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Datasheet for the decision of 16 April 2020

Case Number: T 1831/18 - 3.3.07

Application Number: 06256581.7

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Language of the proceedings: EN

Title of invention:

Polymeric compositions comprising therapeutic agents in crystalline phases, and methods of forming the same

Patent Proprietor:

Cordis Corporation

Opponent:

BIOTRONIK AG

Headword:

Polymeric compositions comprising therapeutic agents in crystalline phases / BIOTRONIK

Relevant legal provisions:
EPC R. 99(2)
EPC Art. 108, 56, 100(a), 123(2), 123(3)

Keyword:
Admissibility of appeal by opponent - (yes)
Inventive step - main request, auxiliary requests 1, 2, 4-6 (no)
Amendments - added subject-matter, auxiliary requests 3, 7 (yes) - broadening of claim, auxiliary requests 4-7 (yes)

Decisions cited:
T 0777/08

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Beschwerdekammern

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Case Number: T 1831/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 April 2020

Appellant: (Patent Proprietor)	Cordis Corporation 14201 N.W. 60th Avenue Miami Lakes, Florida 33014 (US)
Representative:	Prock, Thomas Marks & Clerk LLP 15 Fetter Lane London EC4A 1BW (GB)
Appellant: (Opponent)	BIOTRONIK AG Ackerstrasse 6 8180 Bülach (CH)
Representative:	Keil & Schaafhausen Patentanwälte PartGmbB Friedrichstraße 2-6 60323 Frankfurt am Main (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 May 2018 concerning maintenance of the European Patent No. 1810665 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	C. Schmidt

Summary of Facts and Submissions

I. European patent 1 810 665 (hereinafter "the patent") was granted on the basis of 5 claims. Claim 1 of the patent as granted read as follows:

"An implantable medical device which has a coating over a [*sic*] least a portion thereof formed from a drug-containing polymeric composition which comprises at least one therapeutic agent encapsulated in at least one biocompatible polymer, in which the therapeutic agent includes at least one of rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus and pimecrolimus, characterised in that more than 90% of the rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus that is present in the composition is in its crystalline form."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

During the proceedings before the opposition division, the patent proprietor defended its case on the basis of the patent as granted as main request or on the basis of auxiliary requests 1 to 7, all filed with letter dated 29 July 2016. These requests differed from the main request as follows:

Claim 1 of auxiliary request 1 differed from claim 1 as granted by the following additional feature:

"the crystalline particles of the therapeutic agent have an average particle size ranging from 100 nm to 200 nm."

Claim 1 of auxiliary request 2 differed from claim 1 of auxiliary request 1 by the following additional feature:

"the at least one biocompatible polymer forms a substantially continuous polymeric matrix with the at least one therapeutic agent encapsulated therein."

Claim 1 of auxiliary request 3 differed from claim 1 of auxiliary request 1 by the following additional features:

"the at least one biocompatible polymer forms polymeric particles with the at least one therapeutic agent encapsulated therein."

Auxiliary requests 4-7 were identical, respectively, to the main request and auxiliary requests 1-3 with the exception of the following amendment (additions and ~~deletions~~ emphasized by the Board):

"more than 90% of the therapeutic agent in said composition is crystalline ~~rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus that is present in the composition is in its crystalline form~~."

III. The opposition division took the interlocutory decision that, on the basis of the auxiliary request 1, the patent met the requirements of the EPC. The decision was based on the patent as granted as main request and on auxiliary request 1.

IV. The decision of the opposition division cited among others the following documents:

D4: WO 00/32238 A1
D13: WO 2004/028582

V. The opposition division decided in particular as follows:

(a) The main request complied with the requirements of Article 123(2) EPC, of sufficiency of disclosure and of novelty.

The closest prior art was D4. D4 did not disclose that more than 90% of the active agent was present in the composition in its crystalline form. No effect was shown to arise from this difference. The objective technical problem was the provision of an alternative to D4. The claimed solution was obvious in light of D4. Thus, the main request did not comply with the requirements of inventive step.

(b) Auxiliary request 1 met the criteria of Article 123(2) EPC, of sufficiency of disclosure and novelty for the same reasons as the main request.

Regarding inventive step, starting from D4 as closest prior art, the subject-matter of auxiliary request 1 differed not only by the percentage of crystalline therapeutic agent but also by the average size of the therapeutic agent particles. The technical problem was the provision of an alternative to D4. The claimed solution was not suggested by D4. The same reasoning applied for D4 in combination with D13.

VI. Both the appellant-patent proprietor and the appellant-opponent lodged an appeal against the above interlocutory decision of the opposition division.

VII. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted, or, alternatively, on the basis on one of the auxiliary requests 1-7 filed on 29 July 2016 during the proceedings before the opposition division. The appellant-patent proprietor also requested that the appeal of the opponent be rejected as inadmissible.

VIII. The appellant-opponent requested that the patent be revoked in its entirety.

IX. The Board summoned the parties to oral proceedings.

In a communication pursuant to Article 15(1) RPBA, the Board expressed *inter alia* the preliminary opinion that the subject-matter of the main request as well as the auxiliary requests 1-2 did not involve an inventive step. Auxiliary request 3 did not appear to meet the criteria of Article 123(2) EPC. The same considerations applied to auxiliary requests 4-7. The compliance of auxiliary requests 4-7 with the requirements of Article 123(3) EPC was additionally questioned.

By letter dated 21 February 2020, the appellant-patent proprietor announced that it would not be attending the scheduled oral proceedings and wished to rely on its written submissions to date.

The oral proceedings were cancelled.

X. The appellant-patent proprietor's written arguments, as far as relevant to the present decision, can be summarised as follows:

(a) The appellant-opponent neither requested that the decision under appeal be set aside nor indicated the reasons for doing so, contrary to Rule 99(2) EPC. In the absence of causal relationship between the findings in the decision and the reasoning in the appellant-opponent's statement of grounds of appeal, the appeal of the appellant-opponent should be found inadmissible.

(b) The main request fulfilled the criteria of Article 56 EPC.

D4 represented the closest prior art. The distinguishing feature of claim 1 of the main request over D4 was that more than 90% of the at least one therapeutic agent was in its crystalline form.

The technical effect of this difference was, as discussed on page 4 of the application as filed, an improved stability of the therapeutic agent (in the sense of an improved ability of the therapeutic agent to retain its physical, chemical and therapeutic properties). The objective technical problem was therefore the provision of a medical device coated with a drug-containing polymeric composition wherein the stability of the therapeutic agent was improved.

D4 was solely concerned with the effect of crystallinity on the release time of the therapeutic agent from the delivery device, but was

completely silent about the effect of crystallinity on stability. Moreover, D4 did not motivate the skilled person to minimise the amount of amorphous material in the therapeutic agent. Hence the subject-matter of the main request involved an inventive step.

(c) Auxiliary request 1 fulfilled the criteria of Article 56 EPC.

The distinguishing features of claim 1 of auxiliary request 1 over D4 were as follows:

(i) More than 90% of the therapeutic agent was crystalline; and,

(ii) The crystalline particles of the therapeutic agent had an average particle size ranging from 100 nm to 200 nm.

The associated technical effects were an improvement in stability and bioavailability. Accordingly, the problem was how to improve the stability and bioavailability of a therapeutic agent coated on a drug-eluting implantable medical device.

D4 did not provide any motivation to include the therapeutic agent at more than 90% crystallinity. Furthermore, D4 only mentioned much greater particle sizes (see Example 1) and gave no motivation whatsoever to vary the particle size, let alone to consider the size range of claim 1. D13 did not mention crystalline particles and actively taught the use of non-crystalline, amorphous material (see the final paragraph on page 8), such that the skilled person would not consider this document.

Hence, the subject-matter of auxiliary request 1 was inventive in view of a combination of D4 and D13.

