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D E C I S I O N
of 7 June 2005

Case Number: T 0802/00 - 3.3.2

Application Number: 92308924.7

Publication Number: 0535937

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:
Prolonged release microparticle preparation and production of the same

Patentee:
TAKEDA CHEMICAL INDUSTRIES, LTD.

Opponent:
SkyePharma AB
Bioglan Pharma PLC

Headword:
Microparticle preparation/TAKEDA

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure (yes) - submission of opponent not substantiated"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0802/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 June 2005

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 5 June 2000 revoking European patent No. 0535937 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 535 937 based on application No. 92 308 924.7 was granted with 25 claims.

Independent claims 1 and 12 as granted read as follows:

"1. A microparticle preparation suitable for injection comprising microparticles of a biodegradable polymer which contain a drug and which are coated with a film of an agent for preventing aggregation of the microparticles, wherein said agent is a water-soluble material.

12. A process for the production of a microparticle preparation defined in claim 1 which comprises spraying a solution of the biodegradable polymer containing a drug and an aqueous solution of the water-soluble material separately from different nozzles and contacting them with each other in a spray dryer to produce microparticles of the biodegradable polymer which contain the drug and which are coated with a film of the water-soluble material which prevents aggregation of the microparticles."

II. Opposition was filed against the granted patent under Article 100(a), (b) and (c) EPC.

The following document was cited inter alia during the proceedings before the opposition division and the board of appeal:

(33) Y. Ogawa, "Injectable microcapsules prepared with biodegradable poly(α-hydroxy) acids for prolonged release of drugs", J. Biomater. Sci. Polymer Edn. (5), 1997, 391-409

III. By its decision pronounced on 16 May 2000 and posted on 5 June 2000, the opposition division revoked the patent under Article 102(1) EPC because neither with respect to the set of claims of the main request nor with respect to the set of claims of the first auxiliary request filed during the oral proceedings did the patent disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

Since one of the inventors had himself, several years after the priority date of the opposed patent, published in document (33) that its spray-drying process exhibited as a major disadvantage the possible occurrence of contamination by minute particles of alien substances, rendering it unsuitable for preparing injections, the skilled person was not provided with a way of carrying out the invention of the opposed patent.

IV. The appellant (patentee) lodged an appeal against said decision.

V. On 7 June 2005 oral proceedings took place before the board.

VI. The wording of the claims corresponding to the appellant's sole request is as follows:

"1. A microcapsule preparation suitable for injection comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and which are coated with a film of an agent for preventing aggregation of the microcapsules, wherein said agent which is applicable to humans, is solid at room temperature and non-adhesive in its dried state and is selected from a water-soluble material selected from the group consisting of water-soluble saccharides, water-soluble amino acids, water-soluble proteins and water-soluble cellulose.

2. A preparation according to claim 1, wherein the poly fatty acid ester is a slightly water-soluble or water-insoluble biocompatible poly fatty acid ester having a weight-average molecular weight of about 1,000 to 800,000.

3. A preparation according to claim 1, wherein the poly fatty acid ester is selected from the group consisting of polylactic acid, copolymer of lactic acid and glycolic acid, copolymer of 2-hydroxybutyric acid and glycolic acid and a mixture thereof.

4. A preparation according to claim 1, wherein the microcapsules contain an internal aqueous phase and the internal aqueous phase contains about 0.001% to about 70% (w/w) of the drug.

5. A preparation according to claim 1, wherein the drug is a member selected from the group consisting of biologically active peptides, antibiotics, antitumor agents, antipyretics, analgesics, antiiflamatory agents, antitussive expectorants, sedatives, muscle

relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations and narcotic antagonists.

6. A preparation according to claim 1, wherein the amount of the agent for preventing aggregation is about 0.1 to about 100 times the weight of the poly fatty acid ester.

7. A preparation according to claim 1, wherein the particle size is about 0.5 to 400 μm.

8. A preparation according to claim 1, wherein the microcapsule preparation is a prolonged release microcapsule preparation.

9. A process for the production of a microcapsule preparation defined in claim 1 which comprises spraying a solution of the poly fatty acid ester containing a drug and an aqueous solution of the water-soluble material separately from different nozzles and contacting them with each other in a spray dryer to produce microcapsules of the poly fatty acid ester which contain the drug and which are coated with a film of the water-soluble material which prevents aggregation of the microcapsules.

10. A process according to claim 9, wherein the poly fatty acid ester solution containing the drug is a homogeneous solution.

11. A process according to claim 9, wherein the poly fatty acid ester solution containing the drug is a W/O type emulsion whose internal phase is an aqueous solution containing the drug and whose external phase is a solution containing the poly fatty acid ester.

12. A process according to claim 9, wherein the poly fatty acid ester solution containing the drug is an S/O type suspension containing drug particles.

13. A process according to claim 9, wherein the poly fatty acid ester is a slightly water-soluble or water-insoluble poly fatty acid ester having a weight-average molecular weight of about 1,000 to 800,000.

14. A process according to claim 13, wherein the poly fatty acid ester is selected from the group consisting of polylactic acid, copolymer of lactic acid and glycolic acid, copolymer of 2-hydroxybutyric acid and glycolic acid and a mixture thereof.

15. A process according to claim 11, wherein the internal aqueous phase contains about 0.001% to about 70% (w/w) of the drug.

16. A process according to claim 9, wherein the drug is a member selected from the group consisting of biologically active peptides, antibiotics, antitumor agents, antipyretics, analgesics, antiinflamatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants,

hemostatics, antituberculous agents, hormone preparations and narcotic antagonists.

17. A process according to claim 9, wherein the amount of the agent for preventing aggregation is about 0.1 to about 100 times the weight of the poly fatty acid ester.

18. A process according to claim 9, wherein the particle size is about 0.5 to 400 µm.

19. A process according to claim 9, wherein the microcapsule preparation is a prolonged release microcapsule preparation."

VII. The appellant submitted that the person skilled in the art knew how to overcome difficulties concerning alien substances while producing preparations for injections and that the claimed preparation as well as the claimed process were therefore disclosed in a manner sufficiently clear and complete for it to be carried out.

The inventor having published the review article (33) had not stated that there was a contamination by minute particles in any case. Accordingly, the semi-phrase "rendering it (the process) unsuitable for preparing injections" could only mean that there were difficulties in these cases only, where the contamination occurred in fact.

In addition to these arguments, the appellant submitted affidavits describing inter alia successful experiments based on the teaching of the patent in suit.

VIII. The respondents' arguments may be summarised as follows:

Since in any case it was virtually impossible to provide for experiments proving that a teaching of a patent would not work, it was a good evidence when one of the inventors of the patent in suit himself, being free of any pressure, voluntarily stated that his process was "unsuitable for preparing injections", meaning unsuitable for carrying out the claimed teaching.

As the real specialist in the technical field concerned, the author and inventor apparently made this statement, fully aware of the whole range of knowledge of the person skilled in the art. Thus, the patent in suit lacked information on how to produce a preparation suitable for injection and the invention could not be carried out by the person skilled in the art.

Moreover, at the priority date apparently nobody had considered a possible contamination by particles, and evidence filed by the appellant could only show that somehow, after the patent had been withdrawn by the opposition division, microcapsules could be prepared that were free of such a contamination. In this context, the appellant had not provided all data and parameters enabling the respondent to verify whether this had been done using common general knowledge or making the real invention while working on the examples of the affidavit, after the application date of the patent in suit.

IX. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 12 filed with the grounds of appeal and 13 to 19 filed in the oral proceedings, and that the case be remitted to the first instance for further prosecution.

X. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2. The amended claims filed by the appellant represent a clear response to the arguments set out during the oral proceedings and are therefore admitted into the proceedings.

3. The features contained in the requested set of claims may be derived from the application as filed (see originally filed claims 1 to 27 together with description page 25, lines 12 to 15, and all examples, page 23, paragraph 2, to page 24, paragraph 1, page 15, paragraph 5, and page 5, paragraph 3) and from the patent as granted (see claims 1 to 25 together with description page 7, lines 44 to 45, and all examples, page 5, line 35, and page 3, lines 17 to 21) .

To that extent, the requested claims meet the provisions of Article 123(2) and (3) EPC.

