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**Datasheet for the decision  
of 6 February 2014**

**Case Number:** T 0065/10 - 3.3.07

**Application Number:** 03029897.0

**Publication Number:** 1550439

**IPC:** A61K9/16, A61K9/20, A61K38/11

**Language of the proceedings:** EN

**Title of invention:**  
Method for preparing a solid dosage form of desmopressin

**Patent Proprietor:**  
Ferring B.V.

**Opponents:**  
Pliva Pharma Limited  
PH&T S.p.A.  
Alpex Pharma S.A.

**Headword:**

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
Inventive step - reasonable expectation of success (yes)

**Decisions cited:**

**Catchword:**



**Beschwerdekammern  
Boards of Appeal  
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Case Number: T 0065/10 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 6 February 2014**

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**Decision under appeal:**      **Decision of the Opposition Division of the  
European Patent Office posted on 26 October 2009  
revoking European patent No. 1550439 pursuant to  
Article 101(3) (b) EPC.**

**Composition of the Board:**

**Chairman:**            J. Riolo  
**Members:**            A. Uselli  
                             M. Tardo-Dino

## Summary of Facts and Submissions

- I. The appeal of the patent proprietor (appellant) lies against the decision of the opposition division announced at oral proceedings on 1 September 2009 to revoke European patent N°1550439.

The patent was granted with 15 claims. Claim 1 read as follows:

"1. A method for the preparation of a solid dosage form of desmopressin, or a pharmaceutically acceptable salt thereof, comprising granulating desmopressin or a pharmaceutically acceptable salt thereof and at least one excipient, carrier or diluent or mixture thereof in a fluid bed granulation apparatus, wherein the resulting desmopressin containing granulate is suitable for compression to a pharmaceutically acceptable tablet."

- II. Three oppositions were filed against the patent as a whole. They were based on Article 100(a) together with Articles 54 and 56 EPC and Article 100(b). The opponents relied *inter alia* on the following documents:

D1: US 5,047,398

D2: WO 03/094886

D4: WO 95/255341

D5: WO 95/01185

D9: CRC Granulation technology for Bioproducts, Kiran L Kadam, 1991

D28: EP 1500390

D33: EP 1473029

D37: Declaration by Dr. S. E. Negro Alvarez

D41: FDA Perspective on Peptide Formulation and Stability Issues, 87, 11, 1998.

- III. The decision of the opposition division was based on the patent as granted as main request and on four auxiliary requests filed on 30 July 2009.
- IV. In its decision the opposition division came to the following conclusions:
- a) The patent as granted met the requirements of Article 100(b).
  - b) The subject-matter of the granted claims was considered to lack novelty pursuant to Article 54(3) EPC in view of post-published documents D28 and D33. D28 and D33 were also prejudicial to the novelty of claim 1 of auxiliary requests 1 and 2.
  - c) Auxiliary requests 3 and 4 met the requirements of Article 123(2) and (3) EPC and Article 54 EPC. Starting from D2 as closest state of the art, the distinguishing feature of the claimed process was the use of a fluid bed granulation apparatus which resulted in a reduction of the processing time and better flow properties of the granulate. The objective technical problem was formulated as the provision of an improved wet granulation method for desmopressin. The solution proposed by the opposed patent was obvious since it was already known *inter alia* from D9 that the fluid bed technology required a shorter processing time and provided better flow properties of the granulate.
- V. The patent proprietor lodged an appeal against that decision. With the statement of grounds dated 5 March 2010, he requested as main request the maintenance of the patent as granted and submitted two auxiliary requests.

Claim 1 of auxiliary request 1 was based on claim 1 of the granted patent with the addition at the end of the claim of the following feature:

"..., wherein the preparation of said granulate comprises adjusting fluidising air flow and processing temperature and time."

Claim 1 of auxiliary request 2 was based on claim 1 of the granted patent with the addition at the end of the claim of the following feature:

"..., wherein the granulate contains PVP as a binder, wherein a granulation liquid containing water as sole solvent is utilised, and wherein the preparation of said granulate comprises adjusting fluidising air flow and processing temperature and time."

- VI. Opponent 2 (respondent 2) replied to the statement of grounds of appeal with a letter dated 28 October 2010.
- VII. On 6 February 2014, oral proceedings were held before the Board. They were attended by the appellant, opponent 1 (respondent 1) and respondent 2.
- VIII. The appellant's arguments can be summarised as follows:
  - a) Having regard to the inventive step of all the requests, the closest prior art was represented by D2, which disclosed in comparative example 2 a process for preparing desmopressin tablets by a method of conventional wet granulation. The method according to the claims of the patent differed from the procedure of D2 on account of the use of a fluid bed granulation apparatus. This difference resulted in a shorter processing time, as shown by

the examples of the patent. The technical problem was therefore to be formulated as the provision of an accelerated method of providing a solid form of desmopressin suitable for use as a pharmaceutical. Due to its chemical structure of a peptide containing a disulphide bond, desmopressin was to be regarded as a labile molecule. The labile nature of this molecule was also confirmed by the teaching of documents D1, D4, D5 and D41. Accordingly, aware of these problems of stability, the skilled person would not have envisaged granulating desmopressin in a fluid bed granulation apparatus with a reasonable expectation of success. Other technologies for providing solid forms of pharmaceuticals were already known, as illustrated in D37. The skilled person would therefore have opted for these alternative solutions.

