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Datasheet for the decision of 3 March 2011

Case Number: T 0260/09 - 3.3.10

Application Number: 05250248.1

Publication Number: 1557183

IPC: A61L 31/10

Language of the proceedings: EN

Title of invention:
Local vascular delivery of mycophenolic acid in combination with rapamycin to prevent restenosis

Applicant:
Cordis Corporation

Headword:
Local vascular delivery/CORDIS

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (no)"

Decisions cited:
T 0020/81, T 0939/92

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0260/09 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 3 March 2011

Appellant: Cordis Corporation
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 17 July 2008 refusing European patent application No. 05250248.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: P. Gryczka
Members: J.-C. Schmid
D. S. Rogers

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division which refused European patent application No. 05250248.1 (publication number EP-A-1 557 183) whose independent claim 1 read as follows:

"1. A medical device comprising:
an implantable structure;
a basecoat matrix, including a combination of rapamycin and mycophenolic acid, in therapeutic dosages, incorporated in a first polymeric material, the basecoat matrix being affixed to the surface of the implantable medical device; and
a topcoat, including a second polymeric material, affixed to the basecoat matrix for controlling the elution rate of the rapamycin and mycophenolic acid."

II. The Examining Division refused the application for lack of inventive step (Article 56 EPC) considering that document

(2) EP-A-0 551 182,

describing the administration of rapamycin, alone or in combination with mycophenolic acid via a vascular stent impregnated therewith, represented the closest prior art. The technical problem to be solved vis-à-vis that document was seen as the provision of alternative medical devices with different/slower rapamycin/mycophenolic acid release profiles. According to the Examining Division modifying the medical device of document (2) to include a two-layered polymeric release matrix without any unexpected or surprising

technical effect was considered to be obvious for the skilled person since document

(1) WO-A-03/057218

disclosed *inter alia* medical devices comprising the combination of rapamycin with mycophenolic acid in polymeric layers. *Inter alia* document

(6) US 2003/0060877

disclosed that the elution of drugs from implantable medical devices could be controlled by applying the drugs to these devices in the form of polymeric coatings. The Examining Division concluded therefore that the subject-matter of claim 1 of the application as filed lacked an inventive step.

III. With a letter dated 21 December 2010 the Appellant filed three sets of claims as auxiliary requests 1, 2 and 3.

Claim 1 of auxiliary request 1 differs from claim 1 of the application as filed in that the first polymeric material comprises a fluoropolymer and the second polymeric material comprises an acrylic polymer, and in that the second polymeric material is incompatible with the first polymeric material which comprises an acrylic polymer, thereby creating both a physical and chemical barrier to the elution of the rapamycin and mycophenolic acid.

Claim 1 of auxiliary request 2 differs from claim 1 of the application as filed only in that the first

polymeric material comprises a fluoropolymer and the second polymeric material comprises an acrylic polymer.

Claim 1 of auxiliary request 3 differs from claim 1 of the application as filed in that the basecoat is a PVDF/HFP matrix and the topcoat is BMA.

IV. At the oral proceedings before the Board held on 3 March 2011, the Appellant submitted a set of seven claims as main request, claims 1 to 7 of this request being identical to claims 1 to 7 of the application as filed.

According to the Appellant document (1) was the closest prior art. The technical problem underlying the invention was the provision of a medical device improving the treatment of vascular diseases, in particular restenosis. The claimed medical device was characterized by the selection of a drug delivery means comprising a basecoat matrix including a combination of rapamycin and mycophenolic acid incorporated in a first polymeric material and a topcoat comprising a second polymeric material. Figure 52 of the application as filed revealed that mycophenolic acid potentiated rapamycin in cultured cells, which was not foreseeable from the teaching of document (1). Figure 50 showed a better release control of rapamycin when the polymeric material of the basecoat was incompatible with that of the topcoat. Although figure 50 only related to the release of rapamycin, it had to be assumed that mycophenolic acid would have the same release profile than rapamycin on account of their structural similarities. Hence the results shown for rapamycin

were to be extrapolated to a mixture of rapamycin and mycophenolic acid.

An inventive step objection could only be based on hindsight, since to arrive at the claimed subject-matter from document (1) it was necessary to select: (1) the use of rapamycin rather than a derivative thereof; (2) to use rapamycin with a co-agent; (3) to use mycophenolic acid as the co-agent; (4) to deliver the agent and the co-agent on a device; (5) to used a coated device; (6) to use a two layer coating; and (7) to place both agents in the base layer.

Concerning the deletion in auxiliary request 2 of the feature that the second polymeric material is incompatible with the first polymeric material, the Appellant indicated that it was clear from page 102, lines 14 to 28 of the application as filed that fluoropolymers and acrylic polymers were incompatible. Thus by specifying that one polymer was a fluoropolymer and the other was an acrylate polymer, claim 1 of auxiliary request 2 inherently specified that those polymers were incompatible and performed the function set out in claim 5 as filed. Although not expressly specifying that the second polymeric material was incompatible with the first polymeric material, claim 1 of auxiliary request 2 had the same subject-matter as claim 1 of auxiliary request 1.

Document (1) did not suggest any coated medical device having a basecoat comprising a fluoropolymer and a topcoat comprising an acrylate polymer, let alone any coated device having a basecoat of PVDF/HDF combined with a top coat of BMA. The subject-matter of claim 1

of auxiliary requests 1 to 3 was therefore not obvious in the light of document (1).

V. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of:
1) the main request, filed at the oral proceedings; or alternatively,
2) on the basis of one of the auxiliary requests 1-3, filed under cover of a letter dated 21 December 2010.

VI. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Inventive step*

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is necessary to establish the closest state of the art, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

2.1 The Board considers, in agreement with the Appellant, that document (1) represents the closest state of the

art, and, hence, takes it as the starting point in the assessment of inventive step. The Opposition Division started from document (2). However this document does not describe any coated device and hence it is further away from the claimed subject-matter than document (1).

Document (1) discloses drug delivery systems for the prevention and treatment of proliferative diseases, particularly vascular diseases (see page 1, lines 1 and 2; page 3, lines 28 to 30). The drug delivery device described in claim 5 of that document is a medical device adapted for administration in hollow tubes, e.g. a coated stent (page 12, line 14), comprising a therapeutic dosage of a rapamycin derivative having mTOR inhibiting properties, including rapamycin (page 4, lines 5 and 6), in conjunction with a therapeutic dosage of mycophenolic acid each being releasably affixed to the drug delivery device (also see page 5, lines 3 to 5 and page 7, lines 16 and 17). In particular, the drugs may be affixed to the coated stent by incorporating them into a polymeric matrix comprising two layers, a base layer in which the drugs are incorporated and a top coat which acts as a diffusion-control of the drugs (see page 13, line 15 in combination with page 14, lines 14 to 17).

2.2 The Appellant submitted during the oral proceedings that the technical problem underlying the invention was the provision of a medical device improving the treatment of vascular diseases, in particular restenosis.

2.3 The proposed solution to this technical problem is the coated medical device of claim 1 which is characterized

by selecting a drug delivery means comprising a basecoat matrix including a combination of rapamycin and mycophenolic acid incorporated in a first polymeric material and a topcoat including a second polymeric material.

2.4 In order to demonstrate that the technical problem as defined above has effectively been solved by the claimed device the Appellant relied on the results of the experiments described in figures 52 and 50 of the application as filed.

2.4.1 Figure 52 is a graphical representation of the anti-proliferative activity of rapamycin with varying concentrations of mycophenolic acid in non-synchronized cultured human coronary artery smooth muscle cells stimulated with two percent fetal bovine serum (see page 50, lines 17 and 28 of the application). According to the Appellant, this figure revealed that mycophenolic acid potentiated rapamycin in cultured cells, what was not foreseeable from the teaching of document (1).

However, the experiment referred to in figure 52 does not concern the delivery of rapamycin and mycophenolic acid via a coated medical device according to claim 1 and thus does not reflect the impact of the technical feature characterising the claimed subject-matter, i.e. the fact that a combination rapamycin and mycophenolic acid is incorporated in a coated medical device (see point 2.3 above). In fact the combination of rapamycin and mycophenolic acid is already known from document (1) and does not characterise the proposed solution (see document (1); page 5, lines 3 to 5, page 7, line 16 and

claim 5). Accordingly, the data reported in figure 52 is not appropriate to show any improvement linked to the claimed medical devices over those described in document (1).

2.4.2 Figure 50, also referred to by the Appellant to show that the technical problem was solved, indicates the fraction or percentage of rapamycin released over time from various polymeric coatings during in vitro testing.

However, the coated stents described in this figure do not comprise the combination of rapamycin and mycophenolic acid and, thus, do not fall within the ambit of claim 1, so that this figure also cannot show any improvement of the claimed devices over those described in document (1) in the treatment of vascular diseases.

The Appellant argued that, due to their structural similarities, mycophenolic acid and rapamycin would have the same release profile. Hence the results of the rapamycin release shown in figure 50 were to be extrapolated to the release of a combination of rapamycin and mycophenolic acid.

However, in the absence of any supporting piece of evidence, the Board considers the Appellant's argument as a mere speculation, all the more so since rapamycin and mycophenolic acid are structurally quite different. Furthermore this argument is inconsistent with the teaching of the application which discloses that the selection of the polymeric matrix depends on the drug to be delivered thereby indicating a close relationship between the structure of a drug and its release from

the polymeric matrix (see page 99, line 21 and 22 of the application).

2.4.3 Therefore, figures 50 and 52 do not adequately demonstrate any effect linked to the feature distinguishing the claimed subject-matter from the closest prior art, with the consequence that the technical problem as formulated by the Appellant cannot be considered as having been effectively solved by the claimed solution.

2.5 According to the jurisprudence of the Boards of Appeal, alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the invention (see e.g. decision T 20/81, OJ EPO 1982, 217, point 3, last paragraph of the reasons). Since in the present case the alleged improvement is not plausible from the patent itself and experimental evidence in support is lacking, the technical problem as defined in point 2.2 above needs reformulation and can be defined as the provision of an alternative medical device for treating vascular diseases.

2.6 Finally, it remains to be decided whether or not, in view of the state of the art, the medical device of claim 1 is obvious to the skilled person seeking an alternative medical device for treating vascular diseases.

Document (1) discloses the possibility of stents coated with the mixtures of rapamycin and mycophenolic acid and having a top coat. It is within the routine activity of the skilled person faced with the problem

of providing an alternative medical device for treating vascular diseases to select one lying within the ambit of document (1), this choice being purely arbitrary since no technical effect is associated with it. From the teaching of document (1) alone, the skilled person would therefore arrive at the claimed medical device without the exercise of an inventive step.

Hence, the subject-matter of claim 1 of the main request lacks an inventive step.

2.7 The Appellant argued that the inventive step objection was based on hindsight, since to arrive at the subject-matter from document (1) it is necessary to select: (1) the use of rapamycin rather than a derivative thereof; (2) to use rapamycin with a co-agent; (3) to use mycophenolic acid as the co-agent; (4) to deliver the agent and the co-agent on a device; (5) to used a coated device; (6) to use a two layer coating; and (7) to place both agents in the base layer.

However, each of these possibilities are disclosed in document (1) and an arbitrary choice from a host of possible solutions does not in itself involve inventive activity (see e.g. decision T 939/92, OJ EPO 1996, 309, points 2.5.2 and 2.5.3 of the reasons). Accordingly, this argument does not convince the Board.

2.8 Consequently, the main request has to be refused.

Auxiliary requests 1 to 3

3. *Amendments*

Claim 1 of auxiliary request 1 is based on the combination of claims 1, 5, 6 and 7 of the application as filed.

Claim 1 of auxiliary request 2 as based on the combination of claims 1, 6 and 7 of the application as filed, i.e. the redundant feature of original dependent claim 5 is deleted. The Board concurs with the Appellant that it has the same subject-matter as claim 1 of auxiliary request 1.

Claim 1 of auxiliary request 3 has been limited to the fluoropolymer being PVDF/HFP and the acrylate polymer being BMA according to page 102, lines 14 to 31 of the application as filed.

The requirement of Article 123(2) EPC are therefore fulfilled.

4. Independent claim 1 of auxiliary request 3 is directed to an embodiment comprised within claim 1 of auxiliary requests 1 and 2, namely to the embodiment wherein the basecoat is of PVDF/HFP (polyvinylidenefluoride/ hexafluoropropylene), which is a polymeric material comprising a fluoropolymer and wherein the topcoat is BMA (butylmethylacrylate), which is an acrylic polymer.

In case this embodiment according to auxiliary request 3 lacked inventive step, a consequence must be that the subject-matter of auxiliary requests 1 and 2, which comprises that obvious embodiment, cannot, at least to that extent, involve an inventive step either.

For this reason, it is appropriate that the subject-matter of claim 1 of auxiliary request 3 is examined first as to inventive step.

5. *Inventive step (Article 56 EPC)*

Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the basecoat is PVDF/HDF and the top coat is BMA.

However, it has not been shown that the polymeric materials constituting the layers of the claimed medical device, i.e. the combination of a PVDF/HDF basecoat with a BMA topcoat is linked to any surprising technical effect. Consequently, the objective technical problem as defined in point 2.5 above remains the same, i.e. the provision of an alternative medical device for treating vascular diseases.

Polybutylmethacrylate (BMA) is already disclosed in the closest prior art document (1) as an example of topcoat (see page 14, line 16). Hence, the restriction of the second polymeric material to this specific polymer disclosed in document (1) cannot render the claimed medical devices inventive.

Furthermore, any fluorinated polymer is taught in document (1) to be suitable polymeric material for coating stent incorporating a drug (see page 13, lines 14 to 16; page 14, line 12). Commercially available polymeric fluorinated material for coating stents includes PDVF/HFP copolymers (examples 2 to 7 of document (6)). It was thus obvious for the person skilled in the art, seeking to provide an alternative

medical device, to choose PDVF/HFP copolymers to coat the stent with a fluorinated polymer as taught by document (1), thereby arriving without inventive ingenuity at a medical device in accordance with present claim 1 of auxiliary request 3. For these reasons, the subject-matter of claim 1 of auxiliary request 3 is obvious in the light of documents (1) and (6).

Hence, the subject-matter of claim 1 of auxiliary request 3, and for the same reasons that of claim 1 of auxiliary request 1 and 2, lack an inventive step (Article 56 EPC).

6. In these circumstances, the Appellant's auxiliary requests 1 to 3 also have to be rejected.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka