

Internal distribution code:

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

**Datasheet for the decision
of 26 March 2021**

Case Number: T 2728/16 - 3.3.08

Application Number: 05795434.9

Publication Number: 1802752

IPC: C12N13/00, C12M1/34

Language of the proceedings: EN

Title of invention:
PARALLEL PATCH CLAMP SYSTEM

Patent Proprietor:
Molecular Devices, LLC

Opponent:
Nanion Technologies GmbH

Headword:
Parallel patch clamp/MOLECULAR DEVICES

Relevant legal provisions:
EPC Art. 83
RPBA Art. 12(4)

Keyword:

Sufficiency of disclosure - main request (no) - auxiliary
requests 1-16 (no)
Auxiliary request 4b - admitted (no)

Decisions cited:

T 0487/91, T 0931/91, T 0107/91

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2728/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 March 2021

Appellant:

(Opponent)

Nanion Technologies GmbH
Gabrielenstrasse 9
80636 München (DE)

Representative:

Kirchner, Christian
Ricker, Mathias
Wallinger Ricker Schlotter Tostmann
Patent- und Rechtsanwälte Partnerschaft mbB
Zweibrückenstrasse 5 - 7
80331 München (DE)

Respondent:

(Patent Proprietor)

Molecular Devices, LLC
3860 N. First Street
San Jose, CA 95134 (US)

Representative:

Mollekopf, Gerd Willi
Kahler Käck Mollekopf
Partnerschaft von Patentanwälten mbB
Vorderer Anger 239
86899 Landsberg/Lech (DE)

Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted on 12 October 2016
rejecting the opposition filed against European
patent No. 1802752 pursuant to Article 101(2)
EPC.**

Composition of the Board:

Chairman B. Stolz
Members: D. Pilat
 D. Rogers

Summary of Facts and Submissions

- I. European patent No. 1 802 752 based on European patent application No. 05795434.9 (published as International patent application WO 2006/031612; hereinafter "the patent application") was opposed on the grounds of Articles 100(a), (b), and (c) EPC. An opposition division decided, at the oral proceedings on 8 September 2016, that the patent met the requirements of the EPC and rejected the opposition.
- II. The opponent (appellant) lodged an appeal against the decision of the opposition division. Together with its statement of grounds of appeal, it submitted new documents D35 and D36.
- III. The patent proprietor (respondent) replied to appellant's statement of grounds of appeal.
- IV. The parties were summoned to oral proceedings. In a communication pursuant to Article 17(1) RPBA 2020, the parties were informed of the board's provisional, non-binding opinion, inter alia on issues concerning Articles 123(2), 83, 54 and 56 EPC.
- V. Oral proceedings were held on 26 March 2021 in the presence of both parties.
- VI. Claims 1 and 16 of the main request read as follows:

"1. A system (30) for high-throughput analysis of membranous samples (44) having ion channels, the system comprising:
at least one membranous sample (44);

a multi-compartment structure including an extracellular chamber (33), an opposing intracellular chamber (37) and a partition (40) separating the extracellular and intracellular chambers, the partition (40) having a plurality of apertures (42) fluidly and electrically coupling the extracellular and intracellular chambers, wherein at least one of the apertures is sealed by the at least one membranous sample, and another of the apertures is unsealed; and an electric source configured to apply a voltage and/or a current between the extracellular and intracellular chambers (33, 37), wherein a portion of current travels through the unsealed aperture;

characterized in that

the system further includes a current sensor configured to measure the ensemble current across the extracellular and intracellular chamber through all the apertures (42) of the partition (40); and the system (30) is configured to apply a leak subtraction data acquisition protocol to the measured ensemble current to account for leak current through the unblocked apertures (42) and through the occupied holes that do not have sealed or whole cell configuration cells.