- b) The process according to the second auxiliary request differed from the process of D2 also in the use of a granulation liquid containing water as sole solvent. The skilled person would have not considered using water as sole solvent because this would have required a higher drying temperature with an increased risk of decomposition of desmopressin.

IX. The arguments of respondents 1 and 2 can be summarised as follows:

- a) Comparative example 2 of D2 represented the starting point for the assessment of inventive step. The difference was to be seen in the use of a fluid bed granulation apparatus. The formulation of the technical problem had to take into account



that a wet granulation process for preparing a solid dosage form of desmopressin was already known from D2. Therefore, the technical problem was seen as the provision of a less time-consuming wet granulation method for desmopressin. The solution of using a fluid bed apparatus was obvious in particular in the light of the teaching of D9. There were no documents supporting the assertion of the appellant that the skilled person would have considered desmopressin as a very labile molecule that could not be processed in a fluid bed apparatus.

- b) The wording of claim 1 of auxiliary request 2 did not exclude the presence of other solvents in addition to water. Therefore, the arguments put forward by the appellant with regard to the inventiveness of this request were of no relevance. In any case, D9 suggested on page 13 the use of water as the solvent of choice.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted or on the basis of one of the two sets of auxiliary requests filed with letter of 5 March 2010.

XI. Respondents 1 and 2 requested that the appeal be dismissed.

## **Reasons for the Decision**

### *1. Main request - Inventive Step*

1.1 The invention relates to a method for the preparation of a solid dosage form of desmopressin. It is explained in the description that desmopressin-based tablets

compressed from granulates are already known in the art. The procedure for preparing these granulates suffers from the drawbacks of being time-consuming and labour-intensive (see [0003] to [0005]). The invention of the patent aims therefore at the provision of a process overcoming these problems. It is furthermore stated in the description that an additional advantage of the method is the excellent flow properties for compression of the granulate ([0013]).

- 1.2 The Board concurs with the parties that D2 represents the closest state of the art. This document discloses in comparative example 2 a method for preparing a desmopressin-containing tablet involving "a conventional wet granulation process". The process of claim 1 differs from the method disclosed in D2 in that the granulation of desmopressin is carried out in a fluid bed apparatus.
- 1.3 The technical problem as set out in the description of the invention may be seen in the provision of a process for preparing a desmopressin-containing granulate which is less time-consuming and which provides a granulate having excellent flow properties (see [0005] and [0013]).
- 1.4 It must therefore be investigated whether there is sufficient evidence supporting the alleged effects.
  - 1.4.1 Comparative example 1 and example 2 of the patent relate to the preparation of tablets containing desmopressin acetate, by wet granulation and by fluid bed granulation respectively. It was undisputed by the parties that the method of wet granulation disclosed in comparative example 1 can be regarded as "a conventional wet granulation process" according to the

terminology used in comparative example 2 of D2. It was furthermore not contested by the respondents that the difference in duration of the procedures of comparative example 1 and example 2 (ca. 20 hours vs ca. 40 minutes) is evidence that the problem of providing a less time-consuming process has effectively been solved by the method according to claim 1. On the other hand, no evidence is available to show any difference in the flow properties of the granulate obtained according to the process of the invention as compared with the granulate obtained by a conventional procedure.

1.4.2 In view of the above, the technical problem effectively solved over D2 can be seen in the provision of a granulation method of desmopressin requiring shorter processing time. In contrast to the formulation proposed by the appellant, it is considered necessary to include in the definition of the problem a reference to a granulation method, since this is already part of the prior disclosure of D2.

1.5 The question to be answered is whether the solution proposed in claim 1 would have been obvious to a skilled person in the light of the prior art.

1.5.1 The technologies available for the granulation of bioproducts are reviewed and discussed in D9. Table 4 of page 6 provides an overview of these technologies and compares their major features. The fluid bed granulation is described as being useful for the granulating, drying and coating of pharmaceuticals and enzymes. The major benefits associated with this technology are listed on page 65. These include in particular a reduction in the processing time (lines 9-10). This aspect is underlined also on page 54 (see second paragraph) where it is explained that the

advances in equipment design "have made granulating in the fluidized bed a more precise, reproducible, and trouble-free process leading to improved product quality and shorter process time for the industrial user".

1.5.2 The skilled person looking for a granulation method for desmopressin, less time-consuming than the method disclosed in the comparative example of D2, would therefore find in D9 a clear suggestion to opt for the fluid bed technology. This conclusion is not affected by the argument that other technologies for preparing solid forms, including granulates, were already known before the priority date, as explained in D37 (page 7, paragraph 2.2).

1.6 The appellant argued that a person skilled in the art would not attempt to granulate desmopressin in a fluid bed apparatus with a reasonable expectation of success. He based his argument on the assumption that desmopressin is a very labile compound. Accordingly, the skilled person would not consider granulation with a fluid bed apparatus to be a valid option, in view of the high risk of degradation of the molecule.

