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D E C I S I O N
of 7 November 2001

Case Number: T 0267/00 - 3.3.2

Application Number: 95940381.7

Publication Number: 0796090

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:
Cross-linked microparticles and their use as therapeutic vehicles

Applicant:
Quadrant Healthcare (UK) Limited

Opponent:
-

Headword:
Quadrant Healthcare/MICROPARTICLES

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"Claims 15 and 16 added upon entry into the regional phase adequately supported by the disclosure in the application as filed; no violation of a Article 123(2) EPC; remittal to the department of first instance for further prosecution."

Decisions cited:
T 0201/83

Catchword:
-

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Case Number: T 0267/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 November 2001

Appellant: Quadrant Healthcare (UK) Limited
1 Mere Way
Ruddington
Nottingham NG11 6JS (GB)

Representative: Perry, Robert Edward
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 22 December 1999 refusing European patent application No. 95 940 381 7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
S. U. Hoffmann

Summary of Facts and Submissions

I. European patent application No. 95 940 381.7, published under the PCT as WO 96/18 388, was refused pursuant to Article 97(1) EPC by a decision of the examining division posted on 22 October 1998. The decision was based on claims 1 to 14 as published and claims 15 and 16 filed on 12 June 1997 upon entry into the regional phase before the EPO. The only independent claim is worded as follows:

"1. A sterile powder comprising smooth, spherical microparticles, 0.1 to 50 μm in diameter, of cross-linked materials, the microparticles being hydrophilic and capable of reconstitution in water to give a mono-disperse suspension, and which additionally comprises a physiologically or diagnostically-active component linked directly or indirectly to microparticles *via* free functional groups thereon."

Dependent claims 2 to 14 relate to specific elaborations of the sterile powder according to claim 1. The claims added to those as published read as follows:

"15. A powder according to any of claims 1 to 11, wherein the active component is a cytotoxic agent.

16. Use of doxorubicin for the manufacture of a medicament comprising a powder according to claim 15, for the treatment of tumours showing the multidrug resistance phenotype."

II. The stated ground for the refusal was that claims 15 and 16 contravened Article 123(2) EPC. In its decision, the examining division stated that the features "cytotoxic agent" in claim 15 and "doxorubicin" in claim 16 were disclosed in the application as filed only in the context of specific examples and were moreover closely associated with the other features of these examples. Accordingly, it concluded that claims 15 and 16 contained generalisations of the above-mentioned features which were not supported by the disclosure in the originally filed document.

III. The applicant lodged an appeal against this decision. In its statement setting out the grounds of appeal it referred to the statement made in decision T 201/83 (OJ EPO 1984, 481), to the effect that an amendment in a claim is allowable on the basis of a particular value described in a specific example, provided the skilled person could have readily recognised this value as not so closely associated with the other features of the example as to determine the effect of that embodiment of the invention as a whole in a unique manner and to a significant degree. It argued that the features "cytotoxic agent" and "doxorubicin" were not so closely associated with the other features of the respective examples and that this was immediately evident to the skilled person. The examining division had rejected this argument without explaining why the other features that were allegedly relevant were actually relevant in the context of the invention as opposed to specific embodiments.

IV. The appellant requested that the decision under appeal be set aside and that the application be remitted to the examining division for further examination, based on claims 1 to 16. According to its first, second and

third auxiliary requests, the appellant requested remittal of the case for further prosecution on the basis of claims 1 to 15, 1 to 14 and 16, and 1 to 14, respectively.

Reasons for the Decision

1. The appeal is admissible.

2. All references below to support for the subject-matter of claims 15 and 16 in the application as filed are to the international application as published under the PCT (WO 96/18 388).

3. Working Example 3 (see page 14, line 33, to page 16, line 26) details the production of HSA microcapsules (ie microparticles in accordance with claim 1), which have a mean size of 12 μm, with virtually no microcapsules below 6 μm, and 85% of the mass between 9-18 μm (see page 14, line 34, to page 15, line 28). However, before the example goes on to illustrate the linkage of certain antibodies to the microcapsules mentioned above, the following general technical teaching is inserted: "By removing particles smaller than 6 μm, systemic circulation of microcapsules, following intra-arterial administration, is prevented due to capillary trapping. This has the advantage of localising the deposited drug, thereby reducing the overall amount of drug required to achieve therapeutic activity at the desired site. This is desirable, particularly in the case of **cytotoxics** since toxicity is the major cause of detrimental side-effects" (see the paragraph bridging pages 15 and 16).

3.1 This teaching discloses **in general terms** the possibility of using a cytotoxic agent as the physiologically active component for linkage to microparticles as the therapeutic vehicles in the sterile powder according to claim 1. In the board's view, this approach to the interpretation of the disclosure, which is considered as relevant for the purpose of supporting the subject-matter of claim 15 in the application as filed, follows directly from the choice of the wording "this is desirable, particularly in the case of cytotoxics". The use of this wording alone makes it thus immediately clear to the skilled reader, who must be assumed to have read the entire disclosure of the patent application carefully, that the possible removal of particles smaller than 6 μm is disclosed as an advantageous embodiment only in the case of intra-arterial administration of cytotoxics, but in no way limits the disclosure to the use of microparticles larger than 6 μm as therapeutic vehicles for cytotoxics as the physiologically active agents in accordance with claim 1. Hence, the disclosure on page 5 (see especially line 8 onwards) refers to the production of the microparticle preparations according to claim 1 for intravenous, intra-arterial and *ex vivo* use. Intravenous particle suspensions are, for example, disclosed as preferably containing less than 5% by volume of particles larger than 6 μm.

In view of the foregoing observations, the board cannot share the examining division's opinion in the impugned decision that the use of a cytotoxic agent as the physiologically active component is disclosed in the application as filed only in the context of a particular particle size of the microparticles and that claim 15 contains a generalisation which is not supported by the disclosure in the originally filed document.

4. Example 6 discloses in the first two paragraphs on page 18 the conjugation of doxorubicin to microcapsules produced using the **"general** method described in Example 1". The third paragraph states in entirely general terms that "it has previously been shown that the activity of doxorubicin bound to **polymeric carriers** proves beneficial in tumours showing multidrug resistant phenotype".

4.1 Consequently, what has actually been disclosed in the application as filed is the teaching that the beneficial effect or activity of doxorubicin in tumours showing multidrug resistance is due to the conjugation of doxorubicin to polymeric carriers in general such as, for example, to the conjugation to microparticles used as therapeutic vehicles for preparing the sterile powder within the whole range of claim 1. Thus, contrary to the opinion of the examining division in the impugned decision, the disclosure of this beneficial effect of doxorubicin in the impugned decision is not associated with any other features in Example 6 such as, for example, the particular nature or material or size of the microparticles used, or the method of preparing doxorubicin-microparticle conjugates in accordance with claim 1. Therefore, the board is likewise unable to share the examining division's view that claim 16 contains a generalisation of features which is not supported by the disclosure in the originally filed document.

5. In view of the observation in the foregoing points, the board reaches the conclusion that claims 15 and 16 are acceptable under the terms of Article 123(2) EPC. Since the board has decided to allow the appellant's main request, it is no longer necessary to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution based on claims 1 to 16.

The Registrar: The Chairman:

A. Townend P. A. M. Lançon

GR