

**Internal distribution code:**

- (A)  Publication in OJ  
(B)  To Chairmen and Members  
(C)  To Chairmen  
(D)  No distribution

**D E C I S I O N**  
**of 12 August 2004**

**Case Number:** T 0742/00 - 3.2.2

**Application Number:** 95901627.0

**Publication Number:** 0722288

**IPC:** A61B 5/00

**Language of the proceedings:** EN

**Title of invention:**

Monitoring the concentration of a substance or a group of substances in a body fluid

**Patentee:**

KORF, Jakob, et al

**Opponent:**

Roche Diagnostics GmbH

**Headword:**

-

**Relevant legal provisions:**

EPC Art. 52(4), 54, 56

**Keyword:**

"Novelty (yes, after amendment)"

"Inventive step (yes, after amendment)"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0742/00 - 3.2.2

**D E C I S I O N**  
of the Technical Board of Appeal 3.2.2  
of 12 August 2004

**Appellant:** KORF, Jakob  
(Proprietor of the patent) Houtwallen 11  
NL-9481 ER Vries (NL)

and

TERWEE, Thomas Henricus Marie  
Klimop 12  
NL-9301 PK Roden (NL)

**Representative:** Smulders, Theodorus A.H.J., Ir.  
Vereenigde  
Postbus 87930  
NL-2508 DH Den Haag (NL)

**Respondent:** Roche Diagnostics GmbH  
(Opponent) Patentabteilung  
D-68298 Mannheim (DE)

**Representative:** -

**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 16 March 2000  
revoking European patent No. 0722288 pursuant  
to Article 102(1) EPC.

**Composition of the Board:**

**Chairman:** T. K. H. Kriner  
**Members:** S. S. Chowdhury  
U. J. Tronser

## Summary of Facts and Submissions

I. The decision of the opposition division revoking European patent No. 0 722 288 was dispatched on 16 March 2000. The patent had been opposed on the grounds that its subject-matter lacked novelty and inventive step. In its decision, the opposition division found that the claimed subject-matter lacked an inventive step.

II. On 24 May 2000 the appellants (patentees) filed an appeal against this decision and paid the appeal fee on the same day. The statements of grounds of appeal were received on 26 July 2000.

Oral proceedings took place on 12 August 2004.

III. The following documents were primarily relied upon during the appeal proceedings:

BM1: Diabetologia 1992; 35:1177-1180, J. Bolinder et. al. "Microdialysis measurement of the absolute glucose concentration in subcutaneous adipose tissue allowing glucose monitoring in diabetic patients".

BM2: Journal of Internal Medicine 1991; 230: 365-373, U. Ungerstedt "Microdialysis - principles and applications for studies in animals and man".

BM3: Life Sciences 1990; 46: 105-119, Peter M. Bungay et. al. "Steady-state theory for quantitative microdialysis of solutes and water in vivo and in vitro".

BM4: US-A-4 832 034

BM5: GB-A-2 259 771

IV. Requests

The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 38 and description columns 1 to 19 as submitted at the oral proceedings, Figures 1 to 13 as granted.

The respondent (opponent) requested that the appeal be dismissed.

V. Independent claims 1 and 20 read as follows:

"1. A method for monitoring the concentration of a selected substance or group of substances in a body fluid of a living human or animal body (1), in which the substance or group of substances to be monitored is transferred from the body (1) through an interface (2) and transported away from behind the interface (2) in a perfusion fluid flow, and in which the concentration of the substance or group of substances to be monitored is measured in said perfusion fluid flow downstream from the interface, characterized in that the flow rate of the perfusion fluid flow is less than 60  $\mu$ l/hour and in that the perfusion fluid flow is driven by a fluid absorbing structure, a capillary reservoir, an osmotic membrane or a pressure differential reservoir.

20. A wearable device for monitoring the concentration of a substance or a group of substances in a body fluid of a living human or animal body (1), comprising: an interface (2); a detector (3); and means for maintaining a perfusion fluid flow from the interface (2) to the detector (3) for measuring the concentration of the substance or group of substances to be monitored is measured in said perfusion fluid flow downstream from the interface, characterized in that the means for maintaining a perfusion fluid flow from the interface (2) to the detector (3) are adapted for maintaining said flow at a rate of less than 60  $\mu\text{l}/\text{hour}$  and in that the means for maintaining a constant flow are in the form of a fluid absorbing structure, a capillary reservoir, an osmotic membrane or a pressure differential reservoir."

Claims 2 to 19 and are dependent on claim 1 and claims 21 to 38 are dependent on claim 21.

VI. The parties submitted the following arguments in the written procedure and during the oral proceedings:

(i) Appellants

Examples 4 and 5 of BM4 clearly taught away from using low perfusion flow rates. The flow rate of 366  $\mu\text{l}/\text{hour}$  in Example 5 of BM4 was far from the claimed range, whereas the other Examples stressed the disadvantages of using low flow rates or recommended a flow rate of two or more  $\mu\text{l}/\text{minute}$ . Moreover, contrary to the respondent's arguments this document also did not disclose the fluid driving means claimed.

BM5 mentioned a flow rate of 60  $\mu\text{l}/\text{hour}$  and said that this was a slow rate, and there was no basis for using an even slower flow rate. BM4 did not incite the person skilled in the art in this direction since this clearly recommended the use of much higher flow rates. Nor did BM5 disclose the use of the fluid flow driving means as claimed. Therefore, the combination of these documents would not yield the claimed invention.

(ii) Respondent

Starting from Example 5 of BM4 as the closest prior art, which described an in-flow blood glucose measurement, the person skilled in the art would select a lower perfusion flow rate in order to reduce the depletion of body fluid as described in BM4, and also to increase the recovery rate. Membranes and detectors capable of operating at these flow rates were available. BM4 also disclosed the type of pumps claimed. Therefore, the method of claim 1 did not involve an inventive step.

Alternatively, starting from BM5 the claimed subject-matter did not involve an inventive step since BM5 disclosed an in-flow dialysis measurement method which employed a perfusion flow rate of 60  $\mu\text{l}/\text{hour}$ , which would fall within the claimed range owing to normal variations in the flow rate. Starting from this document the objective problem was to simplify the device, so the person skilled in the art would invoke BM4 which also had as an object to provide a simple device containing no moving parts. This document taught the advantages of a lower flow rate and also the type of pumps claimed.

## Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

Claim 1 consists of the combination of the features of claims 1 and 38 as granted and claim 20 consists of the combination of the features of claims 21 and 38 as granted, and the main claims have been re-worded to stress that the concentration of the substance or group of substances to be monitored is measured in the perfusion fluid flow. The new claims are restricted in scope as compared with the claims as granted. The description has been amended for consistency with the new claims, and the amendments meet the requirements of Article 123(2) and (3) EPC, accordingly. The respondent did not object to the amended patent on formal grounds.

3. *Novelty*

The respondent did not object to the claims on grounds of novelty, a view with which the Board concurs.

4. *Inventive step*

4.1 The patent relates to a method and a device for monitoring the concentration of a selected substance or group of substances in a body fluid of a living human or animal body and is based on the principle of measurement described in the article cited in column 2, by Flentge et al. (*in vivo*) and in BM5 (*in vitro*),

which forms the basis for the preamble of the main claims. In this known method a perfusate fluid flows from a supply reservoir to a waste reservoir via an interface in or on the body and then to a detector which measures the concentration of a substance or group of substances to be monitored in the perfusion fluid flow downstream from the interface, wherein the perfusion fluid flow rate is 60  $\mu\text{l}/\text{hour}$ .

The method of BM5 is an in vitro and "on-line" microdialysis method, wherein by "on-line" is meant that the concentration of a substance to be monitored is measured in the perfusion fluid flow. The on-line method is to be contrasted with methods in which samples are collected for subsequent off-line analysis and in which variations in flow rate are of no consequence. The on-line method has the advantages of allowing monitoring over a prolonged period of time while providing information rapidly and with good time resolution (see the first paragraph of BM5).

The advantages of using perfusion fluid flow rates lower than 60  $\mu\text{l}/\text{hour}$  were well known in the art, for example from BM1, BM2 and BM3, one of the better known advantages being that the recovery rate or dialysis extraction fraction varies inversely with the flow rate, as demonstrated graphically in Figure 3 of BM3. Another prominent advantage is that the body fluid is not depleted with respect to any component thereof. The lower flow rates were used, however, only in sampling methods.

The inventors of the patent in suit found that, notwithstanding the known advantages of using low flow



rates (for example from the sampling methods of BM1 and BM2), there is one great disadvantage, that the flow is not constant (column 1, lines 49 to 54 of the patent). Fluctuations in the flow rate are of no importance in those cases where the fluid is collected in samples, but are significant when the concentration of the substance to be monitored is measured in the perfusion fluid flow with good time resolution. In order to counter this problem, special means for driving the fluid flow were selected, as set out in the patent, column 7, lines 9 to 13 and claim 38, which passages have respective counterparts in the application as originally filed.

As stated in column 3, lines 17 to 27 of the patent, owing to this relatively low flow rate, a very constant, i.e. non-pulsatile and substantially non-fluctuating flow can be maintained for a long period of time with simple means, which need no or very little supply of energy. The energy reservoir of the device can be small and light because little energy is needed for driving the perfusion fluid flow. The means for passing the perfusate from the interface to the detector can be of a simple, low-cost, reliable, compact and lightweight design and the volume of perfusate needed for monitoring during a given period of time is small.

Thus, the combination of features in the characterising parts of the independent claims are predicated on the problem of fluctuations of the flow rate in an on-line method, and the combination of the features solves the problem in a simple manner.

4.2 The respondent has set out two different lines of attack against the claims, one starting from BM4 as the closest prior art, and the other starting from BM5. Each of these approaches is examined in turn below.

4.2.1 Starting from BM4

BM4 describes an anisotropic fibre membrane for ultrafiltration (which is included within the scope of the independent claims of the patent in suit, see claim 15 and the paragraph linking columns 8 and 9 of the patent), the membrane consisting of an outer thin and dense layer and an inner thick, less dense, and more porous layer (see Figure 5 and the associated description linking columns 23 and 24). Some experiments are described regarding the development of the flow and the recovery rate through different membranes.

Experiments were conducted with different fibres, described in Examples 1 to 5, of which Example 1 is a comparison example using dialysis fibres. In one experiment the dialysis fibre was infused with saline at a flow rate as low as 36  $\mu$ l/hour and samples were collected for analysis. The conclusion of this Example is that equilibrium is not obtainable even at the lowest flow rate of 36  $\mu$ l/hour (column 24, lines 40 to 42) and that the very low sweep rates necessary to achieve equilibrium result in longer response times (column 24, lines 57 to 61). This compares unfavourably with the invention of BM4 in which there is virtually instantaneous equilibration of a desired analate in the filtrate and sampled fluid (see, for example, BM4 column 11, lines 53 to 60, column 18, lines 39 to 46,

and column 22, lines 46 to 49). This Example, therefore, does not recommend either the use of dialysis or of flow rates less than 60  $\mu\text{l}/\text{hour}$ .

Example 2 tested the utility of an ultrafiltration anisotropic hollow fibre with an inner skin layer and an outer more porous layer. The blood filtration rate was approximately 2.8  $\mu\text{l}/\text{minute}$  (168  $\mu\text{l}/\text{hour}$ ) but this fell rapidly to 0.4  $\mu\text{l}/\text{minute}$  (24  $\mu\text{l}/\text{hour}$ ) and then asymptotically decayed to undesirably low levels. Therefore, this fibre is not recommended (column 25, lines 17 to 21). This Example merely tested the suitability of the membrane and contains no recommendation either as to the flow rates or of in-flow measurements.

Example 4 demonstrates an embodiment of the invention of BM4 in an *in vitro* system containing human plasma, and explicitly says that it is advantageous to have a filtrate rate of two or more  $\mu\text{l}/\text{minute}$  (120 or more  $\mu\text{l}/\text{hour}$ ) in order to provide an adequate sample in a reasonable time (column 26, lines 60 to 62).