16. A method of high-throughput analysis of membranous samples (44) having ion channels comprising: providing a system (30) including a multi-compartment structure having an extracellular chamber (33), an opposing intracellular chamber (37) and a partition (40) separating the extracellular and intracellular chambers (33, 37), the partition having a plurality of apertures (42) fluidly and electrically coupling the extracellular and intracellular chambers, wherein the apertures are dimensioned and configured for electrically sealing a membranous sample (44);

dispersing a plurality of membranous samples (44) into the extracellular chamber (33) such that the membranous samples seal at least one of the apertures (42); applying electrical voltage and/or current between the extracellular and intracellular chambers (33, 37) while another of the apertures is unsealed; detecting a resulting ensemble current and/or voltage across the extracellular and intracellular chambers (33, 37) through all the apertures (42) of the partition (40), wherein a portion of current travels through the unsealed aperture; and applying a leak subtraction data acquisition protocol to the detected ensemble current to account for leak current through the unblocked apertures (42) and through the occupied holes that do not have sealed or whole cell configuration cells."

Dependent claims 2 to 15 and 17 to 27 define specific embodiments of claims 1 and 16, respectively.

VII. The following documents are referred to in this decision:

D2: US2003/0070923 (published 17 April 2003)

D5: A. Finkel *et al.* "Population Patch Clamp Improves Data Consistency and Success Rates in the Measurement of Ionic Currents". *Journal of Biomolecular Screening*, vol. 11(5), pages 488-496, (2006);

D22: T.J. Dale *et al.* "Population patch clamp electrophysiology: a breakthrough technology for ion channel screening", *Mol Biosyst.*, 3(10), pages 714-722. Epub: 15 June 2007;

- D23: Cecilia Farre & Niels Fertig, "New strategies in ion channel screening for drug discovery: are there ways to improve its productivity?", *Expert Opinion on Drug Discovery*, 9:10, pages 1103-1107, (2014);
- D24: Cecilia Farre *et al.*, "Ion channel screening - automated patch clamp on the rise", *Drug Discovery Today: Technologies*, Volume 5, Issue 1, pages e23-e28, 2008;
- D25 Fertig N, Farre C. "Renaissance of ion channel research and drug discovery by patch clamp automation", *Future Med Chem.* volume 2(5), pages 691-695. May 2010;
- D35: Instruction manual of the "MultiClamp 700A computer-controlled microelectrode amplifier, Theory and Operation", Part Number 2500-129 Rev D November 2001 Printed in USA, pages 89-92, 135-139, (2001).
- D36: Expert opinion of Prof. Hermann Gaub LMU Munchen, dated 21 February 2017.
- Annex A: Affidavit of Dr. E.D. Verdonk dated 30 June 2016.
- Annex B: Expert opinion by Dr. A. Finkel submitted on the 30 June 2016.

VIII. The submissions made by the **appellant**, insofar as relevant to the present decision, are summarized as follows:

Main request

Article 100(b) EPC

Sufficiency of disclosure presupposes that the skilled person is capable of obtaining substantially all the embodiments falling within the ambit of the claims. Claim 1 covered embodiments, regardless of the magnitude of the leakage current, the magnitude of the physiological measurement signal, the aperture size, the number of apertures, the ratio of sealed to unsealed apertures. Hence, claim 1 encompassed a large number of embodiments which cannot achieve the technical effect described in the patent. The patent itself disclosed facts which substantiated that the subject-matter claimed was not reproducible over the entire scope of the claims (see patent, [0143], [0153], Fig. 17). The patent stated clearly that, when a specific cell line was measured, at most 3% of the apertures of a system with 64 apertures could be completely open for a measurement to be successful (page 18, lines 4-5). This ratio limitation was first lacking in claim 1 and second contradicted the technical effect that the system of the invention "can even tolerate multiple open holes in the substrate" (see patent [0094]).

Claim 1 related to systems with two sample wells and a partition with an open aperture and an aperture sealed with a cell. However, the patent description specified that "... when the average seal resistance is below ~30 Mohm the technique generally fails" (patent, paragraph [0143], page 17, lines 56-57). Based on this section of the patent, a patch clamp measurement was reported to fail at a ratio of 50% as well as 90% seal rate, consisting of at least one open aperture for at least every nine sealed apertures. The ionic current added to noise of the leakage current was lost among the total current.