1.6.1 However, documents D1, D4, D5 and D41, cited by the appellant in support of this argument, do not convey the idea that a skilled person would have any particular concern as to the stability of demopressin in relation to a possible degradation during granulation in a fluid bed apparatus. For instance, D5 merely indicates that solutions of desmopressin are not stable at room temperature for long periods and need to be refrigerated (see page 1, lines 21 to 30). Similar considerations are made in D1 (see column 1, lines 42 to 44). Hence, these documents address issues

pertaining to the storage conditions of liquid pharmaceutical compositions containing desmopressin. These issues are of no relevance in the context of the invention of the opposed patent, which concerns a process for manufacturing a granulate to be used in the preparation of a solid dosage form. The same conclusion is to be drawn with respect to the observations made in D4 (see page 1, lines 20 to 25) and again in D1 (column 2, lines 29 to 33) having regard to the lack of stability *in vivo* of desmopressin. The Board considers that information concerning the fate of desmopressin after administration would have no impact on the decisions to be taken by a skilled artisan confronted with a problem of pharmaceutical technology, namely the preparation of a granulate. The document which more closely addresses issues of stability of desmopressin in relation to a granulation process is D41 (see page 1332, last paragraph of left column). In this document it is stated that when tablets containing certain peptides such as desmopressin are manufactured by a wet granulation process "precautions need to be taken to monitor the possible degradation of the peptide during the drying process". However, in the Board's opinion, this statement cannot be read as a warning to avoid the wet granulation of these peptides in view of a high risk of degradation. Instead, D41 simply indicates that provided that certain precautions are followed, some peptides such as desmopressin can be treated in a wet granulation process. Thus, also this document fails to establish the existence of any motivated concern as to the possibility of granulating desmopressin in a fluid bed apparatus.

- 1.6.2 The appellant's argument concerning the reasonable expectation of success is also not convincing in view of the fact that from D2 it was already known that

desmopressin can resist wet granulation treatment. In the absence of any fact suggesting that the fluid bed technology would be more stressful for the stability of the compound to be granulated than the conventional technology used in D2, a skilled person would have no concrete reasons to fear degradation of desmopressin during granulation in a fluid bed apparatus.

1.7 It follows from the above that the main request does not meet the requirements of Art. 56 EPC.

2. *Auxiliary request 1 - Inventive step*

2.1 Claim 1 of this request differs from claim 1 of the main request only in the introduction of a feature indicating that the process comprises a step of "adjusting fluidising air flow and processing temperature and time". The appellant maintained that this request involved an inventive step, relying on the same arguments submitted in respect to the main request.

2.2 The adjustment of certain process parameters such as air flow, temperature and time is a mandatory activity which does not require any inventive skill. Accordingly, this request must be considered obvious for the same reasons given in respect of the main request.

3. *Auxiliary request 2 - Inventive step*

3.1 Compared with auxiliary request 1, this request contains the additional indication that PVP is used as binder and that the granulation liquid contains water as sole solvent.

- 3.2 Since also in comparative example 2 of D2 PVP is used as binder, this feature does not introduce any further distinction over the closest prior art.
- 3.3 Concerning the use of water as sole solvent in the granulation liquid, the appellant argued that the absence of organic solvents implies the use of a higher drying temperature and therefore an increased risk of decomposition of desmopressin. Thus, the argument that a skilled person would have no reasonable expectation of success applies even more in the context of auxiliary request 2.
- 3.4 In respect of this argument, it is observed that in comparative example 2 of D2 the granulation liquid is a mixture of water and ethanol. The Board has some doubts as to whether the feature "water as sole solvent" can be regarded as a distinguishing feature over the disclosure of D2, given that claim 1 contemplates the presence in the granulation mixture of excipients, carriers and diluents and therefore also of ethanol. These concerns were communicated by the Board in a communication sent to the parties in preparation of the oral proceedings. In any case, even if the granulation liquid is regarded as a further distinguishing feature, the process of auxiliary request 2 is considered obvious for the following reasons.
- 3.5 As explained in 1.7.1 and 1.7.2, the Board is not convinced that the skilled person would regard desmopressin as a labile compound that could not be processed in a fluid bed apparatus without risking the decomposition of the molecule. This conclusion is independent of any consideration concerning the granulation liquid used, and it applies therefore also when said liquid contains only water. Thus, the

observations made in respect of the main request apply also to the present request. Furthermore, as pointed out by the respondents, D9 indicates that for a granulation process, water is to be regarded as the solvent of choice (page 13, line 7). Thus, the prior art suggests the granulation liquid of auxiliary request 2.

- 3.6 As a consequence, also the subject-matter of auxiliary request 2 does not involve an inventive step within the meaning of Article 56 EPC.
4. Since none of the requests satisfies the requirements of Article 56, a decision on the other grounds of opposition is not necessary.

## Order

### **For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:



L. Fernández Gómez

J. Riolo

Decision electronically authenticated