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D E C I S I O N
of 30 June 2004

Case Number: T 1116/98 - 3.3.5

Application Number: 92305769.9

Publication Number: 0520748

IPC: B01D 1/14

Language of the proceedings: EN

Title of invention:
Storage of materials

Patentee:
Nektar Therapeutic

Opponent:
-

Headword:
Storage of materials/NEKTAR

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - no, obvious solution to a technical problem"

Decisions cited:
T 0266/00

Catchword:
-

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Case Number: T 1116/98 - 3.3.5

D E C I S I O N
of the Technical Board of Appeal 3.3.5
of 30 June 2004

Appellant: Nektar Therapeutic
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 17 July 1998 refusing European application No. 92305769.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: M. M. Eberhard
Members: G. J. Wassenaar
J. H. van Moer

Summary of Facts and Submissions

I. European patent application No. 92 305 769.9, publication No. 0 520 748, was refused by decision of the Examining Division. The decision was based upon five sets of amended claims filed on 8 July 1998 as a main request and four auxiliary requests.

II. Ground of the decision was lack of inventive step in view of

D2: EP-A-0 383 569 and
D5: JP-A-60/244288 (English translation).

In the contested decision further reference was made inter alia to

D10: Van de Beek et al, The Netherlands Milk Dairy Journal, Vol. 23 (1969), pages 46-54.

III. The appellant lodged an appeal against this decision. With the statement of the grounds of appeal the appellant provided documents to show that spray-drying was not the only possible technical solution for up-scaling the small scale vacuum-drying method disclosed in D2. Further reference was made to some pages in K. Masters' "Spray Drying Handbook". In reply to a communication of the board, wherein, as a preliminary opinion, the position of the examining division was essentially confirmed, the appellant filed further documents originating from the court proceedings concerning D2 in the UK. These documents comprised expert opinions on spray drying by Prof. Kerkhof and Prof. Lee. In a further communication

of the board the appellant's attention was drawn to decision T 181/01, concerning the appeal in the opposition proceedings relating to D2. Thereupon the appellant amended his requests, the second, third and fourth auxiliary requests filed on 8 July 1998 being renumbered as the main, first and second auxiliary requests respectively. In the annex to the summons to attend oral proceedings, which took place on 30 June 2004, the board further drew attention to some statements in the "Handbuch der Biotechnologie" (Paul Präve et al, 3rd Ed. 1987, page 259, point 6.2). During these oral proceedings the appellant filed an amended set of claims as a main request in place of the previous main request.

IV. Claim 1 of the main request filed during oral proceedings read as follows:

"A process of rendering a material suitable for storage a material selected from proteins, peptides, nucleosides, nucleotides, dinucleotides, oligonucleotides and enzyme cofactors comprising spraying into a hot gas stream with a temperature exceeding 80°C, an aqueous mixture of the said material and a carrier substance which is water-soluble or water-swellable and which on its own is able to exist in a glassy amorphous state with a glass transition temperature above 20°C, thereby drying the mixture to a composition in the form of particles which contain the material and the carrier substance and which are in a glassy or rubbery amorphous state, with a glass transition temperature of at least 50°C, and separating the particles from the gas stream."

Claim 1 of the first auxiliary request read as follows:

"A process of rendering a material suitable for storage a material selected from proteins, peptides, nucleosides, nucleotides, dinucleotides, oligonucleotides and enzyme cofactors, comprising spraying into a hot gas stream with a temperature exceeding 80°C, an aqueous mixture of the said material and a carrier substance which is water-soluble and which on its own is able to exist in a glassy amorphous state with a glass transition temperature above 20°C, which aqueous mixture of the said material and carrier substance is an aqueous solution of them both containing up to 50gm per litre of said carrier substance, thereby drying the mixture to a composition in the form of particles which contain the material and the carrier substance and which are in a glassy or rubbery amorphous state, with a glass transition temperature of at least 50°C and separating the particles from the gas stream".

Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request only in the additional requirement that the selected material is ordinarily not stable at ambient temperature of 20°C.

V. The appellant's arguments with respect to inventive step of these claims may be summarised as follows:

D2 represented the closest prior art. It disclosed a process for rendering suitable for storage the same kind of material as those listed in the claims by drying an aqueous mixture of said material and a carrier substance, which on its own could exist in a

glassy amorphous state, to a solid composition having a glass transition temperature (T_g) of at least 30°C. From a combination of features in the description and examples of D2 it could be derived that products with a T_g of more than 50°C were feasible if the carrier itself had a high T_g (97°C or more) and the composition was dried to a very low water content (not more than 4% by weight). Such a low water content required severe drying conditions. Although spray drying was known in the art of biotechnology as a drying method it was also known that it was a potentially harmful method. To reach such a low water content high inlet gas temperatures were needed. The skilled person would not have expected that sensitive and unstable materials as mentioned in the claims were able to sustain such a treatment without substantial degeneration. He would, therefore, not have seriously contemplated spray drying as a drying method for obtaining products with a T_g above 50°C. The inventor had unexpectedly found that, despite the potential harmful effect of spray drying on sensitive material as described in Masters' Spray Drying Handbook, it was actually possible to use spray drying for obtaining products with a T_g above 50°C. During oral proceedings further reference was made to US-A-4 617 272, paragraph 5.10 of the first report of Prof. Kerkhof, the decision T 266/00 (point 3.6.3) and the article of Maa et al in Pharmaceutical Development and Technology, 2(3), 1997, pages 213 to 223.

VI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the set of claims 1 to 9 according to the main request filed during oral proceedings, or in the alternative on the basis of a first auxiliary request, which is the

third auxiliary request filed on 8 July 1998 or, as a second auxiliary request, on the basis of the fourth auxiliary request filed on 8 July 1998.

Reasons for the Decision

1. The appeal is admissible.

2. The allowability of the amendments and the novelty of the claimed subject-matter are not in dispute.

3. For the evaluation of inventive step it is also undisputed that D2 represents the closest prior art. This document discloses a process for rendering suitable for storage the same materials as those mentioned in the present claims by drying an aqueous mixture of said materials and a carrier substance to form the resulting mixture into a glassy or rubbery amorphous state (claims 1 and 9, page 3, lines 20 to 29 and page 5, lines 40 to 56). The carrier substance is a glass-forming substance, which displays a T_g in a range from 20 to 150°C, when anhydrous or nearly so (page 4, lines 12 to 13). The T_g of the dried mixture may be lower or higher than room temperature but preferably at least 30°C. If T_g of the composition is well-above room temperature the composition is better able to withstand storage at an elevated temperature, e.g. in a hot climate (page 3, lines 1 to 2 and page 4, lines 18 to 29). For small samples of solution, e.g. 0.1 to 1 ml, it is proposed to evaporate the water at a temperature not exceeding 40°C at reduced pressure for some hours, for instance 24 to 36 hours to achieve a T_g exceeding 30°C. Once such a sufficiently high T_g has been achieved

the temperature may be raised while evaporation continues to within a range of 40 to 70°C for a shorter time such as two hours (page 5, lines 40 to 54). With the process of D2 materials which are not stable when isolated and held in solution at room temperature can nevertheless be successfully incorporated into a glass formed from a water-soluble substance and can later be recovered. While in the glass, the material is immobilised and stable (page 2, lines 48 to 51).

4. It is further undisputed that a skilled person would regard the drying method outlined above as not very suitable for large scale production. In agreement with the submissions made by the appellant during oral proceedings the problem underlying the invention is therefore to implement the teaching of D2 by an alternative method of rendering a material suitable for storage, which is capable of being performed on a larger scale. In conformity with the present claims, the appellant proposes to solve this problem by spray drying the aqueous solution of material and glass-forming carrier into a hot gas stream with a temperature exceeding 80°C to such an extent that the T_g of the product is at least 50°C, and separating the particles from the gas stream. Example 1 shows that with a lactate dehydrogenase as active material and the substance Ficoll 400 DL®, which is a copolymer of sucrose and epichlorohydrin having a T_g of 97°C, as carrier, it is possible to obtain a solid product with a T_g of 79°C. It is further shown in example 1 that the enzyme activity is effectively preserved through the spray-drying procedure and subsequent storage. Since, furthermore, spray-drying is used in the chemical and pharmaceutical industry on a large scale, the board is

satisfied that the process according to claim 1 (all requests) actually solves the above-mentioned problem.

