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Datasheet for the decision of 20 October 2010

Case Number: T 1039/07 - 3.3.08

Application Number: 96941438.2

Publication Number: 0862648

IPC: C12Q 1/00

Language of the proceedings: EN

Title of invention:
Detection of biological molecules using chemical amplification and optical sensors

Patentee:
Medtronic MiniMed, Inc.

Opponent:
Terumo Kabushiki Kaisha

Headword:
Sensors/MEDTRONIC

Relevant legal provisions:
EPC Art. 53(c), 56

Relevant legal provisions (EPC 1973):
EPC Art. 52(4)

Keyword:
"Ground for opposition not covered by the statement of grounds and not agreed for consideration by patentee: introduction into the appeal proceedings (no)"
"Main and auxiliary requests: inventive step (no)"

Decisions cited:
G 0009/91, G 0001/04

Catchword:
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Case Number: T 1039/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 20 October 2010

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 25 April 2007 concerning maintenance of the European patent No. 0862648 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
D. S. Rogers

Summary of Facts and Submissions

I. Both the patent proprietor (appellant I) and the opponent (appellant II) lodged an appeal against the interlocutory decision of the opposition division, whereby European patent No. 0 862 648 was maintained in an amended form on the basis of the sixth auxiliary request filed at the oral proceedings held on 31 January 2007.

II. The main request (claims as granted) and auxiliary requests 1 to 4 had been refused for reasons of lack of inventive step. Auxiliary request 5 had been refused for reasons of non-compliance with Article 84 EPC (lack of clarity).

III. In its decision the opposition division had refused to take into consideration the objection of non-compliance with Article 52(4) EPC 1973 raised at the oral proceedings by appellant II against claim 1 of auxiliary request 4. The opposition division had considered that this was a fresh ground for opposition as no objection had been raised in the notice of opposition against the similar granted claim 6. In any case, it was not prima facie relevant, as none of the process steps in the claim was of a diagnostic nature.

IV. Appellant I's statement of grounds of appeal was accompanied by 11 auxiliary requests. The claims as granted were the main request.

V. In its statement of grounds of appeal appellant II essentially argued that claim 1 of auxiliary request 6 did not involve an inventive step over a combination of

documents D1 and D2 taken together with one or more of documents D15, D18, D19 and D20 (see Section XI infra), the three latter documents being newly filed. Not document D2 but document D1 was considered to represent the closest state of the art. Claim 1 of auxiliary request 6 was also objected to under Article 52(4) EPC 1973.

VI. Each of the appellants filed a reply to the respective statement of grounds.

VII. On 5 May 2010, the board issued a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing a provisional and non-binding opinion on some of the pending issues.

VIII. On 20 September 2010 appellant I filed additional submissions in reply to the board's communication.

IX. At the oral proceedings which took place on 20 October 2010, appellant I submitted a new main request (claims 1 to 10) corresponding to previous auxiliary request 4, a first auxiliary request identical to previous auxiliary request 1 (claims 1 to 10) and a new second auxiliary request (claims 1 to 6).

X. Claim 8 of the main request and claim 1 of each of auxiliary requests 1 and 2 read as follows:

Main request

"8. A biosensor for measuring the amount of a polyhydroxylated analyte *in vivo,* said sensor comprising:

(a) a subcutaneously implantable amplification system comprising a biocompatible polymer matrix and amplification components which produce a polyhydroxylated analyte signal upon interrogation by an optical system, wherein said amplification components comprise an arylboronic acid moiety attached to an amine-functionalized dye molecule, and wherein said amplification components do not require resonance energy transfer for production of said signal; and
(b) an optical system comprising an optical source and a detector which detects said signal thereby measuring the *in vivo* amount of said analyte subcutaneously."

Auxiliary request 1

"1. An implantable amplification system comprising a biocompatible polymer matrix and amplification components which produce a polyhydroxylated analyte signal upon interrogation by an optical system, wherein said amplification components comprise an arylboronic acid moiety attached to an amine-functionalized dye molecule, and wherein said amplification components do not require resonance energy transfer for production of said signal, and wherein the amplification components are immobilised in the polymer matrix by covalent attachment."

Auxiliary request 2

"1. A method for quantifying the amount of a polyhydroxylated analyte in an individual, said method comprising:
(a) interrogating a subcutaneously implanted amplification system comprising a biocompatible polymer

matrix and amplification components which produce a polyhydroxylated analyte signal upon interrogation by an optical system, wherein said amplification components comprise an arylboronic acid moiety attached to an amine-functionalized dye molecule, and wherein said amplification components do not require resonance energy transfer for production of said signal, and wherein the amplification components are immobilized in the polymer matrix by covalent attachment;
with an energy source to provide an excited amplification system which produces an energy emission corresponding to said amount of said polyhydroxylated analyte; and
(b) detecting said emission to thereby quantify the amount of said polyhydroxylated analyte in said individual."

XI. The following documents are referred to in the present decision:

(D1) GB 2 284 809 A (published on 21 June 1995)

(D2) US 4,344,438 A (published on 17 August 1982)

(D12) US 5,137,833 A (published on 11 August 1992)

(D14) S.A. Barker, "Immobilization of the biological component of biosensors", in 'Biosensors', Oxford University Press, New York, 1987, pages 85 to 99

(D15) G.D. Velho et al., "The design and development of *in vivo* glucose sensors for an artificial endocrine pancreas", in 'Biosensors', Oxford

University Press, New York, 1987, pages 390 to 408

(D17) M. Thompson and E.T. Vanderberg, Clinical Biochemistry, Vol. 19, 1986, pages 255 to 261

(D18) M. Shichiri et al., "Needle-type glucose sensor and its clinical applications", in 'Biosensors, Oxford University Press, New York, 1987, pages 409 to 424

(D19) S. J. Updike et al., ASAIO Journal, Vol. 40, No. 2, 1994, pages 157 to 163

(D20) V. Poitout et al., Diabetologia, Vol. 36, 1993, pages 658 to 663

XII. The submissions made by appellant I, insofar as they are relevant to the present decision, may be summarised as follows:

Introduction in the proceedings of the ground for opposition raised under Article 52(4) EPC 1973

This ground for opposition was raised by appellant II only at the oral proceedings held before the opposition division. It was not in the notice of opposition. Thus, it was a fresh ground which, as ruled in decision G 9/91 (OJ EPO 1993, 408, point 18 of the Reasons), could not be considered by the board, unless appellant I gave its agreement thereto. This agreement was refused.

Substantive issues (inventive step)

Main request

Subcutaneous implantation had implications for the claimed device, in particular as regards the size. No relevant information in this respect was derivable from the prior art documents. Document D1 focused on a group of boronate compounds similar with the ones of the patent. Page 11 of D1 merely speculated on the detection of saccharides in an organ, without further detail, by a spectrometric means using such compounds. Furthermore, there was no indication that an implantable sensor, let alone a subcutaneously implantable one, could be developed. The only information provided was that use could be made of an optical fiber having a boronate compound coated on its tip. Nothing was said regarding said coating which therefore represented a technical hurdle. It was clear from page 2, lines 7 to 15 that such a sensor had not yet been conceived.

Whereas some prior art documents, such as document D18, disclosed biosensors which were subcutaneously implantable for the determination of glucose, all those biosensors relied on an enzyme-based technology. Document D2 described a sensor implanted in the vein of the patient. The sensor which worked perfectly was too large for a subcutaneous implantation. The miniaturisation of the sensor as referred to on column 6, lines 5 to 8, was only an optimistic wish. There were no good technical reasons to combine the teaching of document D2 with the concept of a subcutaneous implantation.

First auxiliary request

Document D1 did not indicate whether the boronate compound was immobilised on the tip of an optical fiber. If the fiber was made of glass, a skilled person would have known how difficult it would have been to covalently attach molecules to it. From page 5, lines 16 to 26, of D1, a skilled person would have gathered that a covalent attachment of a boronate compound to a support would not have been appropriate. There was indeed no indication that the functional group R of formula 7 on page 7 had the specific purpose of participating in a covalent bond. In the sentence bridging pages 6 and 7, an in vitro not an in vivo test was described. The expression “supported on a supporting material" used in this respect was very vague. The boronate compound molecules of document D1 were too small and one could not think of a covalent attachment.

Document D2 involved a competitive binding assay for the performance of which the fluorescent compound had to be free. In contrast to the teaching of document D2, the covalent attachment of the boronate compound in the sensor of the patent led to the design of a chamberless sensor. As a result, the sensor was smaller and therefore appropriate for a subcutaneous implantation. Thus, document D2 taught away from performing an immobilisation of the compound.

A covalent attachment was not obvious from any other prior art document. Document D14 did not say anything about a covalent attachment to a glass surface and did

not refer to any fluorescent system. The boronate compounds of document D12 which were made of an aryl compound such as aminophenylboronic acid that was first diazotized and then coupled to a molecule containing an electron-donating species. There was no definitive teaching of a covalent attachment of these molecules in any part of D12. Thus, there were reasons why a skilled person would not have thought of employing a covalent attachment.

Second auxiliary request

To arrive at the sensor of claim 1, which was subcutaneously implantable with the reactive components being covalently attached to a biocompatible polymer matrix, a skilled person would have had to combine the purely speculative document D1 with a number of documents, such as one or more of documents D18 to D20 disclosing a subcutaneous implantation and document D12 disclosing a covalent attachment. This could be done only with hindsight. There were no reasons why a skilled person would have selected those features.

XIII. The submissions made by appellant II, insofar as they are relevant to the present decision, may be summarised as follows:

Introduction in the proceedings of the ground for opposition raised under Article 52(4) EPC 1973

The ground for opposition was raised in view of the amendments carried out during the written phase of the opposition proceedings. Furthermore, as in the meantime decision G 1/04 (OJ EPO 2006, 334) had been issued, a

decision by the board on this ground would have been helpful.

Substantive issues (inventive step)

Main request

The passage on page 2, lines 7 to 15, of document D1 clearly indicated that there was a view to developing a sensor using boronate compounds for the in vivo detection of glucose. This was confirmed by the paragraph bridging pages 11 and 12 of D1. The reference to a continuous monitoring on page 12 was a sign that a permanent in vivo implantation of the sensor was envisaged. In document D2, there were no contrary indications for the in vivo use of boronic compounds.

Document D15 disclosed in vivo implantable biosensors for the determination of glucose which were based on non-enzymatic approaches (see page 402 et seq.). In document D19, there was a strong recommendation to implant the biosensor subcutaneously rather than using it intravenously.

The size of a biosensor to be subcutaneously implanted was not a relevant criterion for the assessment of inventive step. The patent was silent thereabout. There was no definite size (as illustrated by the biosensors described in documents D18 and D19).

To design an in vivo biosensor using the boronate compounds of document D1, nothing more was required than routine.

First auxiliary request

The sentence bridging pages 6 and 7 of document D1 with the expression "the compound is supported on a supporting material" showed that a fixation of the boronate compound was needed. As the boronate compound was too small, an entrapment in a support was obviously less appropriate that a covalent attachment thereto. The presence of a functional group R in the molecule represented in Formula 7 on page 7 of D1 enabled a covalent attachment. There were no technical obstacles to the creation of such an attachment when starting from document D1.

In the biosensors of document D2, ConA, one of the reacting components, was immobilised.

Document D14 insisted that for a biosensor it was vital that leakage of the biological components did not occur to any extent during use of the biosensor (see page 87, third paragraph). A covalent binding was represented in Figure 6.2 on page 92 of D14. Thus, there was a need for a strong immobilisation.

Document D12 also related to the same field of detection of polyhydroxylated compounds such as glucose. Boronate compounds were used. A preferred one was, as in the patent, aminophenylboronic acid (APB) (see column 2, lines 13 to 14). An immobilisation of the boronate compound was needed (see column 3, lines 5 to 8). Examples 2 and 4 of D12 showed how APB could be attached to a support.

In claim 1, there was no indication how to proceed to covalently attach the boronate compound to the matrix. No more explanation was found in the description as to which functional group was involved.

Second auxiliary request

The patent specification did not say more than the prior art documents as to the design of a biosensor which was subcutaneously implantable and comprised a boronate compound covalent attached to a polymer matrix. Thus, the presence of an inventive step should be denied.

XIV. Appellant I (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of:
1) claims 1 to 10 of the main request; or
2) claims 1 to 10 of auxiliary request 1; or
3) claims 1 to 6 of auxiliary request 2;
all submitted at the oral proceedings before the board.

XV. Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Introduction in the proceedings of the ground for opposition raised under Article 52(4) EPC 1973

1. Appellant II requests that this ground for opposition (now found under Article 53(c) EPC), be introduced in the proceedings.

2. This ground, which was raised by appellant II only at the oral proceedings held before the opposition division, was not covered by the notice of opposition pursuant to Rule 55(c) EPC 1973, and it is thus a fresh ground for opposition. The opposition division considered it to be prima facie irrelevant and did not admit into the opposition proceedings.

3. As appellant I does not agree that this fresh ground for opposition be considered, the board does not admit it into the proceedings (see decision G 9/91, OJ EPO 1993, 408, point 18).

Substantive issues

Main request (inventive step)

4. Product claim 8 is directed to a biosensor for measuring the amount of a polyhydroxylated analyte in vivo which comprises a subcutaneously implantable amplification system and an optical system. The amplification system is made of a biocompatible polymer matrix and amplification components themselves comprising an arylboronic acid moiety attached to an amine-functionalized dye molecule. Furthermore, these components do not require resonance energy transfer for production of a signal upon interrogation by the optical system. According to the description, preferred compounds, such as the FABA compound (see page 11, paragraph 0077, page 12, paragraph 0078, as well as on page 15, paragraph 0102 in the patent specification) consist of a fluorescent dye attached to a phenylboronic acid moiety.

5. The board notes the broad and vague wording of claim 8 regarding in particular the matrix. It is also observed that the description is equally general and fails to actually disclose a working biosensor, let alone a working subcutaneously implantable biosensor.

6. For the assessment of whether the subject-matter of claim 8 involves an inventive step according to the problem-solution approach the first step is the choice of the document which qualifies as the closest state of the art. Two documents, namely documents D1 and D2, have been referred to in this respect.

7. With a view to contributing to the design of a saccharide sensor for in vivo use for diagnosis and treatment of diseases (see page 2, lines 7 to 15), document D1 describes a group of fluorescent compounds comprising a fluorophore attached to a phenylboronic acid moiety (see page 3) and their use for the photoscopic detection of saccharides (see page 6, second paragraph), some emphasis being placed on a material which serves as a support for the compounds. Their use in the detection of a saccharide in situ with respect to a specific organ in the body is envisaged, one particular option mentioned being the use of an optical fiber having one of such compounds coated on its tip, to provide information that can be continuously monitored (see the paragraph bridging pages 11 and 12).

8. Document D2 generally describes sensors which comprise a chamber, inserted into a blood vessel, having a dialysis membrane which allows selected plasma

constituents, such as glucose, to pass therethrough and enter the chamber. The chamber contains specific receptor sites each of which reversibly binds with one of the selected plasma constituents. It also contains ligands which compete with the plasma constituents for the specific receptor sites. The intensity of light emitted from or adsorbed by the receptor-site/competing-ligand complexes or the competing ligand alone is measured. A preferred sensor comprises a chamber created by a cylindrical hollow dialysis fiber, the interior surface of which is coated with an immobilised but permeable layer of concanavalin. A solution in the chamber contains an appropriate amount of the competing-ligand, FITC-dextran. The porosity of the hollow fiber and molecular size of FITC-dextran are chosen such that the competing-ligand cannot diffuse out through the wall of the fiber which serves as a dialysis membrane, and thus the FITC-dextran is trapped within the chamber. The components of the optical system, including a light source and a light detector, are inside or outside the body.

9. From the above outline of the two documents in question, it is clear that document D1 (i) discloses one of the essential features of the biosensor of claim 8, namely a group of compounds which can be used as its amplification components, (ii) indicates that those compounds when supported are capable of reacting with polyhydroxylated molecules such as saccharides and (iii) envisages their use as part of a sensor for the in vivo determination of saccharides. In contrast thereto, document D2 focuses on sensors which are inserted in a blood vessel and use other reactants. Thus, the conclusion must be reached that document D1 represents

the closest state of the art, as it describes the same detection system as the patent-in-suit and it points to the development of an in vivo saccharide sensor based thereupon.

10. In view of this, the technical problem underlying the invention may be regarded as the actual provision of a biosensor for the in vivo determination of a polyhydroxylated analyte such as glucose relying on the use of a compound comprising a fluorophore attached to a phenylboronic acid moiety.

11. In dealing with the question whether a skilled person developing a saccharide sensor based on the boronate compound technology disclosed in document D1 would have arrived at the biosensor of claim 8 in an unobvious manner, due account should be taken of the state of knowledge at the time of the invention.

12. At the time of the invention the concept of biosensors for the in vivo determination of glucose upon subcutaneous implantation had indeed already been explored. A skilled person working in the field would have taken into account the information available on glucose sensors, including those documents cited in the present proceedings. In view of the general knowledge as reflected by those documents, he would have considered the following points:

12.1 Preference would have to be given to a subcutaneous implantation rather than an intravenous one. Such an implantation would have taken advantage of the recognised fact that the glucose concentration of the subcutaneous tissue had been shown to be essentially

identical to plasma concentration (see document D20, left hand column, last sentence). As expressed for example in document D19 (see page 158, left hand column, first full paragraph the last sentence of which reads "*Our goal of creating a clinically safe, practical and low cost sensor had led us to favor subcutaneous over intravascular placement*"), this kind of implantation had been recommended for safety reasons.

12.2 The skilled person would have also known that, whatever its nature, the compound to be reacted with the polyhydroxylated analyte under determination should be attached to a support matrix. This concern is expressed in document D14 (see page 85, first and second paragraphs).

12.3 In the field of biosensors, various types of matrices had been used before the date of the present invention. Some of them are referred to in documents D14 (see Table 6.1 on pages 89 to 91), D18 (see Table 23.1 on page 410) and D19 (see page 163, left hand column, fourth full paragraph, first sentence) which are made of a polymer.

12.4 The skilled person would have of course known that the components of a biosensor should have been biocompatible (this issue was discussed at length in document D17). This was an absolute requirement in order that the biosensor not be involved in infection, clot formation or antigenic response or protein adsorption and it should obviously apply to the polymer matrix supporting the reactive component.

13. Therefore, it is the board's view that the skilled person, developing an in vivo biosensor as suggested in document D1 and relying only on its general background knowledge of the pre-existing in vivo biosensors, would have designed without the exercise of inventive skill a subcutaneously implantable amplification system as featured in claim 8 and necessarily associated it with an optical system basically comprising an optical source and a detector.

14. The appellant I's objection that on page 11 of document D1 the in vivo detection was envisaged only with respect to an organ, which excluded a subcutaneous implantation, is not relevant for the reason that the skin as such may be regarded in a broad sense as an organ and, in any case, as discussed above, subcutaneous implantation was a preferred option.

15. For these reasons, the board concludes that the biosensor of claim 8 does not involve an inventive step. Therefore the main request does not comply with Article 56 EPC.

First auxiliary request (inventive step)

16. Claim 1 is directed to an implantable amplification system and covers embodiments thereof where the system is appropriate for a subcutaneous implantation (in order for it to be used in a method according to claim 5). Such a subcutaneously implantable amplification system differs from the one referred to in claim 8 of the main request only in that the amplification components are immobilised in the polymer matrix by covalent attachment.

17. A skilled person when designing the implantable amplification system according to claim 8 of the main request would have immediately recognised from experience that, as the boronate compounds disclosed in document D1 were small molecules, a covalent attachment to the polymer matrix used as a support would have been more appropriate that an entrapment within the same. In addition he would also have noted the clear indication in the same document that the compounds were effective in a chromatographic arrangement, i.e. when supported (read: bound) on a material (cf. page 6, last paragraph). He would therefore have chosen a covalent attachment without the exercise of inventive skill.

18. The appellant I's counterargument that the small size of boronate compounds of document D1 would have led the skilled person away from the idea of a covalent attachment is not tenable. The structure of the compounds as represented in Formula 7 on page 7 of the document in question clearly indicates the presence of a functional group R which could be involved in a covalent bond. Furthermore, there exists in D1 no prejudice which might have restrained the skilled person from performing such an attachment.

19. The further reference by appellant I to the suggested use of an optical fiber it assumes to be made of glass does not support a valid objection of lack of inventive step. The use of such a fiber is only an hypothetical example and indeed the disclosure in document D1 does not exclude any kind of support which could serve the purpose of covalently attaching the boronate compounds.

20. For these reasons, the board concludes that the amplification system of claim 1 does not involve an inventive step. Therefore the first auxiliary request does not comply with Article 56 EPC.

Second auxiliary request (inventive step)

21. Claim 1 is directed to a method for quantifying the amount of a polyhydroxylated analyte in an individual which comprises a step of interrogating a subcutaneously implanted amplification system wherein the amplification components are immobilised in the polymer matrix by covalent attachment as covered by claim 1 of the first auxiliary request, such step being carried out with an energy source which provides an energy emission which is detected.

22. The board cannot see how the latter feature can confer inventiveness to a system which as seen above in respect to the main request and auxiliary request 1 lacks an inventive step. The use of an energy source to produce a signal is indeed derivable from document D1 itself.

23. Appellant I's argument that the necessity to refer to a mosaic of prior art documents is a sure sign that claimed subject-matter is inventive is not tenable for the reason that, apart from document D1, the other documents have been mentioned for the sole purpose of illustrating what the general knowledge of the skilled person working in the filed of in vivo biosensors was.

24. For these reasons, the board concludes that the method of claim 1 does not involve an inventive step.

Therefore the second auxiliary request does not comply with Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar The Chairman

A. Wolinski L. Galligani