4. With respect to clarity of the claims (Article 84 EPC), the board has no reason to depart from the reasoning or the conclusion of the opposition division in the impugned decision.

5. *Article 100(b) EPC*

5.1 The patent in suit refers to a microcapsule preparation suitable for injection and to a process for the production of such a preparation.

Document (33) is the single evidence to which the reasoning of the opposition division and the respondent refers with respect to the alleged lack of sufficient disclosure.

This article is written by one of the inventors and inter alia deals with different microencapsulation methods, in particular the "phase separation procedure" (see page 393), the "solvent evaporation procedure" (see page 395) and the "spray-drying procedure" (see page 399). As far as the "spray-drying procedure" is concerned, the process of the patent in suit is mentioned as being the most developed state of the art. In the next sentence the author states that microencapsulation by spray-drying procedures had been reported by other scientists (The dates of one of these publications lay before and the others after the priority date of the patent in suit). The spray-drying method, the author continues, is very convenient as the process is quite fast and sequential, and large-scale production under mild conditions is possible. "However, its major disadvantage is that contamination by minute particles of alien substances may occur during the

process, rendering it unsuitable for preparing injections" (see (33), page 399, text following the header "Spray-drying procedure", to page 400, line 4, in particular page 400, lines 2 to 4 below Figure 6.).

Thus, in the absence of any experimental evidence provided for by the respondent and in the absence of any additional document cited by the respondent with respect to the opposition based on Article 100(b) EPC, the only facts to support the allegation that the patent in suit lacked sufficient disclosure of the invention are that while using any spray-drying process "minute particles of alien substances may occur" and that one of the inventors several years after filing the patent in suit seemed to have drawn the conclusion that the process was unsuitable for preparing injections.

However, if the process for producing a preparation may result in contaminated products, meaning that this only occurs in part of the trials aimed at attaining the product, in accordance with the established case law of the boards of appeal such statement does not automatically lead to the conclusion that the teaching in the patent in suit is insufficiently disclosed with respect to this process and product.

The opponent, bearing in the circumstances of the case the burden of proof, did not present any information, for instance on the nature of the particles of alien substances and/or on the percentage of occurrence of contamination or on the amount of contamination while trying to produce the claimed preparation. From the information available, the board can only conclude that

there is sufficient disclosure of the preparation and process as claimed in the patent as granted and the grounds of opposition under Article 100(b) EPC must fail.

5.2 In these circumstances, the arguments of the respondent cannot succeed:

In the present case, nothing is known as to why the author of (33) from general problems concerning product purity in spray-drying processes concluded in somewhat absolute terms that these processes would be unsuitable for preparing injections. From the facts presented in (33), such a conclusion does not follow clearly and automatically. Therefore, even if the inventor, at the time of writing his review article, seems to have abandoned any effort to overcome problems while performing his own invention, the board cannot follow his words blindly, particularly when examining the sufficiency of disclosure of the invention as required by the EPC.

Consequently, a negative conclusion by the inventor with regard to his invention, even when given voluntarily, cannot be regarded as a proven fact.

The respondents attempt to justify the conclusion of the inventor in document (33) in submitting that any risk of contamination in a process for preparation of injections automatically meant that the whole process was not usable at all must also fail.

Firstly, such risk depends on the percentage of batches that would probably be contaminated in a production. The word "may" says nothing about the relevance of that risk.

Secondly, and even apart from the possibility of overcoming such problems on the basis of the general knowledge of the person skilled in the art, such an assumption cannot be followed in absolute terms anyhow. Depending on the ethical and financial value of the resulting medicament, the producer of injections probably would run the risk of obtaining a defined percentage of contaminated product batches if he could recycle the valuable ingredients of these unusable products and/or if the need for the remaining batches not exhibiting such contamination was high enough.

6. Accordingly, the invention as based on the description as granted and as claimed with respect to the single request of the appellant is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

Since subject-matter concerning Article 100(a) EPC was not discussed in the oral proceedings before the opposition division, the board exercises its discretion under Article 111 EPC and remits the case to the 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 for further prosecution.

The Registrar: The Chairman:

U. Bultmann U. Oswald