5. Spray-drying is a well-established technique in the pharmaceutical and biotechnical field; see the earlier mentioned handbooks (Handbuch der Biotechnologie, paragraph 6.2 on page 259, and Masters' Spray Drying Handbook, paragraph 16.1, pages 625 to 626). According to the "Handbuch der Biotechnologie" the spray-drying temperatures for sensitive biological products may be in the range of 150 to 200°C. It is further indicated that by the sudden evaporation the temperature of the particles remain so low that thermal degeneration of the biological products does not take place. This kind of drying is also said to permit drying of high amounts of product in a relatively short time. Vacuum drying of the kind applied in D2 is also discussed in the said paragraph of the "Handbuch der Biotechnologie". As advantage of vacuum drying it is indicated that the material does not suffer from mechanical stress. The disadvantages mentioned there are the batchwise production and the relatively low drying temperatures. Although not explicitly mentioned there, the low drying temperatures imply long drying times. The long drying times are apparent from D2. As already mentioned under point 3 above, D2 requires for drying portions of 0.1 to 1 ml in a two step drying process 24 to 36 hours in the first step and two hours in the second step.

6. Since D2 teaches a preference for products with a T_g of at least 30°C and indicates that a product having a T_g well above room temperature will better withstand storage at an elevated temperature, eg in a hot climate (page 4, lines 28 to 29), the skilled person had a

clear incentive to try to produce products with a T_g above 50°C. The appellant no longer disputed that spray-drying of biological material was state of the art but argued, with reference to US-A-4617272 and Masters' Spray Drying Handbook, that in order to reach the very low moisture content necessary to obtain a Tg above 50°C, the temperature of the particles at the end of the spray-drying process would become so high that a skilled person would fear the degeneration of his product. Maters' Spray Drying Handbook was published in 1991, but it is not revealed when it became actually available to the public. Since the priority date of the patent application is 26 June 1991 it is not sure whether Masters' Spray Drying Handbook belongs to the state of the art within the meaning of Article 54(2) EPC. The board does, however, not dispute that the information given in a handbook generally represents the knowledge of the skilled person some time before its publication. Taking into account the short remaining time if publication of the Handbook had occurred in December 1991, the board is therefore prepared to accept the appellant's argument that the information given in Masters' Spray Drying Handbook reflects the general understanding of the skilled person before the priority date of the patent application. According to the introduction of chapter 8 of Masters' Spray Drying Handbook the drying of the droplets in the spray-drying process takes place in two stages, whereby in the first period moisture is removed at a near constant rate and constant droplet surface temperature until a critical moisture content, followed by a second period in which the removal rate declines (part 8.1 and Fig. 8.1, pages 309 to 311, and part 8.3.1(b), page 331, 2nd paragraph). These observations

are essentially in agreement with the statement under 5.10 of the first expert opinion of Prof. Kerkhof. The board does not dispute his conclusion that after a certain critical level the heat transferred from the air will then cause the particles to heat up, ultimately to a temperature very close to the local air temperature in the dryer. However, according to example 8.3 on page 338 of Masters' Spray Drying Handbook, in the case of a 4% residual moisture content in the spray-dried product, the final product temperature is still 25°C below the outlet temperature of the drying air under the spray-drying conditions used therein. According to this example a 45% by weight aqueous solution of a dissolved salt is spray-dried to a product of 4% moisture at an inlet and outlet drying air temperature of 300°C and 100°C respectively. The critical moisture content is said to occur at 30% moisture content (top of page 337). According to the calculation the total drying time was 1.57 s, but it was observed that experience had shown that the evaporation rate on approach to the 4% residual moisture content level was very low and that the actual drying time to a 190 μm droplet was much longer than 1.57 s (end of the example on page 338). After the critical moisture content is reached the temperature of the droplets will rise, but remains 25°C below the outlet temperature of 100°C, ie 75°C, a temperature which is not much higher than the temperatures in the range of 40 to 70°C given in D2 for the second drying step. Also in the last paragraph of part 8.1 of Masters' Spray Drying Handbook (page 311) it is indicated that heat-sensitive material may be dried by spray-drying. Moreover, D2 requires drying times of about 2 hours at a temperature of 60°C, whereas the

spray-drying process is finished within a minute. According to Masters' Spray Drying Handbook the short process time is a distinct advantage for heat sensitive products (page 628, fourth paragraph of point (a)). In this paragraph it is also pointed out that the evaporation keeps the particle temperature low. In fact, a whole chapter of Masters' Spray Drying Handbook is devoted to the application of spray-drying in the pharmaceutical-biochemical industry (chapter 16, pages 625 to 644). Materials such as antibiotics, enzymes, hormones, single-cell proteins etc. are treated in this way (point 16.1, pages 625 to 626). With respect to enzymes, which in their purified form consist largely of proteins, it is indicated that they are normally very heat-sensitive and mild drying temperatures are paramount. Nevertheless for rennin, used for cheese making, an air inlet temperature of 145°C and an outlet temperature of 70°C are mentioned (page 633).

7. The spray-drying of rennin is also disclosed in D10 where it is performed in the presence of sucrose or lactose at an air-inlet temperature of 150°C and an air outlet temperature of 80 to 85°C. The addition of sugars such as sucrose or lactose protects the biological activity during spray-drying or during heating at constant temperatures (pages 47, 48, 49, Table 1, page 52, last paragraph). D10 does indeed indicate that there are inactivating factors associated with spray-drying, which do not occur during heating at constant temperature, pH and NaCl concentration (bottom of page 50). This sentence is, however, no prejudice against the method of spray-drying as such, but read in combination with the previous sentence it simply expresses the observation that in solution NaCl

stabilizes rennin, whereas in more concentrated form during spray-drying it destabilizes rennin. The skilled person's conclusion would be either not to use NaCl in the composition for spray-drying or to use it at low concentration, but not to reject spray-drying.

8. D5 teaches that the activity of a heat-sensitive enzyme such as serrapeptidase can be conserved by spray-drying at a gas inlet temperature of 120°C in the presence of the glass forming sugar lactose. With a 1:1 mixing ratio of lactose and serrapeptidase a very stable product could be obtained having a residual stability after fifty days at 65°C of 96.1% (example 1, page 5 of the English translation provided by the appellant).

9. The only document on file which seems to reject spray-drying for heat sensitive material is US-A-4 617 272. This document concerns the drying of enzymes in a fluid bed dryer. In the presentation of the background of the invention it is indicated that effective spray-drying requires either tower temperatures which lead to unacceptable enzyme deactivation or expensive enzyme recycling mechanisms (column 1, lines 51 to 54). In the board's view this is a rather isolated statement, which seems to have the purpose to highlight the advantage of the fluidised bed drying process disclosed in US-A-4 617 272. Said isolated remark in US-A-4 617 272, without any indication of the temperatures or other relevant parameters of the spray-drying method, cannot be a sufficient reason for the skilled person to reject the information about the use of spray-drying for drying heat sensitive biological material in D10, D5 and the cited handbooks.

10. According to Masters' Spray Drying Handbook, spray-drying may provide products having a moisture content of about 4%; see earlier cited page 337, top of page 630, bottom of page 633, middle of page 643. It is true that for extremely heat-sensitive enzymes Masters' Spray Drying Handbook proposes a two step drying, whereby in the first step the material is spray-dried to 10 to 20% moisture, which product is then further dried in an after-dryer to 3 to 5% moisture (bottom of page 633). The claims are, however, not limited to such extremely heat-sensitive material. It is also true that the publication of Maa et al mentions for spray-dried compositions comprising protein and lactose higher moisture contents (from 5.4 to 9.7%, tables 2 and 3 on pages 218 to 219). This article was, however, published in 1997 and therefore could not have influenced the skilled person's perception in 1991. In the experiments of Maa the gas inlet temperatures were relatively low, from 80 to 150°C, and the ratio of protein to lactose was relatively high (3:2). The board does not dispute that in order to obtain a moisture content of about 4% the spray-drying conditions must probably be more severe than used by Maa, but holds that higher air inlet temperatures are clearly considered in the prior art for spray-drying sensitive biological material, such as temperatures in the range of 150 to 200°C as mentioned in the "Handbuch der Biotechnologie". The article of Maa may be an argument to accept the novelty of the subject-matter of claim 1 with respect to D5 and D10, but has no impact on the issue of inventive step.

11. In view of the discussed teachings of D10, D5 and the common general knowledge on spray-drying of heat sensitive substances as illustrated by the two cited

handbooks, the appellant's argument that the skilled person would not have contemplated a spray-drying process for drying substances of the kind disclosed in D2 in the presence of a protective glass-forming carrier, is not convincing.

12. According to D2 carriers may be used with a T_g of up to 150°C when anhydrous or nearly so (page 4, lines 12 to 13) and the final composition has desirably a water content of not more than 4% by weight (page 3, line 3). The carrier used in most of the examples is Ficoll 400 DL having a T_g of 97°C. D2 further discloses that for some carbohydrates T_g is reduced by approximately 6°C for each percent moisture added (page 4, lines 40 to 42). It is not specifically disclosed that this reduction of T_g by moisture equally applies to Ficoll 400 DL, which is a modified carbohydrate. Taking into account that D2 also discloses that the formulated composition has a T_g which is typically only 5°C below the T_g of the anhydrous glass forming substance (page 4, lines 30 to 31) the skilled person has no reason to believe that for Ficoll 400 DL the Tg reduction is more than 6°C per percent of water. For compositions comprising Ficoll 400 DL as the carrier and having a water content of 4%, the skilled person would expect a T_g of about 97-4x6=73°C, anyhow substantially above 50°C. He would therefore have reasonably expected that by using a carrier with a sufficiently high Tg the above-mentioned problem could likely be solved by spray drying enzymes in the presence of the glass-forming carrier materials under spray-drying conditions similar to those mentioned in the "Handbuch der Biotechnologie" (150 to 200°C) to a usual moisture content of about 4% as mentioned in D2 and Masters' Spray Drying Handbook,

thereby arriving at the process according to claim 1 of the main request.

13. According to decision T 266/00 of 17 February 2003, point 3.6.3, if in a prior art document it is indicated that a system is difficult to use and to automate the skilled person would be discouraged to apply this system to another type of device. However this is not the case here. Neither D2 nor the handbooks reject spray drying as a means for drying heat-sensitive material. The fact that Masters' Spray Drying Handbook indicates that special care should be taken if extremely heat-sensitive enzymes are dried in this way, does not mean that the skilled person would be discouraged to apply spray-drying for drying the composition disclosed in D2. It is routine experimentation to explore to which extent compositions according to D2, especially those comprising Ficoll 400 DL used in most of the examples, can be dried by spray drying without substantial loss of activity. In doing so, the skilled person will arrive at a process according to claim 1 of the main request.

14. For these reasons the board holds that in order to solve the problem underlying the invention it was obvious to provide the process according to claim 1 of the main request. Thus the subject-matter of that claim lacks an inventive step within the meaning of Article 56 EPC.

15. Claim 1 of the first auxiliary request is restricted to the carrier substance being water-soluble and comprises the additional feature that the carrier substance is present in the aqueous solution to be spray-dried in an

amount of up to 50 g/l. It is uncontested that these conditions were also met by example 5 of D2 and thus cannot provide any contribution to inventive step.

16. Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request in that the material to be stored is ordinarily not stable at 20°C. It is not indicated which materials are actually excluded by this limitation. In view of the fact that the aim of D2 is also to enable storage at ambient temperature of materials whose storage at this temperature has been impossible (page 2, lines 40 to 42) and that in example 1 of the present application the same material (lactate dehydrogenase) has been used as in example 7 of D2, the stability requirement cannot provide any contribution to inventive step either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman:

A. Wallrodt M. M. Eberhard