 7 of the reasons for the decision not only applies to the type of impurity of the specific case (here the threo isomer in the respective erythro isomer) but to impurities in general, namely to any undesired compound present in the desired product.

- 3.4.2 The Appellant considered residual solvent not to be an impurity. It referred to US patent (D20) which defines that "references herein to 'impurities' are to be understood as not including residual solvents ..." (see column 2, lines 36-40). However, the word "herein" in this citation indicates that said definition was made only for the purpose of this document, possibly in contrast to the general meaning of the term "impurity".

Magnesium omeprazole is used as an active agent in pharmaceutical compositions (see document (D7), claims 8 to 11). High contents of organic solvents in general are undesirable and even moderate contents of methanol (the most preferred solvent according to the patent in suit) unacceptable in pharmaceutical compositions (see document (D22), the abstract and Table 1 on page 216; compare paragraphs [0001] and [0008] and claim 2 of the patent in suit).

Consequently, residual organic solvents in general and methanol in particular are to be regarded as impurities whenever present in magnesium omeprazole. Hence, the decision T 0990/96 might be relevant for the present case.

- 3.4.3 Decision T 0142/06 refers to T 0990/96 (see points 3.27 to 3.3.2 of the reasons). Under point 3.29 of the

reasons it bases its deviation from T 0990/96 on the fact that only the low content of chlorine in the latex enables the production of films of the desired oxygen barrier and boil blushing properties. The present case differs from the one of T 0142/06 in that here the desired therapeutical effect is only based on magnesium omeprazole as such. Therefore, the reasons to deviate from T 0990/96 indicated in T 0142/06 do not apply to the present case. Consequently, there is no reason to apply the conclusions drawn in T 0142/06 to the present case.

3.4.4 Decision T 0990/96 states that the absence of impurities cannot contribute to novelty only if said purification can be achieved by conventional means (see point 7 of the reasons). Such conventional means include the evaporation of the solvent as suggested in example 6 of document (D7). Furthermore, detailed methods for the effective removal of residual solvents by drying were known from the review article (D22)(see chapter 3.2 on pages 236-237).

3.4.5 Consequently, there is no reason to deviate from the decision T 0990/96. All the features of claim 4 are explicitly disclosed in example 2, experiment 2-1a, of document (D3) except the requirement that the residual organic solvent content has to be less than 7% by weight. As this range for the organic solvent content cannot contribute to novelty, the subject-matter of claim 4 of the Main Request lacks novelty under Article 54(3) EPC 2000 for the contracting states designated both in document (D3) and in the patent in suit (see Article 54(4) EPC 1973), namely for all the states designated in the patent in suit.

3.4.6 The Board can only decide on a request as a whole.
Hence, the Main Request is rejected.

4. First to Fourth Auxiliary Requests

4.1 Claim 4 of the First, Second and Fourth Auxiliary Requests and claim 3 of the Third Auxiliary Request differ from claim 4 as granted by the additional feature "an equilibrium water content of 5% to 8% depending on the relative humidity of the air" (see under point VII(b) and (c) above). It was under dispute whether or not this feature renders the claim unclear (see under point VIII(b) and IX(b) above).

4.2 Lack of clarity is no ground for opposition under Article 100 EPC. Nevertheless, the compliance with Article 84 EPC is to be examined in opposition and opposition appeal proceedings if an alleged lack of clarity arises from amendments after grant.

4.3 It was not under dispute that the "equilibrium water content" was to be interpreted as the property of the product to reach a certain water content if contacted with air. Hence, a magnesium omeprazole satisfying said requirement may have a water content outside the range of 5% to 8% if it is within that range after being equilibrated in humid air.

4.4 Neither does the patent disclose any details as to the relative humidity at which the "equilibrium water content" is to be determined nor did the Appellant claim that there was a standard method for its measurement.

4.5 It was undisputed that the "equilibrium water content" varied with the humidity of the air in which the sample was equilibrated. The claimed products are preferably substantially amorphous and thus do not contain or absorb any considerable amount of water of crystallisation. Consequently, their "equilibrium water content" will increase continuously with increasing humidity of the surrounding air.

4.6 For these reasons, the equilibrium water content of an amorphous magnesium omeprazole may be within the range of 5% to 8% if determined in relatively humid air, and may be below said range (and thus outside the scope of the claims) if measured in less humid air. Hence, the parameter "equilibrium water content" cannot be clearly and reliably determined. This renders the claims relating to this parameter unclear.

4.7 Therefore, the First to Fourth Auxiliary Request were rejected.

5. Fifth Auxiliary Request

The claims of this request are identical to claims 1 to 3 as granted. Hence, their examination is limited to the grounds for opposition under Article 100 EPC.

5.1 Novelty

The Respondent did not argue that the subject-matter of the claims of this request lacked novelty. It differs from the disclosure in documents (D3) and (D7) which do not teach the flash evaporation of the solvent. Hence,

the Board is satisfied that the subject-matter of these claims is indeed novel.

5.2 Inventive step

5.2.1 The closest prior art

Document (D3) forms part of the state of the art under Article 54(3) EPC and thus shall not be considered when assessing inventive step (see Article 56 EPC).

Therefore, the Board concurs with the parties that document (D7) may be regarded as the closest prior art.

This document discloses in example 6 steps (i) and (ii) of the process of present claim 1, namely

- i) reacting magnesium with methanol to produce magnesium methoxide in solution in methanol,
- ii) adding omeprazole to the solution, the amount of omeprazole being 2 moles per mole of magnesium.

The magnesium omeprazole is recovered by "Evaporation". No details are given as to the temperature, pressure and duration of said "Evaporation".

5.2.2 The problem to be solved

One of the problems addressed in the patent in suit was "... to produce magnesium omeprazole that has acceptable low levels of methanol, ... by a simple process." (see paragraph [0014]). A comparison between examples 2 and 3 of the patent in suit shows that spray drying the reaction mixture (see example 3) may produce a magnesium omeprazole having a methanol content of 0.7

% whereas drying the same reaction mixture under vacuum at 50 °C for four hours (see example 2) yields a product still containing 7.2 % by weight of methanol.

Example 2 of the patent in suit is supposed to be a comparative example according to example 6 of document (D7). This requires that the drying under vacuum at 50 °C for four hours in example 2 can be considered as an appropriate "Evaporation" in the sense of example 6 of document (D7). Taking into account that the magnesium omeprazole is isolated in example 5 of document (D7) from its **aqueous** solution by "drying in vacuum at 40° for 24h", and that methanol is more readily evaporated than water due to its much lower boiling point (i.e. about 65 °C at a pressure of 0.1 MPa), the evaporation step in example 2 of the patent in suit, namely drying in vacuum at 50 °C for four hours to evaporate the methanol, appears to be appropriate when repeating example 6 of document (D7). Therefore, the comparison between examples 2 and 3 of the patent in suit allows for a proper comparison between the process of example 6 of document (D7) with the one of claim 1 of the patent in suit. Consequently, that comparison shows that the problem mentioned above is solved in view of document (D7) by the features of present claim 1.

In view of the outcome of this decision it is not necessary to decide whether or not a more ambitious problem was solved.

5.2.3 The solution

Document (D7) indicates the temperature and duration of the drying step in examples 1, 4 and 5 where the

product is treated under reduced pressure at 40 °C "over night", "for 20h" or "for 24h", respectively. Hence, this document discloses drying at low temperatures for extended periods of time. In contrast to this, flash evaporation as required in present claim 1 means evaporation at high temperatures for short periods of time. Therefore, document (D7) as such does not render the subject-matter of claim 1 obvious.

Document (D8) discloses spray drying of pharmaceutical starting materials and of drug extracts (see the left column, the first sentence under the heading "Sprühtrockner"). Documents (D19) and (D28) mention that spray drying is a common method in the manufacture of pharmaceutical dosage forms (see the abstract of (D19); see (D28), pages 3 and 4). Neither of these documents indicates that organic solvent might be more efficiently evaporated from a solid product by spray drying.

Document (D20) discloses to decrease the residual solvent content of Cefuroxamine Axetil either by evaporation in vacuo of the solvent from its solution in a mixture of diisopropyl ether and ethyl acetate (see preparation 2 in column 7) or by spray drying of its solution in acetone (see examples 1 to 3 and 18). The residual solvent content after evaporation in vacuo (0.2 % by weight) was almost as low as the best results achieved by spray drying (see examples 1 and 18: 0.15 % by weight) and considerably smaller than that of the other spray dried products (see examples 2 and 3). On the one hand these results cannot be compared because the solvents are different (and so are their boiling points). On the other hand, neither these examples nor

the general teaching of the documents indicates that spray drying might more efficiently decrease the residual organic solvent content than evaporation in vacuo.

Document (D22) reports on the drying of pharmaceutical products in order to reduce their residual solvent content (see the first and last sentences of the abstract). It mentions that the residual methylene chloride content in microspheres was 2.1 % when prepared by the solvent evaporation method and 0.3 % when prepared by spray drying (see page 237, right column, lines 14-18). However, these microspheres have walls made of a polymer which may hinder the escape of solvent and thus requires special drying techniques (see page 236, right column, lines 2-3). Hence, the person skilled in the art could not have expected that the same effect occurred when drying magnesium omeprazole.

5.2.4 For these reasons, the subject-matter of claim 1 of the Fifth Auxiliary Request involves an inventive step. The same applies to the subject-matter of claims 2 and 3 which are dependent from claim 1.

6. Neither did the Appellant argue that the claims of the Fifth Auxiliary Request contravened the requirements of any other provision of the EPC nor has the Board found any reason to do so.

Hence, the claims of the Fifth Auxiliary Request meet the requirements of the EPC.

7. Remittal

The claims of the Fifth Auxiliary Request reduce the scope of the claims as granted considerably. In order to ensure that the description be properly adapted under Rule 42(1)(c) EPC to the claims thus amended, the Board exercises its discretion under Article 111(1) EPC by remitting the case to the department of first instance.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of the Fifth Auxiliary Request (claims 1-3), filed at the oral proceedings and after any necessary amendment of the description.

The Registrar:

The Chairman:

B. Atienza Vivancos

P. Ranguis