(d) Auxiliary request 3 complied with Article 123(2) EPC. Coating of an implantable medical device comprising polymeric particles with a therapeutic agent encapsulated therein was disclosed in the application as filed at page 7, lines 12-13; page 7, line 28 to page 8, line 3; page 12, line 28 to page 17, line 21. The paragraph spanning pages 12 and 13 indicated that an implantable medical device could be coated with a substantially continuous matrix with the therapeutic agent encapsulated therein. The subsequent paragraph indicated that the crystalline drug particles could first be individually encapsulated by a protective layer. The following paragraphs on pages 14 to 17 illustrated various methods of achieving this encapsulation, which produced polymeric particles having the therapeutic agent encapsulated therein.

XI. The appellant-opponent's written arguments, as far as relevant to the present decision, can be summarised as follows:

(a) D4 represented the closest prior art. D4 disclosed an implantable medical device coated at least partially with a polymer composition comprising (and therefore encapsulating) a therapeutic agent. Rapamycin was mentioned as therapeutic agent (see page 4, line 16). A major amount of the therapeutic agent was crystalline (see claim 1; page 2, line 15 to page 4, lines 7 to 10; figure 1). The only differentiating feature was that the amount of crystalline therapeutic agent was above 90%.

An effect of the amount of crystalline form on stability was merely asserted and not proven. Furthermore, as set out in T 777/08, the mere provision of the crystalline form of a known pharmaceutically active agent could not be regarded as inventive as long as it did not overcome any prejudice or gave rise to any unexpected technical effect. Thus the subject-matter of the main request did not involve an inventive step.

(b) Regarding auxiliary request 1, the particle size of 100-200nm did not contribute to the solution of the technical problem, and was not linked to the improved bioavailability mentioned in the patent. This particle size was therefore to be seen as a parameter which the skilled person would optimise as a matter of routine experimentation. Even if it was accepted that the particle size gave rise to a modified release profile, this effect would not be surprising in light of D13 (see page 8, lines 22-35).

(c) Regarding auxiliary request 2, the feature pertaining to a continuous matrix was already shown in D4 (page 6, line 11).

(d) Auxiliary request 3 did not meet the requirements of Article 123(2) EPC. The feature that the biocompatible polymer forms polymeric particles with the therapeutic agent encapsulated therein was shown in the description as filed in relation with injectable particles. The combination of this feature with the biocompatible polymer coating and the high content in crystalline form was unallowable.

(e) The same objections were raised in respect of the reworded auxiliary requests 4-7.

Reasons for the Decision

Admissibility of the appeal by the appellant-opponent

1. According to the appellant-patent proprietor, the appeal by the appellant-opponent is inadmissible, because the appellant-opponent, in its statement setting out the grounds of appeal, did not request that the decision be set aside nor indicated the reasons for doing so. The appellant-opponent has provided no counter-arguments to the opposition division's reasoning, i.e. there is no causal relationship between the findings in the decision under appeal and the reasoning in the appellant-opponent's statement of grounds of appeal.

1.1 However, the appellant-opponent with its statement of grounds of appeal dated 13 September 2018 requested that the patent be revoked in its entirety. Since the contested decision maintained the patent on the basis of the 1st auxiliary request, this implies the request that the decision under appeal be set aside.

1.2 Furthermore, for the purpose of assessing admissibility of the appeal pursuant to Article 108, third sentence, EPC and Rule 99(2) EPC, the appeal can only be assessed as a whole. There is no support in the EPC for a notion of "partial admissibility" of an appeal.

Here, at least in respect of inventive step, the statement of grounds of appeal of the appellant-

opponent is sufficiently reasoned, for the following reasons. The impugned decision found the subject-matter of auxiliary request 1 to involve an inventive step because D4 provided no hint about the relevance of particle size to drug release, and briefly mentioned that the same reasoning applied to a combination of D4 with D13 without further details. The reasoning in the appellant-opponent's statement of grounds of appeal in respect of the combination of D4 and D13 is, in comparison, sufficient to allow the board to understand why the decision is alleged to be incorrect and on what facts the appellant-opponent bases its arguments, without first having to make investigations of its own.

1.3 Since the requirements of Article 108, third sentence, EPC are fulfilled for at least one ground of appeal, the appeal of the appellant-opponent is admissible.

Main request (patent as granted)

2. Inventive step

2.1 In agreement with both parties, the Board considers D4 to represent the closest prior art.

D4 discloses a medical device for insertion into a mammalian body, i.e. an implantable medical device, wherein a crystalline therapeutic agent is applied on at least a portion of its surface (see claim 1 of D4). Rapamycin is recited among the suitable therapeutic agents on page 4, line 16 of D4. The crystals of the active compound can be incorporated within a polymeric layer which at least partially coats the medicinal device (see page 5, lines 24-27).

Although D4 discloses the presence of crystalline therapeutic agent on the device (e.g. figure 1), it is not directly and unambiguously derivable from D4 that it is in amounts beyond 90%.

2.2 The subject-matter of claim 1 of the main request thus differs from the implantable medical device of D4 in that more than 90% of the therapeutic agent (rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus) that is present in the composition is in its crystalline form.

2.3 According to the appellant-patent proprietor, the technical effect resulting from this higher crystalline form content is that the stability of the therapeutic agent is improved. The Board notes that the patent contains no evidence of this effect beyond the statements cited by the appellant-patent proprietor (i.e paragraphs [0017]-[0019]). Nonetheless, the Board accepts this effect for the reasons set out below.

2.4 The objective technical problem is the provision of a medical device coated with a drug-containing polymeric composition wherein the stability of the therapeutic agent is improved.

2.5 As mentioned in T 777/08, OJ 2011, 633 (point 5.2 of the reasons), "amorphous forms are generally known to be more soluble and have greater bioavailability than their crystalline counterparts. However, several disadvantages can also generally be expected for the amorphous form, namely, with respect to chemical and physical instability". The skilled person, faced with the above problem, would know from common general knowledge that a crystalline form solves the technical problem defined above. The skilled person is further

prompted to consider higher amounts of crystalline material by D4, where the feature that "the therapeutic agent is in a crystalline form" is described as a solution to the problem of achieving long release times. Contrary to the appellant-patent proprietor's position, no incentive to retain part of the therapeutic agent in amorphous state can be discerned in D4.

2.6 Accordingly, the subject-matter of claim 1 of the main request does not involve an inventive step.

Auxiliary request 1

3. Inventive step

3.1 In comparison with the implantable medical device of the closest prior art D4, the subject-matter of claim 1 of auxiliary request 1 differs in that:
- more than 90% of the therapeutic agent (rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus) that is present in the composition is in its crystalline form, and
- the crystalline particles of the therapeutic agent have an average particle size ranging from 100 nm to 200 nm.

3.2 The appellant-patent proprietor contends that these features lead to improvements in stability and bioavailability.

With respect to the higher content in crystalline form and its effect on stability, reference is made to the consideration given above (see 2.).

As to the average particle size, the patent contains no evidence of any effect on bioavailability beyond the mere statements in the passages of the description cited by the appellant-patent proprietor (see paragraphs [0006] and [0034] of the patent). Furthermore, in these paragraphs, the effect on bioavailability is not related to the claimed particle sizes of 100-200nm but to the "small-size drug particles that can be formed by using nanothechnology", and is only stated to arise for poorly soluble drugs. Consequently, the claimed average particle size of 100-200 nm is not credibly shown to have any effect on bioavailability. This effect cannot be taken into account for the formulation of the technical problem.

3.3 Thus, the objective technical problem remains the provision of a medical device coated with a drug-containing polymeric composition wherein the stability of the therapeutic agent is improved.

3.4 The only mention in D4 of any particle sizes of the therapeutic agent is the length of the crystals formed during the process of example 1, said length being much greater than the upper limit of present claim 1 (see pages 8 and 9). However, the general disclosure of D4 is not limited to any particle sizes, and is also not limited in terms of the process for forming these crystals (see the statement on page 5, lines 28-29). The selected range of 100-200nm is not shown to be associated with any unexpected technical effect. The skilled person, knowing from D13 (see page 8, lines 22-35) the influence of particle size and surface area on dissolution rate, especially for poorly soluble drugs, would select the claimed range in the course of routine optimisation without the exercise of inventive skills. Contrary to the appellant-patent proprietor's

view, the general teaching of D13 is not limited to crystalline forms.

3.5 Accordingly, the subject-matter of claim 1 of auxiliary request 1 does involve an inventive step.

Auxiliary request 2

4. Inventive step

Claim 1 of auxiliary request 2 comprises the further feature according to which the at least one biocompatible polymer forms a substantially continuous polymeric matrix with the at least one therapeutic agent encapsulated therein.

The appellant-opponent considers that this feature is already disclosed in the closest prior art D4 (see page 6, line 11). The Board concurs. Accordingly, the amendments corresponding to auxiliary request 2 do not modify the above conclusions of lack of inventive step.

Auxiliary request 3

5. Article 123(2) EPC

Claim 1 of auxiliary request 3 comprises the further feature according to which the at least one biocompatible polymer forms polymeric particles with the at least one therapeutic agent encapsulated therein.

5.1 The Board share the appellant-opponent's view that the application as filed does not disclose the combination of the feature pertaining to a coated implantable medical device and the feature pertaining to the

encapsulation of the therapeutic agent in particles of biocompatible polymer.

The application as filed generally pertained to drug-containing polymeric compositions suitable for forming implantable medical devices and nano/micro-particulate formulations. Compositions of biocompatible polymeric particles appear to be considered only in the context of formulations for injection (see page 7, lines 12-27), and not in the context of a coating on an implantable medical device. Contrary to the appellant-patent proprietor's view, the passages on pages 12-17 do not disclose an implantable medical device coated with particles of the biocompatible polymer encapsulating the therapeutic agent, but only the encapsulation of the crystalline therapeutic agent in a protective coating layer before mixing with the polymeric solution. Accordingly, the subject-matter of claim 1 cannot be derived directly and unambiguously from the content of the original application. Thus the requirements of Article 123(2) EPC are not met.

Auxiliary requests 4-7

6. Auxiliary requests 4-7 are respectively identical to the main request and auxiliary requests 1-3 with the exception of the following amendment (shown by the Board):

"more than 90% of the therapeutic agent in said composition is crystalline ~~rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus that is present in the composition is in its crystalline form~~."

6.1 This amendment extends the protection conferred by the patent, because amended claim 1 no longer requires that more than 90% of the rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus present in the composition be crystalline.

In claim 1, the therapeutic agent includes, but is not limited to rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus. In claim 1 as amended, the requirement that more than 90% of the therapeutic agent is crystalline is not limited to the specific agents recited in the first part of the claim. Consequently, a crystalline content in the therapeutic agent of more than 90% does not necessarily entails that the rapamycin, rapamycin ester, everolimus, zotarolimus, biolimus, tacrolimus or pimecrolimus contained therein is crystalline for more that 90%. As a result, none of the auxiliary requests 4-7 comply with the requirements of Article 123(3) EPC.

6.2 Additionally this amendment does not modify the conclusions reached above in respect of the higher-ranking requests. No additional differentiating features over the closest prior art D4 are introduced in auxiliary requests 4-6, with the consequence that these requests do not meet the requirements of Article 56 EPC. Auxiliary request 7 still contains the combination of features found to infringe Article 123(2) EPC above (see 5. above).

7. It follows from the above that none of the requests of the appellant-patent proprietor can be allowed. Accordingly, the decision under appeal has to be set set aside and patent has to be revoked. The Board could take this decision in writing since the appellant-patent proprietor who is adversely affected by this

decision announced not to attend oral proceedings scheduled for 19 March 2020. The statement not to attend oral proceedings is treated as equivalent to a withdrawal of the request for oral proceedings (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, III.C.4.3.2 and the decisions sited there).

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated