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**Datasheet for the decision
of 9 July 2015**

Case Number: T 1121/12 - 3.3.10
Application Number: 03078948.1
Publication Number: 1407726
IPC: A61F2/06
Language of the proceedings: EN

Title of invention:

Local delivery of rapamycin for treatment of proliferative sequelae associated with PTCA procedures, including delivery using a modified stent

Applicant:

Cordis Corporation

Headword:

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - obvious to try - no deterrent

Decisions cited:

T 0249/88, T 1053/93

Catchword:



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1121/12 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 9 July 2015

Appellant: Cordis Corporation
(Applicant) 14291 N.W. 60th Avenue
Maimi Lakes,
Florida 33014 (US)

Representative: Kirsch, Susan Edith
Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted on 15 December 2011 refusing European patent application No. 03078948.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman P. Gryczka
Members: J. Mercey
T. Bokor

Summary of Facts and Submissions

- I. This appeal lies from the decision of the Examining Division posted on 15 December 2011 refusing European patent application No. 03 078 948.1 with the European publication No. 1 407 726.
- II. The following documents were cited in the contested decision:
- (1) US-A-5 288 711,
 - (2) US-A-5 674 242 and
 - (3) US-A-5 624 411.
- III. This is the second appeal which has been filed in connection with this application. In the decision on the first, T 2287/08 (not published in OJ EPO), the Board of Appeal remitted the case to the first instance for further prosecution, since the amended claim 1 submitted before the Board generated new issues yet to be addressed in examination proceedings thus constituting a fresh case. In the decision of 4 July 2008 leading to that first appeal, the Examining Division found that the subject-matter according to the then pending requests lacked inventive step over a combination of documents (1) and (3).
- IV. Claim 1 of the set of claims (and present main request) underlying the contested decision of 15 December 2011 reads as follows:
- "A stent having a coating applied thereto, said coating formed from a mixture of (i) a polymer and (ii) rapamycin or a macrocyclic lactone analog of rapamycin".

- V. In the decision presently under appeal, the Examining Division held that the subject-matter according to the then pending request lacked inventive step over a combination of documents (1) and (3), document (1) disclosing a stent impregnated with rapamycin for the treatment of restenosis, document (3) teaching that sustained release of therapeutic agents for the treatment of restenosis was achieved by using a stent coated with a polymer mixed with the therapeutic substance.
- VI. With a letter dated 9 June 2015, the Appellant (Applicant) submitted a main request and an auxiliary request, said requests superseding all previous requests. Claim 1 of the main request is identical to claim 1 underlying the contested decision. Claim 1 of the auxiliary request differs therefrom in that the polymer is specified as being nonabsorbable and biocompatible.
- VII. The Appellant submitted that the coated stent was inventive, regardless of whether document (1) or document (3) was considered to represent the closest prior art. Starting however from the disclosure of document (3), it could not have been reasonably expected that rapamycin could be incorporated into the polymer coating of the stents according to document (3) in quantities high enough to provide sustained prevention of smooth muscle proliferation at the site of angioplasty without serious systemic complications. This was because document (1) taught that rapamycin must be used in high amounts to achieve any sort of anti-proliferative effect *in vitro* and must be delivered immediately after injury. By incorporating rapamycin into a polymer coating on a stent, its delivery would be automatically slowed, such that the

skilled person would not consider that fast delivery in high concentrations to cells *in vivo*, as required by document (1), to be achievable. In addition, document (2) taught that polymer-coated stents for drug delivery had a limited capacity for carrying a drug.

Furthermore, the post-published document:

(4) P. S. Teirstein, *Circulation*, 2001, 104, pages 1996 to 1998

filed with a letter dated 22 April 2010 before the Examining Division was evidence of the commercial success of the claimed stents which was proof that they were the first stents to solve the problem of avoiding restenosis in an efficient manner. With letter dated 9 June 2015, the Appellant provided estimated revenues from stents according to the invention. With regard to the auxiliary request, document (3) taught away from using nonabsorbable polymers.

VIII. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or, subsidiarily, on the basis of the auxiliary request, both requests filed with letter dated 9 June 2015.

IX. At the end of the oral proceedings, held on 9 July 2015, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Inventive Step*

Main request

- 2.1 The application in suit is directed to a stent wherein the therapeutic agent for preventing restenosis, namely rapamycin or a lactone analog thereof, is incorporated into a polymer material which should be able to release the drug in a controlled way over a period of several weeks (see page 7, lines 10 to 20 of the description).
- 2.2 The Board considers that the disclosure of document (3) is the closest prior art, since it also addresses the problem of providing a drug-containing stent which allows for a sustained release of the drug to vascular tissue (see col. 2, lines 23 to 25) in order to solve the "restenosis problem" (see col. 1, line 12 to col. 2, line 14), namely smooth muscle proliferation at the site of angioplasty (see col. 1, lines 40 to 45). To solve this problem, document (3) teaches the inclusion of a polymer in intimate contact with the drug, e.g. heparin (see col. 6, line 4) on the stent which slows the administration of the drug following implantation (see col. 2, lines 36 to 40).
- 2.3 In view of this state of the art, the Appellant submitted that the problem underlying the present application was the provision of a stent which provides sustained prevention of smooth muscle proliferation at the site of angioplasty without serious systemic complications.
- 2.4 As the solution to this problem, claim 1 of the main request proposes a stent which is characterised in that its coating is formed from a mixture of a polymer and rapamycin or a lactone analog thereof.
- 2.5 The Board has no reasons to doubt that said problem has been successfully solved by the claimed stents.

2.6 Finally, it remains to be decided whether or not the proposed solution to the problem underlying the present application is obvious in view of the cited prior art.

2.6.1 The skilled person looking for a stent which provides sustained prevention of smooth muscle proliferation at the site of angioplasty without serious systemic complications knows from document (3) itself that for the treatment of restenosis **"any** therapeutic substance which possesses desirable therapeutic characteristics for application to a blood vessel" (see col. 5, line 66 to col. 6, line 2; emphasis added) may be used in the polymer-coated stent of the invention described therein. The skilled person also knows from document (1) that vascular disease resulting from smooth muscle proliferation can be treated by administering rapamycin via an impregnated vascular stent (see claim 1) and would thus consider that rapamycin is a therapeutic substance possessing desirable therapeutic characteristics for application to a blood vessel which could be incorporated into the polymer-coated stent of document (3). That polymers existed which did not cause any serious systemic complications is taught by document (3) itself, namely biostable polymers with low chronic tissue response (see. col. 5, lines 34 to 35). Indeed, the specification of the application in suit itself teaches that "In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The **conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent**" (see page 7, lines 11 to 14; emphasis added), namely that at the filing date of the application in suit it was already usual to combine the therapeutic agent with a polymer. Although the specification goes on to read "To date, the ideal coating material has not been developed for

this application", the Board fails to see how defining the coating material merely as a "polymer" is anything other than the "conventional approach".

In the Board's judgement, it was thus obvious, or at least obvious to try, incorporating rapamycin into the polymer-coated stents of document (3) with a reasonable expectation that they would provide sustained prevention of smooth muscle proliferation at the site of angioplasty without serious systemic complications.

- 2.7 For the following reasons the Board cannot accept the Appellant's arguments in support of inventive step.
- 2.7.1 The Appellant submitted that the purpose of the treatment described in document (1) was to provide localized effects **immediately** after injury (see col. 7, lines 16 to 20), such that the skilled person would not have combined its teaching with that of document (3), since document (3), like the present invention, required **delayed** release, which was contrary to the requirement of document (1). In addition, the *in vitro* results given in document (1) for rapamycin (see table bridging col. 3 and 4) showed that at least 1 nM of rapamycin was required to obtain an anti-proliferative effect in the cell culture studied, which meant that in order to obtain an anti-proliferative effect *in vivo*, an even larger amount of rapamycin would be needed. The skilled person thus had no expectation that he could successfully achieve the necessary high concentration of rapamycin in the polymer coating to give an anti-proliferative effect *in vivo* from such a coated stent, even over a short period, let alone over a longer period, particularly given the fact that said polymer coating must be extremely thin, the maximum thickness of coating taught by document (3) being 0.002 inches

(see col. 3, lines 2 to 4) and document (2) teaching (see col. 1, lines 48 to 50) that polymer-coated stents for drug delivery had a limited capacity for carrying a drug. Furthermore, document (3) disclosed no clinical data for the stents described therein, such that, in contrast to the stents of the present application, there was no evidence that they actually worked *in vivo*.

However, when assessing inventive step it is not necessary to establish that the success of an envisaged solution of a technical problem was predictable with certainty. In order to render a solution obvious, it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success (see decisions T 249/88, point 8 of the reasons; T 1053/93, point 5.14 of the reasons; neither published in OJ EPO and Case Law of the Boards of Appeal, 7th Edition 2013, Chapter I.D.7.1.).

In the present case, the Board cannot agree with the Appellant's argument that due to some purported uncertainty about the predictability of success, the skilled person would not have considered incorporating rapamycin into the polymer-coated stent of document (3) in order to provide sustained prevention of smooth muscle proliferation at the site of angioplasty. The skilled person has a clear incentive from document (1) to do so (see point 2.6.1 *supra*). It was merely necessary to confirm experimentally by routine work that incorporating rapamycin into the polymer coating known from document (3) indeed results in a stent providing the desired properties, thus arriving at the claimed invention without inventive ingenuity. Nothing was submitted by the Appellant from which the Board

could reasonably conclude that the skilled person has been deterred from following the straight teaching of the art. On the contrary, document (3) teaches that a wide ratio of therapeutic substance to coating polymer could be used, ranging from about 10:1 to about 1:100 (see col. 5, lines 63 to 65) and that the rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer and by the ratio of drug to polymer in the solution (see col. 3, lines 4 to 14). Hence, the Appellant's arguments do not convince the Board.

2.7.2 The Appellant also submitted that the post-published document (4) taught that "scores of devices, hundreds of drugs, and innumerable revascularization "strategies" have failed to eliminate the 10% to 50% risk of recurrence after angioplasty", document (4) going on to eulogise rapamycin-eluting stents, it being "hard for many of us who have witnessed the growth of interventional cardiology to contain our enthusiasm". This document was thus evidence that the success of such stents was unexpected. The Appellant also referred to the financial data provided showing that stents according to the invention were significant commercial successes.

However, commercial success alone cannot be regarded as indicative of inventive step, in particular since in the present case said success cannot be attributed only to the technical features defined in claim 1, the commercial data concerning stents coated with very specific polymers, namely an acrylate-based and a vinylidene fluoride/hexafluoropropylene (VDF/HFP) copolymer, present claim 1 being directed, however, to **any** polymer.

- 2.8 Therefore, in the Board's judgement, the subject-matter of claim 1 represents an obvious solution to the problem underlying the patent application. As a result, the Appellant's main request is not allowable as the subject-matter of claim 1 lacks an inventive step pursuant to Article 56 EPC.

Auxiliary request

3. Claim 1 of the auxiliary request differs from claim 1 of the main request only in that the polymer is specified as being nonabsorbable and biocompatible.

- 3.1 However, since the closest prior art document already discloses (see. col. 5, lines 15 to 17) that the polymer used for the stent coating **must** be biocompatible and minimises irritation to the vessel wall when implanted (emphasis added), this amendment does not contribute to inventiveness of the subject-matter of claim 1 of this request *vis-à-vis* this document.

Furthermore, document (3) also discloses (see col. 5, line 17) that said polymer may be biostable (i.e. essentially nonabsorbable), no experimental data having been provided showing any unexpected effect for stents coated with nonabsorbable as opposed to with absorbable rapamycin-containing polymers. Thus, the specification that the polymer is nonabsorbable also cannot contribute to inventiveness of the subject-matter of claim 1 of this request *vis-à-vis* this document.

- 3.2 The Appellant argued that document (3) taught against using nonabsorbable polymers, since absorbable polymers were described as being more desirable since, unlike biostable polymers, they would not be present long

after implantation to cause any adverse, chronic local response. In addition, all the Examples in document (3) employed absorbable polymers.

However, document (3) clearly indicates that biostable polymers may be used (see point 3.1 above), so long as they have a relatively low chronic tissue response (see col. 5, lines 34 to 54), the polymers exemplified in this passage overlapping with those specified in dependent claim 5 of the auxiliary request. Indeed, document (3) indicates (see col. 5, lines 17 to 19) that biostable polymers may in fact be preferable, depending on the desired rate of release or the desired degree of polymer stability. The Board thus sees no deterrent in document (3) from selecting biostable, i.e. nonabsorbable, polymers, such that this argument of the Appellant does not convince the Board.

3.3 Therefore, the auxiliary request is also not allowable for lack of inventive step pursuant to Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



C. Rodríguez Rodríguez

P. Gryczka

Decision electronically authenticated