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D E C I S I O N
of 18 April 2002

Case Number: T 0969/00 - 3.3.3

Application Number: 94926894.0

Publication Number: 0719295

IPC: C08G 64/02

Language of the proceedings: EN

Title of invention:
Polymeric matrices and their uses in pharmaceutical compositions

Applicant:
Novartis AG, et al

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 54, 56, 123(2)
EPC R. 67, 71(2)

Keyword:
"Novelty (yes)"
"Inventive step (yes)"
"Reimbursement of appeal fee (no)"

Decisions cited:
G 0001/93, T 0002/80

Catchword:
-

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Case Number: T 0969/00 - 3.3.3

D E C I S I O N
of the Technical Board of Appeal 3.3.3
of 18 April 2002

Appellant: Novartis AG
Lichtstrasse 35
SZ-4002 Basel (SZ)

Representative: -

Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 6 April 2002, and issued in writing on 27 April 2002 refusing European patent application No. 94 268 894.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: R. Young
Members: C. Idez
U. Tronser

Summary of Facts and Submissions

I. European patent application No. 94 926 894.0, based on International application PCT/EP94/02833, filed on 26 August 1994, claiming the priority of four earlier patent applications in the United Kingdom and published under No. WO 95/06077 on 2 March 1995, was refused by a decision of the Examining Division announced orally on 6 April 2000 and issued in writing on 27 April 2000.

II. The decision was based, as main request, on a set of Claims 1 to 19 filed on 22 October 1998, and, as auxiliary request, on a set of Claims 1 to 10 filed on 16 March 2000.

Claim 1 of the main request read as follows:

"A biodegradable polymer, comprising ethylene carbonate units of the formula A

$-(-C(O)-O-CH_2-CH_2-O-)-$ A

and having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C."

Dependent Claims 2 to 9 were directed to specific embodiments of the polymer according to Claim 1.

Independent Claim 10 related to a process for the production of a polymer according to any of Claims 1 to 7. Dependent Claims 11 to 16 referred to specific features of the process of Claim 10.

Independent Claim 17 dealt with a process for making a polymer according to Claim 9. Independent Claim 18 was directed to a pharmaceutical composition in a polymer according to Claims 1 to 7. Dependent Claim 19 related to a preferred embodiment of the composition of Claim 18.
Claim 1 of the auxiliary request read as follows:

"A pharmaceutical composition comprising

(i) a biodegradable polymer, comprising ethylene carbonate units of the formula A

$-(-C(O)-O-CH_2-CH_2-O-)-$ A

having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C and

(ii) GM-CSF as a pharmceutically active agent."

Dependent Claims 2 to 10 referred to preferred features of the composition according to Claim 1

III. The decision held that the subject-matter of Claims 1 to 17 of the main request was anticipated by documents D1 (US-A-3 953 383) and D2 (US-A-3 585 168) and that document D3 (Chemical and Pharmaceutical Bulletin, Volume 32, No. 7, 1984, pages 2795 to 2802, Tsuyoshi Kojima et al."Preparation and Evaluation in vitro of Polycarbonate Microspheres Containing Local Anaesthetics") was novelty destroying for the subject-matter of Claims 1 to 9 and 18 of the main request. The

decision further held that Claim 19 of the main request lacked inventive step in view of D3 and D4 (EP-A-0 535 937) and that Claim 1 of the auxiliary request was obvious in view of the combination of D3 with D4.

IV. On 24 May 2000, a Notice of Appeal against the above decision was lodged by the Appellant (Applicant). The prescribed fee was paid on the same date.

With the Statement of Grounds of Appeal, filed on 6 September 2000, the Appellant submitted six sets of claims forming respectively a new main request and five auxiliary requests.

V. In a communication issued on 5 November 2001, the Board indicated that the grant of patent could be envisaged on the basis of a set of claims resulting from he combination of Claims 1 and 3 of the main request submitted with the Statements of Grounds of Appeal provided several objections under Articles 84 and 123(2) EPC would also have been overcome.

VI. With a letter dated 28 January 2002, the Appellant submitted a set of 17 claims as new main request.

Claim 1 reads as follows:

"A biodegradable polymer comprising ethylene carbonate units of the formula A

$$-(-C(O)-O-CH_2-CH_2-O-)- \quad A$$

and having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C, and a glass transition temperature of from 15 to 50°C and having a molecular

weight (Mw) of 200,000 to 2,000,000, determined by gel permeation chromatography, with methylene chloride as the eluant and polystyrene as the reference with the proviso that the polymer having molecular weight of 200,000 is excluded."

Dependent Claims 2 to 5 relate to preferred features of the polymer according to Claim 1.

Independent Claim 6 refers to a process for the production of a polymer according to Claim 1 and dependent Claims 7 to 10 are directed to specific embodiments of the process of Claim 6.

Independent Claim 11 deals with a pharmaceutical composition containing a polymer according to Claim 1 and dependent Claims 12 to 17 relate to elaborations of the composition according to Claim 11.

VII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 to 17 submitted with its letter dated 28 January 2002.

It also requested the refund of the appeal fee.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Amendments*:

2.1 Claim 1 differs from Claim 1 as originally filed by

(a) the indication of the temperature at which the intrinsic viscosity of the claimed polymer is determined,

(b) the incorporation of the range of molecular (Mw) of the claimed polymer and the indication of the method for its determination,

(c) the proviso that the polymer having a molecular weight (Mw) of 200 000 is excluded.

2.1.1 For amendments (a) and (b), support can be found on page 12, lines 2 to 4 and on page 18, lines 23 to 26 of the application as originally filed, respectively.

2.1.2 Amendment (c) amounts, in effect, to the deletion of the lower limit of the preferred range of molecular weights of the polymer, without however, thereby permitting the range to become open-ended in this respect and, as such, it cannot normally be held to involve the addition of subject-matter (cf. T 2/80, OJ EPO, 1981, 431).

2.1.3 Nor can it result in the Applicant getting, contrary to Article 123(2) EPC, an unwarranted avantage by obtaining patent protection for something he had not properly disclosed not even invented on the date of filing the application (cf. G 1/93, OJ EPO 1994, 541; Reasons 16.). On the contrary, in the present case, the feature (c) excludes protection for part of the subject-matter of the claimed invention which was covered by the application as filed, since the range of molecular weight from 200 000 to 2 000 000 was

expressly mentioned as particularly preferred in the application as filed, and the exclusion of the originally disclosed lower value of this molecular weight range (ie 200 000) neither results in an inventive selection not disclosed in the application as filed or not derivable therefrom, nor provides a technical contribution to the claimed subject-matter.

2.1.4 Therefore, the feature (c) is not to be considered as subject-matter extending beyond the content of the application as filed.

2.2 Dependent Claims 2, 4 and 5 are supported by original Claims 3, 5, and 13, respectively. Dependent Claim 3 finds its support on page 12, lines 4 to 5 of the application as originally filed.

2.3 Independent Claim 6 is supported by the combination of original Claims 16, 17 and 18. Original Claims 20, 21, 22 and 23 support respectively dependent Claims 7, 8, 9 and 10.

2.4 Independent Claim 11 is supported by lines 6 to 7 on page 19 of the application as originally filed. Original Claim 34 provides support for dependent Claim 12. Dependent Claims 13 to 15 find their support on page 21, lines 3 to 5 of the application as originally filed. Dependent Claims 16 to 17 are supported by line 18, on page 19 of the application as originally filed.

2.5 Thus, Claims 1 to 17 meet the requirements of Article 123(2) EPC.

3. *Clarity*

3.1 In view of the documents "Ullmann's Encyclopedia of Industrial Chemistry 5th Edition; Volume A 12, pages 340 to 341" and "Römpp Chemie Lexikon; 10th edition, page 2393" submitted by the Appellant with its letter of 28 January 2002, it is accepted that the abbreviations G-CSF, M-CSF, GM-CSF and LIF have a well recognized meaning in the pharmaceutical field.

3.2 Thus, the Board is satisfied that Claims 1 to 17 meet the requirements of Article 84 EPC.

4. *Novelty*

4.1 In its decision, the Examining Division has relied on documents D1, D2 and D3 for supporting the objection of lack of novelty of the subject-matter of the application in suit. In the Board's view, and, as indicated in its communication of 5 November 2001, document "Applied Polymer Symposium No. 26, 1975, pages 257 to 267" submitted by the Appellant with its telefax of 20 October 1998 (referred below as document D5) as well as document "Die Makromolekulare Chemie, Volume 130, (1969), pages 210 to 220, (Nr. 3170)" (referred below as document D6) are highly relevant too for assessing the novelty of the subject-matter of the application in suit.

4.2 Document D1 relates to a catalytic process for copolymerizing epoxy compounds with carbon dioxide in order to obtain a high yield of alternating copolymer (ie having in chain carbonate groups). In particular, it discloses in its Example 1 a process for the manufacture of an ethylene carbonate polymer by reacting ethylene oxide (EO) with CO_2 in a molar ratio

EO/CO_2 of 1:2.95 at a temperature of 50°C for 24 hours in the presence of a catalyst prepared from $Zn(C_2H_5)_2$ and water in a molar ratio 1:0.95. The obtained polymer is described as being a substantially alternating copolymer which shows no absorption band in infrared at 1100 cm^{-1} (i.e. absorption band of polyether) and which exhibits an intrinsic viscosity of 0.65 dl/g (dioxane, 30°C), but neither its molecular weight nor its Tg are disclosed.

4.3 It is true, as submitted by the Appellant in the Statement of Grounds of Appeal, that no direct comparison is possible between intrinsic viscosities determined in different solvents and at different temperatures. However, in view of document D5 which refers to the synthesis and the thermal degradation of alternating copolymers of CO_2 with ethylene oxide or propylene oxide having a molecular weight between 50 000 and 150 000 and which discloses intrinsic viscosities for EO/CO_2 copolymers up to 1.24 dl/g in dioxane at 30°C (cf. table II of D5), it can be deduced that the copolymer of Example 1 of D1, which has an intrinsic viscosity of 0.62 dl/g under the same conditions, most likely exhibits a molecular weight of less than 150 000, ie well below the lower value of the molecular weight required in Claim 1 of the main request. Thus, at least for this reason, D1 cannot destroy the novelty of the subject-matter of Claim 1 of the application in suit.

4.4 Document D3 refers to the preparation and the *in vitro* evaluation of microspheres made of polyethylene carbonate or polypropylene carbonate containing local anesthetics. It discloses only a polyethylene carbonate polymer having a molecular weight of 50 000 and an

intrinsic viscosity of 0.37 dl/g in dioxane at 25°C (cf. D3, page 2795, line 1 to page 2796, line 19; paragraph "Dibucaine-Poly(ethylene carbonate) Microspheres", and Figure 8 on pages 2800 and 2801). Thus, D3 cannot destroy the novelty of the subject-matter of Claim 1.

4.5 Document D6 deals with the copolymerization of carbon dioxide and epoxide compounds such as ethylene oxide, propylene oxide, styrene oxide, isobutylene oxide or epichlorohydrin in the presence of organometallic compounds as catalysts. In its Example 43, it discloses a copolymer EO/CO_2 having an intrinsic viscosity of 0.98 dl/g (chloroform, 30°C), a carbon content of 40.96%, ie corresponding to a carbonate unit content of 99.3% by mole (cf. D6, page 212, "Polymerization procedure"; pages 217 to 219, "Copolymerization of carbon dioxide with epoxide other than PO"). There is, however, no mention of the molecular weight and of the Tg of the copolymer of Example 43 in D6.

4.6 Document D2, whose authors are the same as those of D6, also deals with the copolymerization of carbon dioxide with epoxide such as ethylene oxide, propylene oxide, epichlorohydrin, styrene oxide or isobutylene oxide in the presence of an organometallic catalyst. According to D2, the molecular weight of the copolymers obtained is in the range between 10 000 and 200 000 ((cf. D2; column 2, lines 2 to 37). More specifically, D2 discloses in its Example 13 the preparation of an EO/CO_2 copolymer having an intrinsic viscosity of 0.98 dl/g in chloroform at 30°C (ie exactly the same intrinsic viscosity as the copolymer of Example 43 of D6). In view of the general statement made in D2 concerning the molecular weight of the copolymers prepared according

to the process disclosed therein, it follows that the molecular weight of the copolymer of Example 13 of D2 cannot be greater than 200 000. It is also noted by the Board that the process conditions for obtaining this copolymer exactly correspond to those of Example 43 of D6. Thus, in view of the similarity of both the process conditions used and the intrinsic viscosity with the copolymer obtained in Example 13 of D2, it can be deduced that the molecular weight of the copolymer disclosed in Example 43 of D6 cannot be greater than 200 000.

4.7 Consequently, neither D2 nor D6 can destroy the novelty of the subject-matter of Claim 1 of the application in suit.

4.8 The same conclusion applies for document D5, since it refers only to copolymers of carbon dioxide with ethylene oxide or propylene oxide having a molecular weight in the range 50 000 to 150 000, ie below the minimal value required for the copolymer according to Claim 1 of the application in suit.

4.9 It follows from that the subject-matter of Claim 1 is novel over the cited prior art (Article 54(1)(2) EPC). Similar considerations apply to the subject matter of dependent Claims 2 to 5.

By the same token, Claims 6 to 10, which refer to a process for making a copolymer according to Claims 1 to 5, and Claims 11 to 17 which relate to a pharmceutical composition comprising a copolymer according to Claims 1 to 5, meet the requirements of Article 54(1)(2) EPC.

5. *The application in suit; the technical problem*

5.1 The application in suit is concerned with biodegradable polymers of ethylene oxide with carbon dioxide for use in pharmaceutical compositions with sustained release. Such polymers are, however, known from D3, which the Board regards as the closest state of the art.

5.2 Starting from D3 the technical problem may be seen in the provision of biodegradable polyethylene carbonate polymers which are not degradable by hydrolysis in the presence of hydrolytic enzymes or under basic conditions but which are degradable *in vitro* and *in vivo* by non hydrolytic surface erosion, and which allow the manufacture of sustained drug delivery systems having an almost constant release rate *in vivo*.

5.3 According to the application in suit, this problem is solved by a EO/CO_2 polymer having a molecular weight between 200 000 and 2 000 000 as defined in Claim 1.

5.4 In view of Figures 1/13 and 9/13 which refer to the hydrolysis resistance, of Figures 3/13 and 8/13 which deal with the surface erosion *in vitro* and *in vivo,* and of Figures 10/13 and 11/13 which show respectively an almost constant drug release *in vivo* and a 1:1 correlation between mass degradation and drug release, the Board finds it credible that the claimed measures provide an effective solution of the stated problem.

6. *Inventive step*

6.1 It remains to be decided whether the proposed solution was obvious in the light of the cited prior art.

6.2 Document D3 discloses the use of polyethylene carbonate polymers having a molecular weight of 50 000 as matrix materials in sustained release compositions comprising pharmacologically active compounds. The release patterns *in vitro* (buffer solution, pH 7.4) of these polyethylene carbonates (cf. Figure 8) show a large initial drug burst followed by a slow release thereafter (ie a non linear release with time, based on diffusion process and dependent on the drug content). It cannot therefore suggest that polyethylene carbonates having a much higher molecular weight as defined in Claim 1 of the application in suit would show essentially no release of the drug *in vitro* (buffer solution pH 7.4; cf. Figure 9/13 of the application in suit), would be degradable *in vitro* and *in vivo* by non hydrolytic surface erosion and would allow the manufacture of pharmaceutical compositions having a linear drug release with time *in vivo.* Consequently, D3 itself cannot lead to the solution of the technical problem.

6.3 Document D4 deals with microparticle preparations of a polymer containing a drug and having improved prolonged release properties. D4 discloses the use of polymers having a molecular weight in the range 1 000 and 800 000 as matrix material. These polymers are either slightly water-soluble or water-insoluble and should preferably be biodegradable. Although D4 mentions polyethylene carbonates among the biodegradable polymers which may be used, without, however, specifying their molecular weight and their structure (e.g. relative amount of carbonate units), there is no suggestion in D4 that polyethylene carbonates as defined in Claim 1 of would, as such, allow the manufacture of sustained release pharmaceutical

compositions having an almost linear release with time. On the contrary, D4 places no specific emphasis on which polymer may be used as matrix, and, independently of the polymer used for the matrix material, indeed solves the problem of the large initial drug release, in other words of the non linear release of the drug from the preparation, by coating the microparticles with an aggregation preventing agent such as water soluble saccharides or proteins (cf. D4, page 2, lines 15 to 35; page 3, lines 3 to 4 and lines 13 to 21; page 5, lines 25 to 50; Claims 1, 2, 3, 7). Thus, D4 cannot provide any assistance in the solution of the technical problem.

6.4 Document "Chem. Pharm. Bull. Volume 31, No. 4, 1983; pages 1400-1403" (acknowledged in the description of the application in suit at page 9, third paragraph; referred below as D7) discloses that polyethylene carbonate polymers having a molecular weight of 50 000 are biodegradable *in vivo* and resistant to hydrolytic degradation *in vitro* (phosphate buffer system, pH 7.4, 37°C). It thus presumes that their degradation *in vivo* might be an enzymatic degradation but gives no information whether on their degradation kinetics (ie bulk erosion or surface erosion, hydrolytic degradation or non-hydrolyic degradation) or on their release properties *in vivo.* It cannot therefore provide any suggestion of the specific *in vitro* and *in vivo* degradation behaviour (cf. paragraph 5.2 above) of polyethylene carbonates having a much higher molecular weight as defined in Claim 1 of the application in suit. Thus, document D7 cannot lead to the solution of the technical problem.

6.5 The information contained in documents D1, D2, D5, and

D6 is, in the Bord's view, even less relevant, since they are neither concerned with pharmaceutical compositions, nor with the drug release behaviour thereof.

6.6 Consequently the subject-matter of Claim 1, and by the same token, of Claims 2 to 17 involves an inventive step (Article 56 EPC).

7. *Procedural matters*

7.1 According to Rule 67 EPC the appeal fee shall be reimbursed in the event of interlocutory revision or where the Board deems the appeal allowable, if reimbursement is equitable by reason of a substantial procedural violation.

7.2 In the present case, the Appellant has requested the reimbursement of the appeal fee without, however, submitting any arguments in support of its request.

7.3 It has not been contested by the Appellant, and the Board itself sees no reason to do so, that the decision of the Examining Division to refuse the application was based on grounds and evidence on which the Appellant has had the opportunity to comment.

7.4 It is true that the Examining Division has not accepted to postpone, as requested by the Appellant in the consultation by phone of 4 April 2000, the oral procedings scheduled on 6 April 2000. In that respect, however, it is noted by the Board, that the Appellant has had ample opportunities (two communications in the European phase, following a written opinion and international examining report in the PCT phase) and

time (e.g. more than 8 months between the issue of the summons to oral proceedings, in which the Examining Division clearly warned the Appellant that a decision persuant to Article 97 EPC would most likely be announced at the end of the oral proceedings, and the date thereof) to present arguments and amendments. Thus, the decision of the Examining Division not to postpone the oral proceedings but to hold them in the absence of the Appellant, was, in the Board's view, in the interest of a speedy completion of the proceedings and cannot, in any case, represent a procedural violation (cf. Rule 71(2) EPC).

7.5 Thus, in the Board's view, no substantial procedural violation, which could justify the reimbursement of the appeal fee, has taken place in the proceedings up to refusal by the Examining Division. It follows that the request for reimbursement of the appeal fee must be rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted back to first instance with the order to grant a patent on the basis of Claims 1 to 17 submitted with letter of 28 January 2002, after any necessary consequential amendment of the description.

3. The request for reimbursement of the appeal fee is rejected.

The Registrar: The Chairman:

E. Görgmaier R. Young