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**Datasheet for the decision  
of 8 December 2015**

**Case Number:** T 0885/12 - 3.3.07

**Application Number:** 03784384.4

**Publication Number:** 1530457

**IPC:** A61K9/14, A61K9/16

**Language of the proceedings:** EN

**Title of invention:**

PHARMACEUTICAL COMPOSITIONS OF DRUGS IN SEMI-ORDERED FORM AND  
POLYMERS

**Patent Proprietor:**

BEND RESEARCH, INC.

**Opponents:**

AbbVie Deutschland GmbH & Co. KG  
Elend, Almut Susanne  
Sandoz GmbH /  
Sandoz International GmbH

**Relevant legal provisions:**

EPC Art. 100(b)

**Keyword:**

Sufficiency of disclosure - (no)



**Beschwerdekammern  
Boards of Appeal  
Chambres de recours**

European Patent Office  
D-80298 MUNICH  
GERMANY  
Tel. +49 (0) 89 2399-0  
Fax +49 (0) 89 2399-4465

Case Number: T 0885/12 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 8 December 2015**

**Appellant:**  
(Patent Proprietor)

BEND RESEARCH, INC.  
64550 Research Road  
Bend, OR 97701-8599 (US)

**Representative:**

Beckmann, Claus  
Kraus & Weisert  
Patentanwälte PartGmbH  
Thomas-Wimmer-Ring 15  
80539 München (DE)

**Respondent:**  
(Opponent 1)

AbbVie Deutschland GmbH & Co. KG  
Max-Planck-Ring 2a  
65205 Wiesbaden (DE)

**Representative:**

Thalhammer, Wolfgang  
Reitstötter, Kinzebach & Partner (GbR)  
Patentanwälte  
Sternwartstrasse 4  
81679 München (DE)

**Respondent:**  
(Opponent 2)

Elend, Almut Susanne  
Venner Shipley LLP  
Byron House  
Cambridge Business Park  
Cowley Road  
Cambridge CB4 0WZ (GB)

**Representative:**

Elend, Almut Susanne  
Venner Shipley LLP  
Byron House  
Cambridge Business Park  
Cowley Road  
Cambridge, Cambridgeshire CB4 0WZ (GB)

**Respondent:**  
(Opponent 3)

Sandoz GmbH /  
Sandoz International GmbH  
Biochemiestr. 10  
Industriestr. 25 - 83607 Holzkirchen / DE  
6250 Kundl (AT)

**Representative:** Sandoz GmbH  
Biochemiestrasse 10  
6250 Kundl/Tirol (AT)

**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted on 13 February 2012 revoking European patent No. 1530457 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. 1 530 457, based on European application 03784384.4, was granted on the basis of fifteen claims.

Claim 1 as granted read as follows:

"1. A composition comprising:  
(a) a solid comprising a low-solubility drug and a concentration-enhancing polymer;  
(b) said concentration-enhancing polymer being present in said composition in a sufficient amount so that said composition provides enhanced concentration of said low-solubility drug in a use environment relative to a first control composition consisting essentially of a mixture of an equivalent amount of said drug in crystalline form and an equivalent amount of said concentration-enhancing polymer; and  
(c) wherein at least a portion of said drug is present in drug-rich regions and said drug-rich regions are interspersed throughout drug-poor, polymer-rich regions, and wherein at least 20 wt% of said low-solubility drug is in a semi-ordered state".

- II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC) and it was not sufficiently disclosed (Article 100(b) EPC). The following documents were among those cited during the first-instance proceedings:

D29: Introduction to X-ray Powder Diffractometry, 1996, pages 89-91 and 356-385

D30: Solid-State Chemistry of Drugs, 2nd Edition, 1999, pages 64-66 and 119-125

- III. By decision posted on 13 February 2012, the opposition division revoked the patent. The decision was based on a single set of claims filed on 25 February 2011. Claim 1 of this request was identical to claim 1 as granted.
- IV. In its decision the opposition division came to the conclusion that the requirement of sufficiency of disclosure was not met *inter alia* because the description did not provide enough information as to the methods for determining the amount of drug in semi-ordered state.
- V. The patent proprietor (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal filed on 25 June 2012 the appellant submitted the following document:
- D31: Experimental report by Dr Scott B. McCray (dated 15 June 2012)
- VI. On 22 October 2014 the parties were summoned to attend oral proceedings scheduled to take place on 8 December 2015. By letter sent on 27 October 2014, the appellant notified the Board of its intention not to attend them.
- VII. The Board issued a communication pursuant to Article 15(1) RPBA on 15 September 2015. In paragraph 2.1.3 of this communication the Board underlined the presence of some deficiencies in relation to the methods for the quantitative determination of the amount of drug in semi-ordered state. It was concluded that these deficiencies could affect the possibility of carrying out the invention.

- VIII. Respondents 1 and 2 informed the Board on 10 November 2015 and 25 November 2015 respectively, of their intention not to attend the oral proceedings.
- IX. The oral proceedings held on 8 December 2015 were attended only by respondent 3.
- X. In the context of the assessment of the requirement of sufficiency of disclosure, the appellant submitted in writing the following arguments as to the possibility of quantifying the amount of drug in semi-ordered state:
- The description of the patent illustrated several techniques which could be used to determine the amount of drug in semi-ordered state. These included in particular the powder X-ray diffraction (PXRD) and the differential scanning calorimetry (DSC) which were used to analyse the products of examples 1 to 3. PXRD and DSC were well established analytical techniques that the skilled person was well acquainted with. Documents D29 and D30 confirmed that PXRD was an useful technique for quantitative assessments. Document D30 described quantitative analysis based on the use of DSC. The possibility of using DSC for an exact quantitative determination of the amount of drug in semi-ordered state was furthermore illustrated in the experimental report D31.
- XI. Counter arguments were submitted by all the respondents. The issue as to whether the patent sufficiently disclosed a method for determining the amount of drug in semi-ordered state was elaborated in particular by respondent 3. Its arguments in this regard are summarised as follows:

Measuring the amount of drug in semi-ordered state was essential to carrying out the invention of the patent in suit. While the examples of the patent alleged that the amount of drug in semi-ordered state could be determined by PXRD or DSC, there was no detailed information on how these techniques were to be used for that purpose. Example 1 used a method based on the comparison of the PXRD peaks area to calculate the amount of drug in semi-ordered state. However, there were no indications about how to use the peak area information to arrive at the percentage of drug in semi-ordered state. In the same way, there was also no explanation on how to use the peak width information to determine the amount of drug in semi-ordered state. In example 3 the percentage of semi-ordered state was determined by a DSC method which consisted in measuring the heat absorbed by a melting crystalline phase. However, this method did not make it possible to discern between bulk crystalline and semi-ordered drug. The same conclusion applied to the measurements of the endothermic events associated to the crystallisation of the amorphous drug and to the determination of the glass transition temperature. These methods could also not be used to discern between bulk crystalline and semi-ordered drug.

XII. The appellant requested in writing that the decision under appeal be set aside and the patent maintained according to the set of claims submitted on 25 February 2011. The appellant furthermore requested that the case be remitted to the department of first instance for examination of the grounds of opposition not dealt with in the decision under appeal.

XIII. The respondents requested that the appeal be dismissed. Furthermore, in the event that the patent were found to

comply with the requirement of sufficiency of disclosure, the respondents requested the Board to consider also the remaining grounds of opposition.

## **Reasons for the Decision**

### Sufficiency of disclosure

1. The subject-matter of claim 1 relates to a pharmaceutical composition comprising a low-solubility drug, at least 20 wt% of which is in a semi-ordered state.

A "semi-ordered state" is defined in paragraph [0035] of the patent as a state in which the "drug is less ordered than drug in bulk crystalline form alone" and "the drug has greater order than amorphous drug". In the same paragraph it is explained that "bulk crystalline form alone" means that the crystals exhibit long range order, for example, having at least about 100 repeat units in the shortest dimension. Thus, in a semi-ordered state the drug may be in the form of extremely small crystals of less than 100 repeat units in at least one dimension.

2. The opposition division came to the conclusion that the the invention was not sufficiently disclosed *inter alia* because the patent did not provide enough information as to the methods for determining the amount of drug in semi-ordered state.

This issue will be considered in the following sections.



2.1 Two principal techniques are disclosed in the patent for determining the amount of drug in semi-ordered state, namely the powder X-ray diffraction (PXRD) and the differential scanning calorimetry (DSC). In paragraph [0043] it is furthermore stated that "another method for evaluating whether the drug is semi-ordered is spectroscopic analysis". It is however not indicated in the rest of the description whether and how methods based on spectroscopic analysis can be used also to quantify the amount of drug in semi-ordered state.

In view of the above, the Board will consider in the following paragraphs whether the information disclosed in the patent with regard to PXRD and DSC would enable the skilled person to determine the amount of drug in semi-ordered state.

2.2 *Powder x-ray diffraction (PXRD)*

2.2.1 The use of PXRD for a quantitative analysis of the semi-ordered state is briefly discussed in paragraph [0216] of the description which is part of example 1. The amount of drug in semi-ordered state in the sample of example 1B is calculated by comparing the areas under the peaks in the region  $16-19.5^{\circ} 2\theta$  of the diffraction patterns of the tested sample and control 1D, i.e. a composition containing the same drug of example 1B in crystalline form. The result obtained is that 55% of the drug of example 1B is estimated to be in semi-ordered state.

Example 1 fails however to provide an indication on how the data concerning the areas under the peaks are compared in order to provide the amount of drug in semi-ordered state. In particular, it is not stated in example 1 which calculations are to be made in order to

generate the percentage of semi-ordered state from the data concerning the areas under the peaks. Nor is this information to be found in any other part of the patent. The skilled person is therefore left without any guidance as to the way of processing the data concerning the areas under the peaks gathered from the PXRD patterns in order to determine the amount of drug in semi-ordered state.

2.2.2 A further PXRD parameter considered in the patent is the full-width at half-height of the principal peaks. In paragraph [0037] of the patent it is explained that the PXRD peaks of a drug in semi-ordered state may be broader than the peaks of the same drug in bulk crystalline state. A measure of the peak's broadness is the full-width at half-height. The principal peaks of a drug in semi-ordered state have a full-width at half-height which is greater than that of the corresponding peaks of the same drug in bulky crystalline state.

However, as for the peaks area, also in respect of the peaks width no information is given in the patent on how to use this parameter to measure the amount of drug in semi-ordered state. The results disclosed in the examples do not demonstrate any apparent correlation between changes in the peaks width and percentage of semi-ordered drug. Hence, also an analysis of these results would not help a skilled person to derive any clear rule for converting an increase of peak width, from bulky crystalline drug to semi-ordered drug, into a value representing the amount of drug in semi-ordered state.

2.2.3 Referring to documents D29 and D30 the appellant argued that PXRD was well-known before the priority date as an useful tool for quantitative analysis.

The Board notes that both documents are extracts from textbooks which can be considered to illustrate the common general knowledge in the field of X-ray powder diffractometry. Indeed these documents discuss the possibility of using PXRD for quantitative analysis. However, neither D29 nor D30 disclose methods for determining the amount of a substance in semi-ordered state by the use of PXRD or of any other analytical method. Hence, these documents are not helpful to close the information gap of the patent.

2.2.4 Conclusion on PXRD

In view of the foregoing, the Board concludes that the information contained in the patent in suit as to the PXRD is not sufficient to enable a skilled person to use this technique to make quantitative assessments of the semi-ordered state. Nor would the common general knowledge provide the skilled person with any relevant information in this respect.

2.3 *Differential scanning calorimetry (DSC)*

2.3.1 Thermal methods based on the use of the DSC technique are discussed in paragraphs [0040] to [0042] of the patent in suit. It is reported that the DSC can be used to measure the glass transition temperature (T<sub>g</sub>) of the pharmaceutical compositions or to measure exothermal or endothermal events.

2.3.2 In paragraph [0040] it is explained that the T<sub>g</sub> of a composition of drug and polymer is a function of the

amount of drug that is in the amorphous form. Respondent 3 observed that the Tg cannot discern between bulk crystalline and semi-ordered state. This statement has never been disputed by the appellant and is not in conflict with the considerations made in the paragraph [0040] of the patent in suit in which the issue of distinguishing bulk crystalline and semi-ordered state is ignored. However, in view of the definition given in the patent of "semi-ordered state" (see point 1 above) this distinction is essential in order to determine the amount of drug in semi-ordered state. Indeed the patent does not explain how to calculate the amount of drug in this state from the Tg of the composition.

2.3.3 Similar considerations apply in respect to the use of the DSC for the determination of exothermal events. As explained in paragraph [0041], drug which is amorphous may exhibit an endothermal event upon heating as a result of the conversion into crystalline form due to the heat of crystallization. However, as observed by respondent 3, since both the bulk crystalline and semi-ordered state are crystalline forms, the measurement of the heat of crystallization cannot discern between these two states. The appellant did not submit any argument in this respect. The experimental report D31 submitted by the appellant during the appeal phase refers to a method for determining the amount of drug in semi-ordered state based on the measurement of the heat of crystallization. However, also in this document no reference is made to the issue of distinguishing bulk crystalline and semi-ordered state.

2.3.4 The endothermal events considered in the patent are associated with the melting of the drug in semi-ordered

state or in bulk crystalline form. It is explained in paragraph [0042] that the endothermal events of the two forms may be different. The onset of the event for the semi-ordered drug and its peak (i.e. the maximum temperature) may be shifted to lower temperatures. Moreover the endothermal event of the semi-ordered drug can exhibit a broader width.

The general information provided in [0042] of the patent, suggests that DSC can be used for a qualitative distinction between semi-ordered state and bulk crystalline state by determining the endothermal events associated with the melting of the drug. It remains unclear, however, how this technique can be used for a quantitative assessment.

The disclosure of example 3 does not provide in this respect more information than the description. In this example the percentage of drug in semi-ordered state is obtained by comparing the endothermic events of the tested sample and of a sample containing the same drug in crystalline form. It is reported that about 58% of the drug of the tested sample is in semi-ordered state. However, as for the method based on PXRD analysis (see point 2.2.1 above), no indication is given on how the DSC data relating to the endothermic events are processed in order to provide the percentage of drug in semi-ordered state.

2.3.5 The appellant argued that the use of DSC for quantitative analysis was part of the general knowledge of the skilled person. Document D30 was mentioned in this regard. However, as already discussed above (see point 2.2.3 above), document D30 does not provide any information as to the determination of the amount of a substance in semi-ordered state. Hence, this document

cannot support the conclusion that the skilled person could remedy the deficiency of information of the patent by relying on his general knowledge.

#### 2.3.6 Conclusion on DSC

It follows from the considerations made above that neither the patent nor the common general knowledge provides the skilled person with the necessary information on how to use the DSC analysis in order to determine the amount of a substance in semi-ordered state.

### 3. Conclusion on the disclosure of the invention

3.1 Providing a sufficient disclosure as to the methods for determining the amount of drug in a semi-ordered state, is an important factor for enabling the skilled person to perform the invention.

3.2 The general procedure disclosed in the patent in suit for preparing the drug in semi-ordered state consists essentially of two steps, namely the formation of an amorphous dispersion comprising the drug and a concentration-enhancing polymer and the conversion of at least 20% of the drug into a semi-ordered state (see section "Preparation of Compositions"). The step of conversion, is disclosed in paragraphs [0097] to [0112]. One of the methods, which is used in the three examples of the patent, consists in heating the dispersion to a temperature  $T$ , such that the ratio  $T_g/T$  is less than about 1.0. An alternative method involves the addition of a "mobility enhancing agent", such as water or an alcohol (see [0100]). Often the conversion requires both heating and adding a mobility enhancing

agent (see [0103]) and takes place in more than one day (see [0104] and examples 2 and 3).

3.3 The quantitative assessment of the drug in semi-ordered state makes it possible to verify whether the process of conversion of the dispersion is complete, i.e. whether at least 20% of the drug is in semi-ordered state. Such assessment is an important aspect of the process because if the conversion is too slow, the drug will form into large crystals and will have characteristics of bulk crystalline form (see paragraph [0105]). Thus, depending on the results of this quantification, the skilled person may possibly intervene on the process by modifying the conditions of the conversion in order to enhance its rate, for instance by combining the methods of heating and adding a mobility enhancing agent, as suggested in [0104] of the description. In other words, determining the amount of drug in semi-ordered state, is a step of the process for preparing the claimed composition. The results of this quantitative analysis have an impact on the prosecution of the process itself. Accordingly, a deficiency of information on the methods for determining the amount of drug in semi-ordered state directly affects the possibility of performing this process and therefore the possibility of obtaining the composition claimed in the patent.

3.4 Since the skilled person would not be able to determine the amount of drug in semi-ordered state on the basis of the information provided in the patent and of his general knowledge, the Board concludes that the subject-matter of the patent is not sufficiently disclosed.

**Order**

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

The appeal is dismissed

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated