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Datasheet for the decision of 15 January 2016

Case Number: T 2454/12 - 3.3.06

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Language of the proceedings: EN

Title of invention:
DEVICE FOR ANALYSING A FLUIDIC SAMPLE BY MICRODIALYSIS AND METHOD OF MONITORING A PARAMETER OF A FLUIDIC SAMPLE

Patent Proprietor:
Joanneum Research Forschungsgesellschaft mbH

Opponent:
GAMBRO LUNDIA AB

Headword:
Mikrodialyse/Joanneum

Relevant legal provisions:
EPC Art. 52(1), 54, 56

Keyword:
Novelty - (yes) -
Combination of features as claimed not directly and unambiguously disclosed
Inventive step - (yes) - non-obvious combination of features

Decisions cited:
T 1756/11

Catchword:

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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 2454/12 - 3.3.06

D E C I S I O N
of Technical Board of Appeal 3.3.06
of 15 January 2016

Appellant: (Opponent)	GAMBRO LUNDIA AB Magistratsvägen 16 22643 Lund (SE)
Representative:	Perchenek, Nils Gambro Dialysatoren GmbH Legal and Intellectual Property Holger Crafoord-Strasse 26 72379 Hechingen (DE)
Respondent: (Patent Proprietor)	Joanneum Research Forschungsgesellschaft mbH Steyrergasse 17 8010 Graz (AT)
Representative:	Dilg, Haeusler, Schindelmann Patentanwaltsgesellschaft mbH Leonrodstrasse 58 80636 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 October 2012 rejecting the opposition filed against European patent No. 1962993 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman B. Czech
Members: G. Santavicca
C. Vallet

Summary of Facts and Submissions

I. The appeal lies from the decision of the Opposition Division to reject the opposition against European patent 1 962 993.

II. The patent in suit comprises 11 claims, independent Claims 1, 10 and 11 reading as follows:

"*1. An apparatus for analyzing a fluidic sample by microdialysis, comprising*
a permeable membrane (100);
wherein the permeable membrane has a first surface (200) to be brought in contact with the fluidic sample to traverse the permeable membrane;
wherein the permeable membrane has a second surface (104) to be brought in contact with a dialysis fluid;
wherein the first surface is smoother than the second surface so that a surface roughness of the first surface is smaller than a surface roughness of the second surface;
wherein the permeable membrane comprises a hollow tube, an outer surface of the hollow tube forming the first surface;
wherein the permeable membrane comprises pores having a mean size which increases from the first surface towards the second surface, wherein the pores have a size (d_1) at the first surface smaller than essentially (d_1) 0.1 µm, wherein the pores have a size (d_2) at the second surface in the range between essentially (d_2) 0.1 µm and essentially 0.4 µm ; and
wherein the permeable membrane has a molecular cut-off in a range between 1 kDa and 100kDa."

"*10. A method of monitoring a parameter of a fluidic sample by microdialysis, the method comprising*

bringing a first surface of a permeable membrane in contact with a fluidic sample to traverse the permeable membrane;
bringing a second surface of the permeable membrane in contact with a dialysis fluid;
wherein the first surface is smoother than the second surface so that a surface roughness of the first surface is smaller than a surface roughness of the second surface;
wherein the permeable membrane comprises a hollow tube, an outer surface of the hollow tube forming the first surface;
wherein the permeable membrane comprises pores have a mean size which increases from the first surface towards the second surface, wherein the pores have a size at the first surface smaller than essentially 0.1 µm, wherein the pores have a size at the second surface in the range between essentially 0.1 µm and essentially 0.4 µm; and wherein the permeable membrane has a molecular cut-off in a range between 1 kDa and 100kDa."

"*11. A method of using an apparatus of any one of claims 1 to 9 for monitoring an analyte concentration, particularly for glucose monitoring.*"

Dependent claims 2 to 9 as granted are directed to more specific embodiments of the apparatus of Claim 1.

III. Lack of novelty and lack of an inventive step (Article 100(a) EPC) had been invoked as grounds of opposition. The documents relied upon included

D1: WO 2008/0467779 A1;

D2: US 4,832,034 A;

D3: N. Torto et al, *Optimal membrane choice for microdialysis sampling of oligosaccharides*, Journal of Chromatography A, 806(1998), 265-278;

D4: WO 01/78805 A1; and,

D5: O.A. Boubriak et al, "*Monitoring of lactate and glucose levels in engineered cartilage construct by microdialysis*", Journal of Membrane Science, 273 (2006), 77-83.

IV. In the decision under appeal, the Opposition Division came to the following conclusions:

a) D1 (claimed priority date 18 October 2006) did not fall under the provisions of Article 55(1)a EPC, thus was state of the art under Article 54(3) EPC.

b) The claimed subject-matter was novel over D1.

c) The claimed subject-matter was neither obvious in view of D2 taken alone, nor in view of combinations of either of D3 or D5, taken as the closest prior art, with D4.

V. Third Party Observations were filed during the course of the appeal proceedings, together with the further document

DTPO: Wolfgang Künnecke and Rolf Schmid, "*Gas-Diffusion dilution flow-injection method for the determination of ethanol in beverages without sample pretreatment*", Analytica Chimica Acta, 234 (1990) 213-220,

allegedly showing that the use of membranes of different roughnesses on their opposite surfaces was known.

VI. In its statement setting out the grounds of appeal, the Appellant maintained that D1 was novelty-destroying prior art for all the independent claims of the patent as granted and that the claimed subject-matter was not inventive in the light of D2 or of combinations of D3 or D5 with D4. It also called into question the effects allegedly attributable to the pore size at the inner surface of the membrane, and referred in this connection to the further document

D7: Tsuyuhara, Tomoo, "*Influence of membrane pore size and material on membrane fouling in membrane bioreactors operated under different sludge retention time*", Hokkaido University, 2010.

VII. In its reply of 15 July 2013, the Respondent rebutted the Appellant's objections and defended the patent as granted (Main Request). With its reply, it nevertheless submitted three sets of amended claims as First to Third Auxiliary Requests.

It maintained *inter alia that* D1 was a non prejudicial disclosure pursuant to Article 55(1)a EPC and enclosed several items of supporting evidence (Annexes A to F), but also that, in any case, D1 did not disclose subject-matter falling within the ambit of Claim 1 or 10 as granted. It also rebutted the objection raised in the third party observations based on document DPTO, considered irrelevant. With respect to the disclosure and terminology of D2, it filed some dictionary excerpts (Annexes 4 to 6).

VIII. The parties were summoned to oral proceedings. In a communication, the Board gave its preliminary opinion on salient issues of the case, i*nter alia* regarding novelty over the disclosure of D1 and inventive step in the

light of documents D2, D3 and D5. More particularly, D2 was provisionally considered as a less appropriate starting point than D3 or D5.

IX. With its written submission dated 5 January 2016, the Respondent submitted two sets of amended claims as new Second and Third Auxiliary Requests and additional experimental data in support of inventive step.

X. Oral proceedings took place on 15 January 2016. The debate focused on the issues of novelty over the disclosure of D1 and inventive step in the light of D3 or D5, taken as the closest prior art, and their combination with D4.

XI. Requests

The Appellant (Opponent) requested that the decision under appeal be set aside and that the European patent be revoked.

The Respondent (Patent Proprietor) requested that the appeal be dismissed (Main Request) or, in the alternative, that the patent be maintained on the basis of the First Auxiliary Request filed with letter dated 15 July 2013, or of one of the Second or Third Auxiliary Requests filed with letter dated 5 January 2016.

XII. The arguments of the Appellant of relevance here, i.e. regarding the claims as granted (Main Request), can be summarised as follows:

Novelty

Example 4 of D1 disclosed a hand bundle of hollow fibre membranes with a hydraulic permeability identical to the

upper limit of a preferred range of values ensuring a molecular size diffusive transport up to 100000 Dalton. Hollow fibre membranes with molecular cut-off according to Claim 1 were known. Figures 4c and 4d of D1 respectively showed inner and outer surface of the membranes of Example 4. According to measurements carried out on these figures, the inner surface had an average pore size of 0.15 µm and the outer surface had an average pore size of 0.07 µm. The objection of the Respondent, that it had not been shown how these pore sizes were measured, was not convincing, as the patent in suit did not disclose any methods for determining the claimed pore sizes. The presence of bigger pores in the inner surface implied that the mass density there was lower than that at the outer surface. As also mentioned in paragraph [0028] of the patent in suit, this meant that the inner surface was rougher than the outer surface, having smaller pores and higher mass density. The higher roughness of the inner surface was also apparent from the different scales used for the inner surface picture (Figure 4c, 20000X) and for the outer surface picture (Figure 4d, 40000X). The inner surface of the membrane of Example 4 was rougher than the outer surface. The membranes of D1 were expressly disclosed as being suitable for microdialysis (page 7, lines 26-27; see also page 16, lines 3-4). Thus, the microdialysis membrane mentioned in D1 could be used in a method for monitoring analytes based only on diffusion, in accordance with a corresponding statement in paragraph [0041] of the patent in suit. Also the further limitations implied by the feature "*microdialysis*", acknowledged in the decision under appeal, e.g. the connections on the lumen side for the dialysate, were met by the bundle formed with the membranes of Example 4, with which diffusion experiments were carried out (Page 21, lines 16-17, and page 15, line 22 ff).

Therefore, the features defined in Claim 1 were all disclosed in D1, and the claimed apparatus was not new.

Inventive step

As to inventive step, D2 was an appropriate closest prior art, but in view of the preliminary opinion of the Board, lack of inventive step was also arguable taking any of D3 or D5 as the closest prior art. Like the patent in suit, D5 concerned apparatuses for microdialysis. These apparatuses permitted high, stable recovery, as apparent from the relevant figures of D5.

The technical problem objectively solved in the light of such apparatuses, could thus arguably be formulated as providing a microdialysis apparatus which avoided the decrease of recovery at the beginning of the microdialysis operation. However, the feature of Claim 1 concerning the smoother and rougher surfaces was relative, and no absolute values had been given. Hence, this feature could not be argued to result in any effect whatsoever. The range of pore sizes defined in Claim 1 had not been shown, by appropriate evidence, to produce the alleged effect of creating turbulence. The patent in suit did not contain sufficient data showing that the claimed solution effectively solved said technical problem. Indeed, D7 showed that the reduction of reversible fouling with increasing pore size could be experimentally demonstrated, so that the choice of the claimed pore size was an arbitrary measure, which thus did not solve any technical problem.
As to the parts in the patent in suit particularly invoked by the Respondent:
Figure 8 showed recoveries higher than 100%, which were not possible. Its X-axis was not the time. It was not disclosed how these results were obtained, with which

apparatus, with which material, under which operating conditions, nor whether any functionalisation of the membrane had been carried out. In contrast, D5 and D3 clearly disclosed the materials used. Therefore, the patent in suit contained no data convincingly supporting an improvement in resistance to fouling attributable to the pore size range of the inner surface, acknowledged in the decision under appeal. Hence, this range of pore sizes was arbitrary.

Also, a simple calculation based on fluid dynamic equations showed that no turbulent flow arose, even under the most extreme conditions such as maximum flow-rate and minimum inner diameter as given in the patent in suit. The finding in the decision under appeal that the choice of a membrane with an inner surface that was rougher than the outside surface promoted (transient) turbulent flow was wrong. Thus, not even the problem of preventing the initial decrease of recovery was solved by the claimed solution.

Consequently, the problem effectively solved was merely the provision of an alternative apparatus and use thereof.

As regards the obviousness of the solution claimed, it was acknowledged that the following features of the claimed subject-matter were not disclosed in any of D5 and D3:

- the first outer surface being smoother than the inner second surface;
- pores increasing in mean size from the outer first surface towards the inner second inner surface of the membrane;
- the pores at the first surface having a size of less than 0.1 µm; and,
- the pores at the second surface having a size of from 0.1 µm to 0.4 µm.

However, all these features, except for the pore size at the inner second surface, were disclosed in D4. The table for ultrafiltration applications on page 5 of D4 disclosed the pore sizes as claimed, and Figure 2 of D4 showed that the inner surface was rougher than the outer one. This was in line with the teaching of D4 that the material density of the outer surface was higher than that of the inner surface. D4 (Page 4) also taught that the outer surface was biocompatible, to prevent adhesion of biomaterials such as proteins. Although D4 concerned membranes for ultrafiltration, it was known that these membranes could also be used for microdialysis. The skilled person confronted with the problem posed would have combined D5, or even D3, with D4, thereby arriving at the claimed subject-matter in an obvious manner.

XIII. The relevant counter-arguments of the Respondent can be summarised as follows:

Novelty

D1 was not prior art opposable against the patent in suit, as it was a non-prejudicial disclosure under Article 55(1)a EPC.

Even if D1 were held to be prior art opposable against the patent in suit, it would not take away novelty. Example 4 thereof disclosed a hand bundle of hollow fibre membranes, which was not an apparatus for microdialysis. The term "*microdialysis*" implied transport by diffusion only, without transmembrane pressure, with a perfusate/dialysate flowing inside the lumen. Apparatuses for microdialysis were disclosed in D3 and D5, and were not made up of bundles of hollow fibre membranes, but consisted of a membrane. The disclosure of Example 4 of D1, not concerning

microdialysis, could not be combined, without hindsight, with the general disclosure on pages 7 and 8 of D1, concerning microdialysis, nor with that on page 15 of D1, concerning a use of the bundle fibres that did not mention microdialysis either. The alleged lack of novelty was the result of combining separate items of different embodiments, not being unambiguously disclosed in combination in D1. Further, an apparatus for microdialysis implied not only the membrane but also the accessories (tubing, pump, connection), which made it suitable for analyzing by microdialysis. The connections for the lumen side of the hollow fibre membrane bundle, in which the dialysate was flown, were not disclosed in Example 4 of D1. The terms smoother and roughness should be understood/measured as disclosed in paragraph [0050] of the patent in suit. A similar definition was given on page 2 of D1. The pore size had an influence on roughness. As disclosed in D1 (page 4, lines 7 to 8), also the inner surface (i.e. in addition to the outer surface) might be made smooth, to reduce the risk of haemolysis, despite the pores being bigger than those at the outer surface. No roughness information could unambiguously be deduced from Figures 4c and 4d of D1, let alone any pore size from both surfaces. It was contested that pore size might be measured from Figures 4c and 4d, such as the alleged value of 0.07 µm. These figures were not complete, as apparent from the lines of the scales lacking one of the barrier. Figures 4c and 4d did not represent entire pictures. The Appellant had not submitted any information on the measurements carried out, which would permit a repetition/check thereof. As it had not been shown that a skilled person could determine the pore size from Figures 4c/4d, pore sizes as claimed were not disclosed in Example 4 of D1.

Inventive step

D2 taught away from the claimed invention, as it did not deal with microdialysis but with a pressure-driven process. It also did not disclose pores of different size on opposing surfaces of the tubular membrane, let alone a different roughness as specified in Claim 1. Finally, D2 was non-enabling. The reference to "*ultrafiltration*" in the patent in suit did not make D2 any more relevant, nor could this indication in the patent in suit be used as prior art against the patent itself.
D3 and D5 disclosed standard microdialysis membranes, whereby D3 disclosed a membrane with an outer pore size as large as 2 micrometers, thus without any hint towards the claimed invention.

D5 could be considered as the closest prior art for assessing inventive step, as it addressed the problem of fouling and its effects on recovery change with time.

During the oral proceedings, the Respondent countered the objections of the Appellant and maintained that the problem to be solved over D5 was the providing of an apparatus and of a method for analysing a fluidic sample by microdialysis over a sufficiently long time interval with high recovery, even in the initial phase, and that this problem had been effectively solved, as evidenced by Figure 8 of the patent in suit and by the additional experimental report filed with letter of 5 January 2016, arguing that both showed the absence of any fouling-related initial decrease of the relative recovery upon using the claimed apparatus. It also noted, as a matter of comparison, that Figure 3b of D5 showed that the recovery was not so stable, as Figure 3a of D5 showed a recovery of less than 30%.

However, prompted by the Board, the Respondent asserted that even if this formulation for the technical problem were not acceptable, i.e. even if the technical problem were seen in the providing of a further apparatus and method for analytical microdialysis, as argued by the Appellant, the solution to this minimal problem was still not obvious over the cited art.

D5 did not disclose the following features of the apparatus of Claim 1 at issue:
- a first surface being smoother than a second surface;
- the membrane comprising pores increasing in mean size from the first surface towards the second surface;
- the pores at the first surface having a size smaller than essentially 0.1 µm; and,
- the pores at the second surface having a size in the range between essentially 0.1 µm and essentially 0.4 µm.
D5 did not hint at reducing the initial fall of recovery. It considered biofouling as being simply unavoidable, to be accepted. Hence, D5 did not render obvious an apparatus as defined in Claim 1 at issue.

D3 did not disclose more than D5.

The skilled person had not motivation to combine D5 with D4, which did not disclose membranes for microdialysis, but for ultrafiltration or plasmapheresis. D4 had already been considered in the examination proceedings, and was found to be irrelevant. D4 could thus not be combined with D5 without hindsight. Even if it were, the skilled person would not obviously arrive at the claimed invention, as D4 did not disclose that one surface was rougher than the other, nor the pore sizes on the lumen surface of the membrane as claimed.

Thus, the patent should be maintained unamended.

Reasons for the Decision

Respondent's Main Request (patent as granted)

Novelty over D1

1. The prior art status of D1

1.1 D1 claims the priority of two national applications filed on 18 October 2006, i.e. one day before the priority date claimed by the patent in suit. D1 was published on 24 April 2008, i.e. after the filing date of the patent in suit (18 October 2007). The validity of the priority dates claimed, respectively, by the patent in suit and D1 is not in dispute.

D1 thus forms part of the prior art pursuant to Article 54(3) EPC.

1.2 Article 55(1)a EPC

The Respondent also argued that the publication of D1 was the result of an evident abuse of confidential information by the Applicant of D1 (Gambro), i.e. the present Appellant.

Since D1 does **not** disclose (see points 2 *et seq., supra)* novelty-destroying subject-matter, i.e. subject-matter falling within the ambit of Claim 1 of the patent in suit, issues possibly arising under Article 55(1)a EPC regarding the prior art status of D1 need not be dealt with in the present decision.

2. According to long standing case law of the Boards of Appeal of the EPO, a claimed subject-matter lacks

novelty if the prior art discloses directly, or at least implicitly, and unambiguously subject-matter with all the features in combination as claimed. In the present case, the Board sees no reason to call into question the finding in the decision under appeal for the following reasons.

2.1 D1 concerns asymmetric hollow fibre membranes, which may be made of up to five layers (see e.g. page 3, lines 13 to 14 and 29 to 30) and a method for their preparation. D1 also generally mentions microdialysis as one among several fields of application (see e.g. page 7, lines 26 to 28).

2.1.1 Figures 4c and 4d respectively show the inner and outer surface of such a five-layer membrane, described in Example 4 of D1. The outer, separation-active layer thereof has the smallest pores and the highest mass density (page 21, lines 25 and 26). Example 4 also mentions the roughness value of the outer surface (page 22, first paragraph) and the hydraulic permeability of 27 x 10-4 cm3/(cm^2 bar sec) of this membrane (page 21, lines 17 to 18).

2.1.2 According to the general description (page 4, lines 16 to 23), a membrane with such a hydraulic permeability provides for minimised convective transport and high diffusive transport with respect to molecular sizes up to 100kDa.

2.1.3 However, in Example 4 of D1 mentions is neither made of the roughness of the **inner** surface of the hollow fibre membrane, nor of the pore sizes at outer and inner surfaces thereof.

2.2 Regarding these features of Claim 1 at issue, the Appellant argued that Figures 4c and 4d showed that the pores at the inner surface of the membrane of Example 4 of D1 were bigger than those at its outer surface. Hence the material density had to be lower at the inner surface than at the outer surface. Bigger pores and lower mass density implied that the inner surface was rougher than the outer surface, as stated in the patent in suit. Moreover, measurements carried out on Figures 4c and 4d showed that the pore sizes at both surfaces were within the ranges according to Claim 1 at issue.

2.3 Regarding the roughness of the membrane of Example 4

2.3.1 The Board accepts that it is apparent from a comparison of Figure 4c, showing the inner surface, with Figure 4d, showing the outer surface, that (considering the different scales) the pores are larger at the inner than at the outer surface of the membrane.

2.3.2 The conclusion that this implied a lesser smoothness for the inner surface was contested by the Respondent, arguing that Example 4 of D1 did not disclose a membrane having an outer surface roughness smaller than the inner surface roughness, determined according to DIN 4768 as indicated in the patent in suit, and that the Opponent did not submit evidence showing the contrary. Moreover Figures 4c and 4d were not complete, so that no determination of the roughness could be carried out on them by way of measurement.

2.3.3 The Board notes that, as regards pore size and mass density of membranes with five layers, D1 generally requires the outer surface to have the smallest pore size and the highest mass density (page 3, lines 14 to 15). Moreover, in membranes comprising five layers (as

the one of Example 4), a fifth layer forming the inner wall surface can have either a larger pore size and a lower mass density than all the other layers (page 3, lines 22 to 25), or smaller pore size and higher mass density than the fourth layer (page 4, lines 5 to 7). As also apparent from D1 (page 7, lines 18 to 19: "if the pore sizes were increased and the low roughness were kept"), an increase of pore size, hence a reduction in mass density, does not necessarily result in an increase of roughness.

2.3.4 D1 generally requires the outer surface to be "smooth, continuous and homogeneous" (page 2, lines 5 to 7). More particularly, the outer surface should have appropriate roughness and biocompatibility if the membrane is to be used in contact with blood (see e.g. page 7, lines 12 to 16, and line 33). However, D1 also discloses that in membranes with five layers, the inner surface can be smooth (Page 4, lines 7 to 8), if the membranes are to be used when both fluids (inside and outside the membrane) have high fouling potential (page 4, lines 8 to 10).

Thus, the Board holds that according to the teaching of D1, the choice of a smooth surface depends on the intended use of the application, rather than on the mass density only. Hence, the inner surface of the five-layer membrane of Example 4 could also have a smooth surface. In Example 4 only the roughness value of the outer surface is expressly mentioned.

2.3.5 The Board concludes that it is not directly and unambiguously derivable from the description and Figure 4c of D1 that the membrane of Example 4, although having bigger pores at its inner surface than at its outer surface, has an inner surface which is rougher than its

outer surface. A rougher inner surface is also not an inevitable result of the preparation method described in Example 4 of D1.

2.4 Regarding the pore size at inner and outer surfaces

2.4.1 As to the question whether pore sizes can actually be determined from Figures 4c and 4d and the description of Example 4, the Board notes the following:
- No pore size values are mentioned in the text of Example 4. Only the hydraulic permeability of the membrane is mentioned, apparently the sole parameter measured.
- Figures 4c and Figure 4d only comprise incomplete scale bars, rendering values determined based on these scale bars rather speculative.
- It was not possible to establish the accuracy of the figures, as the original pictures were not available.
- No further evidence was provided as regards the way in which the pore sizes were determined using these pictures. Neither the Respondent nor the Board could thus assess the appropriateness and correctness of such determination.
- The meaningfulness of the values provided by the Appellant was thus contested by the Respondent.

2.4.2 Considering the above, the Board concludes that the Appellant has not discharged its onus to convincingly prove its allegation that the membrane of Example 4 has surface pore sizes as defined in Claim 1 at issue.

2.4.3 There is also no evidence on file convincingly showing that the membrane obtained when reproducing the preparation method described in Example 4 of D1 would inevitably display all the features of the membrane defined in Claim 1.

2.5 Hence, in the Board's judgement, D4 does not directly and unambiguously discloses a hollow fibre membrane having an inner surface which is rougher than its outer surface and pore sizes at its inner and outer surfaces as defined in Claim 1 at issue.

2.6 Furthermore, Example 4 does not, in any case, directly and unambiguously disclose that a membrane prepared according to Example 4 is supposed to be used in a **microdialysis** apparatus or method. Nor can the skilled person directly and unambiguously gather this intended application from the hydraulic permeability value disclosed in Example 4 (27 x 10-4 $cm^3/(cm^2$ bar sec), as according to page 4, line 20, this permeability value is at the boundary of the range given for membranes with "minimised" convective transport. Thus, the membrane of Example 4 is not necessarily intended to be used in microdialysis; it could also be foreseen for an application such as hemodialysis, involving a "combination of diffusion and convection" (page 7, lines 18-20).

2.6.1 Moreover, an "*apparatus for analyzing a fluidic sample by microdialysis*" (Claim 1 at issue), or methods involving microdialysis (Claims 10 and 11), implicitly require more features than just the membranes.

2.6.2 The only instance where microdialysis is expressly mentioned in D1 (paragraph bridging pages 7 and 8) merely refers to "direct blood applications", and to the requirement that the surface of the membrane in contact with blood should be "highly biocompatible". This generic part of the description is not, however, linked to the membrane of Example 4 in particular.

2.6.3 Apparatuses including membranes as described and claimed in D1 are only mentioned in the following parts of D1, which relate to permeability/diffusion tests performed on
- "hand bundles" (page 12, line 16, to Page 13, line 5) for performance testing;
- "mini-modules" (page 13, lines 7-16) for biocompatibility testing; and/or,
- "filters" ("dialyzer") (page 13, lines 18-32) including e.g. the fibre bundles.
These parts do not reveal any features (roughness, pore size, cut-off) or suitability of the tested membranes.

The diffusion experiments described in the paragraph bridging pages 15 and 16, in particular page 15, lines 29-31, are carried out with a bundle of fibres, with diffusion from inside to outside. This description merely deals with the way of carrying out the diffusion measurements, to characterize the diffusion of the membrane, without indicating any physical feature of the membrane used.

2.7 Therefore, the use of a membrane as illustrated by Example 4 in an apparatus for analyzing a fluidic sample by microdialysis can only be the result of an at least two-fold choice from, on the one hand, the various membrane applications mentioned in D1, and, on the other hand, various possibilities in terms of membrane properties encompassed and/or specifically illustrated by D1. However, without hindsight, the skilled person does not find in D1 a direct and unambiguous link between the application in "microdialysis" and the combination of membrane properties (cut-off, surface pore sizes and roughnesses) as defined in Claim 1 at issue.

2.8 In the Board's judgement, an apparatus according to claim 1 as granted, its use according to claim 11 as granted, and a method according to claim 10 as granted, involving microdialysis by means of membranes with the features also defined in Claim 1, are not directly and unambiguously disclosed in D1.

2.9 The subject-matter of the claims as granted is thus novel over D1 (Article 52(1) and 54(3) EPC).

Inventive step

3. The invention

The invention relates to an apparatus for analysing a fluid sample using microdialysis, to a method for monitoring a parameter of a fluidic sample by microdialysis, and to the use of the claimed apparatus (see independent Claims 1, 10 and 11).

4. Closest prior art

4.1 The Appellant submitted different inventive step objections, based on either D2, D3 or D5 as the closest prior art. Thus, the question arises which document is the most appropriate starting point for the assessment of inventive step according to the problem-solution approach.

4.2 In this connection, it must be taken into account that the present invention relates to **microdialysis**. As indicated in paragraph [0041] of the patent, a semi-permeable hollow fibre membrane separates the milieu to be investigated ("*sample*" fluid), containing the analyte(s) to be monitored, from the the liquid phase ("*dialysis fluid*"), into which the analyte(s) of

interest migrates. The migration through the membrane is "*mainly based on diffusion*" and results in partial or full equilibration of the analyte concentration in the two fluid phases, without systematically altering the concentration of the analyte in the first phase. The liquid "*dialysis fluid*" also transports or sweeps away the diffused analyte through the lumen to the point of analysis.

Also, the concentration of the diffused component is not immediately proportional to its concentration in the milieu under investigation (see e.g. [00153], fourth sentence: "*[t]he dialysis procedure will in general not yield equilibrium ...*"). The efficiency of the microdialysis is described in terms of "*relative recovery*" (paragraphs [0034] and [0153]), i.e. the ratio between the concentrations of the analyte of interest in the dialysis fluid and the sample fluid.

4.3 Document D5 - closest prior art

4.3.1 D5 expressly concerns microdialysis to monitor cell metabolism, *inter alia* glucose, within engineered tissue (Abstract). The authors of D5 investigated the occurrence of fouling of the microdialysis probes (Points 2.6 and 2.9). According to D5, evaluation of fouling is necessary to distinguish, in the context of long term monitoring, a decrease of monitored molecules due to a lower metabolic cell activity from a decrease caused by fouling. Figure 3b of D5 shows an initial decrease in relative recovery as well as stable operation at a relative recovery of 30%. This initial decrease lasts 15 h whilst the stable regime lasts 75 h (Point 3.2, last paragraph).

4.3.2 D5 thus identifies the problem of the initial decrease in recovery. It discloses microdialysis probes formed from polyethersulfone (PES) dialysis membrane with a 15 kDa cut off. These probes are used for long-term (8-94 hours, see Point 2.8, last sentence) measuring of the concentration of low molecular weight solute (<1kD) (see Point 2.6). They are thus comparable to the membranes to be used according to the claims of the patent in suit.

4.4 D3 not closest prior art

4.4.1 D3 too is concerned with microdialysis, in particular with the choice of optimal membranes for microdialysis sampling of oligosaccharides (Abstract). The membranes investigated were "evaluated with respect of their EF, permeability, high temperature stability and for their interaction with enzymes (proteins)" (see point 1, last sentence; Points 2.3 and 3.6). In this latter respect, "membrane fouling" is mentioned on page 269, left column, second line, and "hydrodynamic resistance" is mentioned on page 274, left column, fourth line. D3 also teaches that the "initial decrease (membrane fouling) in extraction fraction (EF) with time observed, which eventually stabilises" must be taken into account (page 269, left column, first paragraph). The membranes evaluated have a cut-off ranging between 3 and 100 kDa (point 2.4).

4.4.2 However, according to Point 3.8, first sentence, the evaluated membranes have "outer pore diameters as large as of 2 µm".

4.4.3 Hence, although D3 addresses the initial decrease in extraction fraction due to membrane fouling in the context of microdialysis, it only mentions membranes with pore sizes on the outside surface which are way

beyond the upper limit of 0.1 µm defined in this respect in Claim 1 at issue, and is thus, for the Board, as less appropriate starting point for the assessment of inventive step.

4.5 D2 not closest prior art

4.5.1 This document relates to the use of asymmetric and anisotropic hollow fibre membranes for sampling and analysing portions of complex body fluids such as blood. D2 does not expressly mention microdialysis. Instead, the permeation through the membrane is expressly based on convective flow (see Claim 1) induced by a pressure gradient, without the need to provide a sweep liquid inside the lumen of the membranes. Reference is made in particular to the following parts of D2: Column 3, line 64, to Column 5, line 41; Column 11, line 37, to Column 12, line 34; Column 17, line 26, to Column 18, line 58. The analyte may be glucose (claim 3) and the pores on the outer (skin) surface are in the range from 0.0025 to 0.02 µm (claim 15).

4.5.2 However, this document does not address the same objectives as the patent in suit (see paragraphs [0041]. The deliberately different underlying transport mechanism (solute transport by filtration driven by transmembrane pressure, rather than by concentration difference, see Column 4, lines 59-61) does not imply response time lags (see paragraph [00153] of the patent in suit, fourth sentence), i.e. the concentration of the permeated component is immediately proportional to the concentration of the same component in the milieu under investigation, as (part of) the milieu itself is permeated through the membrane. Therefore, D2 is not an appropriate starting point for objectively assessing inventive step of a microdialysis apparatus.

4.5.3 The argument of the Appellant that the patent in suit also mentions ultrafiltration has no bearing on this finding since
- the mentioning of ultrafiltration in the patent in suit appears to be due to an incomplete adaptation of the description to the claims finally granted (the claims of the application related to both microdialysis and ultrafiltration), and
- there is no evidence on file showing that membranes for ultrafiltration are also suitable for microdialysis.

5. Technical problem

5.1 At the oral proceedings, the Respondent maintained that the problem to be solved in the light of D5 consisted in providing an apparatus and a method for analysing a fluidic sample by microdialysis over a sufficiently long time interval with high recovery, even in the initial phase, which problem had been effectively solved, as apparent from the evidence in the patent in suit (Figure 8) as well as from the additional evidence submitted.

5.2 However, in the course of the debate, the Respondent also submitted that if it were not accepted that this technical problems was effectively solved, the technical problem solved could at least be seen in providing a further apparatus and method for analytical microdialysis, as argued by he Appellant.

6. Solution

As a solution to the technical problem posed, the patent in suit proposes (emphasis added) the "*apparatus for* ***analyzing*** *a fluidic sample by* ***microdialysis***" according to claim 1 as granted, which is characterised in particular

- in that it comprises "*a permeable membrane*" in form of a "***hollow tube***" having "*a **first surface** ... to be brought in contact with the **fluidic sample to traverse** the permeable membrane*" and *"a **second surface** ... to be brought in **contact with a dialysis fluid***",
- in that "*the **first surface** is **smoother than** the **second surface** so that a **surface roughness** of the **first surface** is **smaller than** a **surface roughness** of the **second surface***",
- in that "*the permeable membrane comprises **pores** having a mean **size** which **increases from** the **first surface towards** the **second surface***",
- and in that the **pores** which "*have a **size** (d_1) **at the first surface smaller than** essentially (d_1) **0.1 µm***" and "*a **size** (d_2) **at the second surface** in the range **between** essentially (d_2) **0.1 µm and** essentially **0.4 µm***" and *"a **molecular cut-off** in a range **between 1 kDa and 100kDa***".

7. Success of the solution

7.1 For the Board, the less ambitious technical problem (Point 5.2, *supra*) of providing a alternative microdialysis apparatus is effectively solved by the apparatus according to Claim 1, as apparent *inter alia* from the experimental data shown in Figure 8. This was not in dispute.

7.2 In the present case, the Board reached the conclusion (points 8., *et seq., infra*) that the claimed subject-matter was not obvious in the light of the prior art even when considering, *arguendo* but in the Appellant's favour, that only the less ambitious technical problem of providing a further apparatus for analytical microdialysis was effectively solved. Hence, there is no need to decide the question (controversially debated at the oral proceedings) of whether the evidence invoked by

the Appellant is actually sufficient to demonstrate that the more ambitious technical problem formulated by the respondent (Point 5.1, *supra*) is also successfully solved across the full ambit of the claims. Accordingly, the Board also sees no need for commenting on the relevance of document D7, which was cited to in response to the alleged lack of evidence regarding an effect attributable to the lumen pore size.

Solution not obvious

8. The question that remains to be decided is thus whether it was obvious to the skilled person seeking to provide a further microdialysis apparatus as claimed to incorporate membranes with all the claimed features into an apparatus as disclosed by D5.

8.1 Document D5 taken alone

8.1.1 At the oral proceedings, it was not in dispute that D5 does not directly and unambiguously disclose hollow fibre membranes

- having an outer surface which is smoother than their inner surface;
- pores increasing in mean size from the outer surface towards the inner surface of the membrane;
- pores at the outer surface having a size smaller than essentially 0.1 µm; and,
- pores at the inner surface having a size in the range between essentially 0.1 µm and essentially 0.4 µm.

8.1.2 Neither does D5 contain elements of information which could induce the skilled person to incorporate specifically such membranes into the microdialysis apparatus of D5.

8.2 Document D3

8.2.1 D3 does not disclose these features either. Indeed, as the authors of D3 appear to assume that the initial decrease in extraction fraction is unavoidable, they recommend, in order to enhance the performance, choosing optimal parameters and membrane material for specific sampling conditions (page 267, left column, last sentence). According to Point 3.8, first sentence, this choice results in the investigated membranes having outer pore diameters as large as 2 micrometers, i.e. well beyond the range defined in Claim 1 at issue. D3 does also not suggest the different roughnesses as claimed. Whether these membranes are homogeneous rather than asymmetric, as alleged by the Respondent, need thus not be elucidated.

8.2.2 Hence, D3 does not hint at the claimed solution, even if considered together with with D5.

8.3 Combinations with documents D4

8.3.1 D4 (Claim 1) concerns membranes for *in-vivo* plasmapheresis or ultrafiltration. The membranes are in form of hollow fibres and have an asymmetrical fibre wall morphology. The fibre wall has a higher mass density and smaller pores adjacent to the outer wall surface, and a lower mass density and larger pores adjacent to said inner wall surface. In the assemblies disclosed, the lumen of the hollow fibre is in fluid communication with the catheter. The body fluid being subjected to the separation operation thus apparently contacts the inner wall surface having relatively larger pores (Claim 17, page 2, first full paragraph).

8.3.2 Moreover, according to D4 (see also tables on page 5)
- the membranes for plasmapheresis have a nominal average pore diameter of from 1 to 60 µm at the inner (lumen) lower mass density surface (Claim 8), preferably of from 5 to 40 µm,
whilst
- the membranes for ultrafiltration have a nominal average pore diameter of from 0.005 to 0.05 µm at their inner surface, preferably of from between about 5 µm and about 40 µm (Claim 24).
In particular, the pore sizes at the inner surface of the hollow fibre ultrafiltration membranes exemplified (tables on page 5 of D4), are in the range of from 5 to 40 µm, hence much bigger than the ones of the membrane used in the apparatus according to Claim 1 at issue.

8.3.3 Although D4 discloses (page 4, lines 24-27) that the membrane material should be highly biocompatible, such as to prevent e.g. protein adhesion, microdialysis is not mentioned as one of the listed possible applications of the disclosed membranes (see the paragraph bridging pages 5 and 6, or Claim 26). Indeed, the applications referred to in D4 (see page 4, line 29) would all appear to rely on a transport mechanism based on convection, not on diffusion as in the case of microdialysis.

8.3.4 Furthermore, no measurement of surface roughness appears to be mentioned in D4, which merely mentions different material densities for both surfaces.

8.3.5 From the above analysis of the content of D4, the Board concludes that without the benefit of hindsight, the skilled person has no motivation whatsoever to consider to incorporate the membranes disclosed in D4 into an apparatus for analytical microdialysis as taught in D5.

8.3.6 But even assuming *arguendo* that the skilled person would actually have wanted to consider combining the teachings of D5 and D4, he would nonetheless not arrive at a microdialysis apparatus comprising a membrane with all of the features of Claim 1 at issue.

9. In the Board's judgement, the apparatus according to Claim 1 thus involves an inventive step over the cited prior art (Articles 52(1) and 56 EPC).

The use of such an inventive apparatus according to Claim 11 at issue and, for analogous reasons, the "*monitoring by microdialysis*" using a membrane with the features defined in Claim 1 at issue, as defined in Claim 10, also involve an inventive step.

Conclusion

10. The grounds of opposition invoked by the Appellant do not prejudice the maintenance of the patent as granted.

Third party observations

11. The Appellant chose not to rely on these observations, which were also expressly considered of little relevance by the Respondent. The Board does not consider it appropriate to dealt with this document any further pursuant to Article 114(1) or (2) EPC. In this respect, reference is made to decision T 1756/11 of 14 January 2015 (Reasons, 2 to 2.10).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Magliano B. Czech

Decision electronically authenticated