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**Datasheet for the decision
of 15 June 2010**

Case Number: T 0012/07 - 3.3.02

Application Number: 95921031.1

Publication Number: 0762897

IPC: A61K 47/26

Language of the proceedings: EN

Title of invention:

Method of preventing aggregation of proteins/peptides upon rehydration or thawing

Patentee:

Quadrant Drug Delivery Limited

Opponent:

Novartis Vaccines and Diagnostics, Inc.
National Blood Authority

Headword:

Aggregation of proteins/QUADRANT DRUG DELIVERY LIMITED

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

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Keyword:

"Inventive step - (no): The subject-matter of all requests constitutes an arbitrary selection over the closest prior art."

Decisions cited:

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Catchword:

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Case Number: T 0012/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 15 June 2010

Appellant-opponent: Novartis Vaccines and Diagnostics, Inc.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
8 November 2006 concerning maintenance of the
European Patent No. 0762897 in amended form.

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
J.-P. Seitz

Summary of Facts and Submissions

- I. European patent No. 0 762 897 based on application No. 95 921 031.1 was granted on the basis of a set of 9 claims.
- II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step and under Article 100(b) EPC for insufficiency of disclosure. Opponent II (National Blood Authority) withdrew its opposition by letter of 15 April 2004.
- III. The documents cited during the opposition and appeal proceedings included the following:
- (4) S.J. Prestrelski et al., *Biophysical Journal*, vol. 65, 661-671 (1993)
 - (5) Y.M. Newman et al., *Biotechnology and Genetic Engineering Reviews*, vol. 11, 263-294 (1993)
 - (14) M.S. Hora et al., *Pharmaceutical Research*, vol. 9, no. 1, 33-36 (1992)
 - (15) M.J. Pikal, *Pharmaceutical Technology International*, 40-43 (1991)
- IV. The present appeal lies from an interlocutory decision of the opposition division dated 28 September 2006 maintaining the patent in amended form on the basis of auxiliary request 2, filed during the oral proceedings before the opposition division.

Independent claim 1 of auxiliary request 2 reads as follows:

"1. A method of reducing or preventing aggregation during dehydration and rehydration of a protein the method comprising: adding to a solution or suspension of the protein an amount of trehalose sufficient to prevent or reduce aggregation upon rehydration; dehydrating the solution or suspension, wherein the dehydrating comprises lyophilization; storing the dehydrated solution or suspension at a temperature below that which causes denaturation or other chemical changes; and rehydrating the protein to obtain a solution or suspension of the protein in a substantially nonaggregated form, wherein the protein is a hormone, growth factor, insulin, monoclonal antibody, interleukin or interferon."

- V. As regards the main request, the opposition division found that the feature "in multiple doses", although clear in itself, was not clear in the context of the method as claimed; nor had it originally been disclosed in the context of such a method. The subject-matter of auxiliary request 1 did not meet the requirements of Article 84 EPC either, as the feature "useful in medicine", which had been introduced into claim 1, was not clear.

The opposition division came to the conclusion that auxiliary request 2 met the requirements of Rule 57(a) EPC 1973 and of Articles 123(2) and 84 EPC. Moreover, the subject-matter claimed therein was sufficiently disclosed, novel and involved an inventive step. The opposition division reasoned that the requirements of sufficiency were met, as the contested patent disclosed substances and steps to be used for carrying out the

claimed method, means for analysing the results and a concrete example. As regards novelty, none of the available prior art documents disclosed the particular proteins as claimed in combination with trehalose in the context of freeze-dried preparations. As for inventive step, document (4), where aggregation of a growth factor was reduced by a protecting agent such as sucrose, was defined as the closest prior art. However, the available prior art did not provide any incentive for the skilled person to replace sucrose by trehalose in order to improve the prevention of protein aggregation.

VI. Both the patentee (appellant-proprietor) and opponent I (appellant-opponent) lodged an appeal against that decision.

VII. In a communication dated 2 June 2010 according to Article 15(1) RPBA), the board informed the parties that, if amendments are made in the course of the opposition/appeal procedure, the board is entitled and even obliged to examine whether said amendments are allowable under Article 123(2) EPC.

VIII. With a letter dated 8 June 2010, the appellant-patentee filed a new main request and auxiliary requests 1 to 5. The sole independent claims of each request read as follows:

i) main request:

"1. A method of reducing or preventing aggregation during dehydration and rehydration of a protein, the method comprising: adding to a solution or suspension

of the protein an amount of trehalose sufficient to prevent or reduce aggregation upon rehydration; dehydrating the solution or suspension, wherein the dehydrating comprises lyophilization; and rehydrating the protein to obtain a solution or suspension of the protein in a substantially nonaggregated form, wherein the protein is a growth hormone, growth factor, insulin, monoclonal antibody or interferon."

ii) auxiliary request 1:

"1. The use of trehalose for reducing or preventing aggregation during dehydration and rehydration of a protein, in a method comprising: adding to a solution or suspension of the protein an amount of trehalose sufficient to prevent or reduce aggregation upon rehydration; dehydrating the solution or suspension, wherein the dehydrating comprises lyophilization; and rehydrating the protein to obtain a solution or suspension of the protein in a substantially nonaggregated form, wherein the protein is a growth hormone, growth factor, insulin, monoclonal antibody or interferon."

iii) auxiliary request 2:

Claim 1 of auxiliary request 2 is identical to claim 1 of the main request, except that the passage at the end now reads: "... wherein the protein is a growth hormone, growth factor, insulin, monoclonal antibody, interleukin or interferon."

iv) auxiliary request 3:

Claim 1 of auxiliary request 3 is identical to claim 1 of auxiliary request 1, except that the passage at the end now reads: "... wherein the protein is a growth hormone, growth factor, insulin, monoclonal antibody, interleukin or interferon."

v) auxiliary request 4:

Claim 1 of auxiliary request 4 is identical to claim 1 of auxiliary request 2, except for deletion of the words "wherein the dehydrating comprises lyophilization".

vi) auxiliary request 5:

Claim 1 of auxiliary request 5 is identical to claim 1 of auxiliary request 3, except for deletion of the words "wherein the dehydrating comprises lyophilization".

IX. Oral proceedings were held before the board on 15 June 2010.

X. In connection with inventive step, the appellant-proprietor's arguments can be summarised as follows:

The invention of the contested patent related to the prevention or reduction of protein aggregation and in particular of dimer and trimer formation during the dehydration and rehydration process. In contrast, document (15) concerned denaturation and loss of activity, which concerned separate problems and were

independent of aggregation. For that reason alone, document (15) was not pertinent. Moreover, the skilled person had no reason to select trehalose from the list of lyoprotectants disclosed in document (15). The lyoprotectants used in document (15) were not confined to the four compounds specifically mentioned in the last paragraph of the second column on page 41 but disclosed numerous other lyoprotectants. In the group of lyoprotectants specifically mentioned in document (15), trehalose was not even among the preferred excipients in view of the fact that, in contrast to compounds such as mannitol, glycine, arginine and lactose, there existed no established history for parenteral therapy.

In addition, the skilled person was further dissuaded from selecting trehalose by the specific example on page 42 of document (15), in which polyvinylpyrrolidone or sucrose rather than trehalose was used as lyoprotectant during lyophilisation of human growth hormone. Although there existed a second example involving trehalose as lyoprotectant, this example was not pertinent either, as phosphofructokinase had been chosen as protein, which in its natural state existed as tetramer and dissociated to its inactive monomers after degradation. As a consequence, it behaved totally differently from the proteins listed in the present claims.

Document (5) was not limited to trehalose either but identified carbohydrates and polyols in general as active agents for biopreservation. The fact that trehalose remained amorphous during freeze-drying with a protein did not allow the conclusion that trehalose

reduced or prevented aggregation. Neither did the knowledge about the beneficial effect of a high glass transition temperature for protein stability during freeze-drying lead the skilled person to choose trehalose. In that case, he would have taken maltose or an oligomer instead.

Starting from document (15) as the closest prior art, the skilled person had no reasonable expectation of success for using trehalose, as he had many possibilities at his disposal for choosing an effective lyoprotectant. In view of these numerous options, he could but would not have chosen trehalose. The fact that the use of trehalose for preventing aggregation of proteins during lyophilisation involved an inventive step was demonstrated by document (21), where this effect of trehalose was characterised as surprising four years after the priority date of the contested patent.

XI. In connection with inventive step, the appellant-opponent's arguments can be summarised as follows:

The problem of the present invention concerned prevention or reduction of aggregation. Document (15), which constituted the closest prior art, related to the stability of proteins during freeze-drying and storage. Document (15) specifically referred to the minimisation of protein aggregation by addition of a lyoprotectant. The list of lyoprotectants in the paragraph bridging pages 41 and 42 was short: it only encompassed three compounds in addition to trehalose.

XII. The appellant-proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request or alternatively of one of auxiliary requests 1 to 5, all filed with letter dated 8 June 2010.

XIII. The appellant-opponent requested that the decision under appeal be set aside and that the European patent No. 0 762 897 be revoked.

Reasons for the Decision

1. The appeals are admissible.

2. Admissibility of the new requests:

The main request and auxiliary requests 1 to 5 were filed by letter of 8 June 2010, i.e. at an advanced stage of the appeal proceedings. However, the amendments made were a reaction to the board's communication of 2 June 2010. Moreover, the appellant-opponent did not raise any objections against the admission of these requests. As a consequence, the board decided to admit them into the proceedings (Article 13 RPBA).

3. As regards sufficiency of disclosure and novelty, the board sees no reason to deviate from the decision of the opposition division. In view of the subsequent decision on inventive step (see point 4 below), it does not appear necessary to elaborate on these issues. As a consequence, the grounds of opposition according to Article 100(a) EPC in connection with Article 54 EPC as

well as according to Article 100(b) EPC do not prejudice the maintenance of the patent on the basis of the present requests on file.

4. Inventive step:

4.1 Main request:

4.1.1 The present invention relates to methods of preventing or reducing aggregate formation of growth hormones, growth factors, insulin, monoclonal antibodies and interferons upon dehydration and rehydration (see paragraphs [0001], [0016] and [0017]).

4.1.2 Document (15) relates to the stability of proteins during freeze-drying (see summary and second complete paragraph of the first column on page 40). For deciding whether document (15) qualifies as the closest prior art, it is important to evaluate whether or not stability in the context of document (15) includes prevention or reduction of aggregate formation. In the light of the disclosure in the above-mentioned paragraph on page 40, the board is convinced that this is the case. The relevant passage reads as follows:
"Manufacturers can minimize the degradation that arises from aggregation and other mechanisms by paying careful attention to the details of the freeze-drying process. Most often, however, stability problems are addressed by varying the formulation. For example, excipients, or *lyoprotectants*, are added to improve stability of the dried product." The board concludes from this passage that lyoprotectants are used for improving stability and that prevention or reduction of aggregation is one aspect of stability according to document (15). Further

evidence that resistance to aggregate formation is comprised in the term stability is provided by the specific examples in the first full paragraph of the first column on page 42 ("The stability (resistance to aggregate formation)of..."). It is not denied that loss of protein activity and denaturation are not necessarily linked to aggregation, as was pointed out by the appellant-patentee. However, this fact is of no relevance, as document (15) contains the teaching that the lyoprotectants disclosed therein, which include trehalose as one of the preferred lyoprotectants (see the paragraph bridging pages 41 and 42 of document (15)), are *inter alia* used for protecting the proteins against aggregation.

4.1.3 As a consequence, document (15) constitutes the closest prior art and the problem to be solved can be defined as the provision of a further method of preventing aggregation during lyophilisation and rehydration of proteins. This problem was solved by the method as claimed in claim 1 of the main request, i.e. by choosing trehalose as protective agent for growth hormones, growth factors, insulin, monoclonal antibodies or interferon. In the light of the data in Tables 1 and 2, the board is satisfied that the problem defined above was plausibly solved.

4.1.4 In view of the teaching that the lyoprotectants according to document (15) and in particular those listed in the paragraph bridging pages 41 and 42 are all suitable to suppress or reduce aggregate formation during freeze-drying and storing of proteins in general, the specific combination of trehalose with one of the proteins according to present claim 1 is nothing but an

arbitrary selection, which in the absence of any non-obvious effect does not involve an inventive step. The skilled person concludes from the teaching of document (15) that the problem defined in paragraph 4.1.3 could be solved no matter whether trehalose or any of the other lyoprotectants according to document (15) was chosen. Such an arbitrary selection cannot give rise to an inventive step.

- 4.1.5 The appellant-patentee held that the proteins defined in present claim 1 were used parenterally and in multiple doses. Although not specifically mentioned in the claims, this feature was implicitly disclosed by the selection of the proteins. As a consequence, the skilled person would not select trehalose, sucrose, human serum albumin or bovine serum albumin, which had the drawback of not having an established history in the formulation of pharmaceutical products for parenteral therapy (see lines 2-5 from the bottom of the second column on page 41).

Not having an established history in the formulation of pharmaceutical products for parenteral therapy does not mean, however, that these lyoprotectants are not suitable. It simply means that this suitability must possibly be verified by standard tests, which do not require inventive skill and which do not keep the skilled person from taking these lyoprotectants into consideration. On the contrary: as trehalose and the three further lyoprotectants mentioned above are commonly used as lyoprotectants (see lines 6-8 from the bottom of the second column on page 41), they are preferred by the skilled person, as their stabilising effect and, as a consequence, their aggregate-reducing

effect is beyond any doubt. This argument can therefore not succeed, even it is assumed in favour of the appellant-patentee that the parenteral application in multiple doses is an implicit feature of claim 1.

- 4.1.6 The appellant-patentee further argued that the skilled person, starting from the teaching of document (15), had no reasonable expectation of success by selecting trehalose in combination with the specific proteins as defined in claim 1, in view of the numerous options that were at his disposal. He could but would not have made this selection.

As was mentioned above in point 4.1.4, the skilled person made an arbitrary selection from the teaching of document (15) in order to arrive at the claimed invention. The method according to present claim 1 is just one of many possibilities for solving the problem defined in point 4.1.4 above. As a consequence, the "could/would-approach" does not apply in the present case.

- 4.1.7 As a consequence, the subject-matter of claim 1 and of dependent claims 2 to 4 does not meet the requirements of Article 56 EPC.

- 4.1.8 In view of the fact that the claimed subject-matter is rendered obvious by document (15) alone, an evaluation of the combination of document (15) with further documents is not necessary.

- 4.2 In auxiliary request 1, claim 1 was transferred from a method claim to a use claim in order to emphasise that the effect of aggregate reduction was caused by

trehalose. As in document (15) this effect is also attributed to the lyoprotectants (see point 4.1.2 above), the reasoning of point 4.1 for the main request applies *mutatis mutandis* to auxiliary request 1. The subject-matter claimed in auxiliary request 1 does therefore not meet the requirements of Article 56 EPC.

4.3 Auxiliary requests 2 and 3:

Auxiliary requests 2 and 3 are identical to the main request and to auxiliary request 1, respectively, except for the addition of interleukin to the list of proteins in both requests. This addition, to which no particular effect can be attributed, cannot not change the above evaluation of inventive step. As a consequence, the reasoning of point 4.1 applies *mutatis mutandis* to auxiliary request 2 and the reasoning of point 4.2 applies *mutatis mutandis* to auxiliary request 3. The requirements of Article 56 EPC are therefore not met.

4.4 Auxiliary requests 4 and 5:

Auxiliary requests 4 and 5 are identical to auxiliary requests 2 and 3, respectively, except for the deletion of the term "wherein the dehydrating comprises lyophilisation" in both requests. The generalisation from lyophilization to dehydration does not change the above evaluation of inventive step. As a consequence, the reasoning of point 4.3 applies *mutatis mutandis* to auxiliary requests 4 and 5. The requirements of Article 56 EPC are therefore not met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

N. Maslin

J. Riolo