Example 5 demonstrates a method using the asymmetric hollow fibre of BM4 for monitoring blood glucose concentrations, with a filtration flow rate of approximately 366  $\mu\text{l}/\text{hour}$  and a monitoring device with a sensor. This flow rate is far removed from 60  $\mu\text{l}/\text{hour}$ .

In conclusion, all those Examples where the properties of the asymmetric hollow fibre of BM4 are demonstrated the only clear teaching is that the flow rate should be 120 or more  $\mu\text{l}/\text{hour}$ . The potential usefulness of lower

flow rates cannot be deduced from these or the other Examples.

Moreover, the driving force for the fluid in BM4 (column 22, lines 26 to 33) is one that involves the application of a partial vacuum or evacuation of the fibre lumen by connecting the fibre to a micropump or other source of vacuum. The Board is of the opinion that the "micropump or other source of vacuum" disclosed in this document does not anticipate a pressure differential reservoir or any of the other driving means claimed in the patent in suit since by pressure differential reservoir in the patent is meant a gas filled excess pressure or vacuum reservoir as described in column 6, line 53 to column 7, line 8, whereas a micropump is simply a miniature pump which does not necessary have only non-moving parts, and "other means" is vague in the context.

The method of claim 1 of the patent in suit is novel over Example 5 of BM4 by virtue of the perfusion fluid flow rate of less than 60  $\mu\text{l}/\text{hour}$  and the specific driving means for the perfusion fluid flow. These are inter-dependent features since at low flow rates the flow becomes inconstant and means must be provided to maintain constancy of flow.

Neither BM4 nor any other prior art document suggests lowering the perfusion fluid flow rate to less than 60  $\mu\text{l}/\text{hour}$  in an in-flow measurement, together with the specific driving means for the perfusion fluid flow. In particular BM5 describes examples employing a perfusion flow rate of 60  $\mu\text{l}/\text{hour}$  in an in-flow measurement using a syringe pump, but this document does not recommend

the use of a lower flow rate or disclose any pump other than a syringe pump, nor does it mention the problem of fluctuations in the flow rate.

#### 4.2.2 Starting from BM5

The respondent argues that owing to variations which typically occur in flow rates, the flow rate BM5 must temporarily have fallen below 60  $\mu\text{l}/\text{hour}$ . This argument is not convincing since by "less than 60  $\mu\text{l}/\text{hour}$ " would be understood by the person skilled in the art as a rate significantly less than 60  $\mu\text{l}/\text{hour}$  so as to take such variations into consideration. The teaching of BM5 is that 60  $\mu\text{l}/\text{hour}$  in an in-flow measurement is already considered a slow flow rate (page 3, lines 22 and 23) and no further lowering of this rate is contemplated. Moreover, there is no disclosure in BM5 of any specific driving means for the flow other than a syringe pump.

The respondent also argues that the problem of the patent, starting from BM5, is to make a simpler device using a lower flow rate, and the solution for this is disclosed in BM4, for example there are no moving parts and the device can be miniature in size (column 16, lines 37 to 39), and this document also discloses the use of a fluid driving means as claimed.

These arguments too are not accepted since there is a clear teaching in BM4 that a filtrate rate of two or more  $\mu\text{l}/\text{minute}$  (120 or more  $\mu\text{l}/\text{hour}$ ) should be used, as discussed above, so that were the person skilled in the art to combine these documents, then the Examples of BM5 would be replicated using a perfusate flow rate higher than 60  $\mu\text{l}/\text{hour}$  rather than a lower flow rate,

whereas the patent requires a flow rate of less than 60 µl/hour as an essential feature. Moreover, Example 1 of BM4 clearly says that dialysis is not a promising method, which is a disincentive to combine these documents. Also, as discussed above, BM4 is not considered to disclose the specific fluid driving means claimed.

Therefore, there is neither an incentive to combine these documents, nor would the desired solution of the patent in suit result even if they were to be combined.

- 4.3 For the above reasons the subject-matter of claims 1 and 20 involves an inventive step.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent in amended form on the basis of on the basis of claims 1 to 38 and description columns 1 to 19 as submitted at the oral proceedings, Figures 1 to 13 as granted.

The Registrar:

The Chairman:

V. Commare

T. K. H. Kriner