The subject-matter of claim 1 was not limited to systems having, by applying the necessary conditions in practice, an acceptable occupancy rate and sealing rate of the cells on the apertures. The technique was observed to fail when the average seal resistance of the system was below ~30 Mohm. This failure was deemed to be due to poor cell quality and was an uncommon occurrence (< 2% of runs). At best, the patent could prevent the system from not providing a meaningful measurement of ionic current in membranous samples only if further steps mentioned in the description were included (paragraphs [0093], [0101], [0143]).

The "Functional PPC range" area identified in Fig.17 of the patent illustrated clearly that the ionic current could not be isolated from the total current measured (see document D5, Fig 7). The patent thereby described conditions under which the invention was conversely not practicable: "non-functional PPC range". In the two parallel patch-clamp (PPC) seal resistance models proposed, "... there is probably a mixture of successful seals, partially occluded holes, and completely open holes, suggesting that the seal rates must be 88% or greater, once a cell line was optimized. Although this was not difficult to achieve on a routine basis" (see patent [0153]). Hence, the skilled person had insufficient technical information and guidance how to measure and distinguish the ionic current through a membranous sample from the whole current measured in a system with any ratio of sealed/unsealed apertures.

The fact that failure was an uncommon occurrence in practice (< 2% of runs [0143]) remained without effect on the assessment of the practicability of the teaching over the entire area of claim 1, as the system of claim

1 was precisely described in the patent to be capable of measuring a meaningful ion channel current, and thus of providing meaningful high-throughput analysis results, even when the sample wells had several open apertures.

Auxiliary request 12

Sufficiency of disclosure Article 83 EPC

The method of claim 1 was not limited to a minimal ratio of sealed to unsealed apertures in the system's partition when the cells are administered to the system. Claim 1 still embraced non-working embodiments where at least one aperture is unsealed and one or more apertures of the at least 10 total apertures are sealed (see Figure 17). There was no disclosure in the patent how the skilled person, carrying out the method of claim 1, should manage to keep only one single aperture unsealed among all the partition's apertures, after the membranous sample is administered. A method according to claim 1 could not rely on statistics to achieve this specific requirement of having one single aperture unsealed.

- IX. The submissions made by the **respondent**, insofar as relevant to the present decision, are summarized as follows:

Main Request

Article 100(b) EPC

The patent disclosed the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 100(b) and Article 83 EPC), when firstly at least one way of performing the claimed invention and secondly the invention can be

implemented without undue burden across the whole scope claimed.

No facts or experimental data substantiating that the invention could not be carried out across the entire scope claimed had been provided by the appellant. First, there was no proof that a system with two apertures in a sample well would fail, second that the skilled person could not select parameters providing reasonable results for a system with two apertures and thus worked in practice.

The use of the parallel patch-clamp (PPC) technique on ion channels exogenously expressed in stable cell lines was described in paragraph [0134] of the patent onwards, while experimental data resulting from the application of PPC were reported in Fig. 14 and 15. Thus, at least one way of performing the claimed invention was disclosed in accordance with Article 83 EPC.

A patent had to be construed with a mind willing to understand and not a mind desirous of misunderstanding (see decision T 190/99, headnote), which meant that a skilled person considering a claim should rule out interpretations which are illogical or which do not make technical sense.

The skilled person reading the patent was guided to select appropriate conditions to successfully measure the current through the apertures and was accordingly capable of implementing the invention without undue burden over the whole scope of the claims. For example, paragraph [0143] of the patent mentioned that for a same cell line using the 64 aperture substrate, instead of a single aperture substrate, the average seal

resistance in each chamber normalized to a per-aperture value was usually lower for a successful experimental run, averaging 50 to 110 Mohm. Ionic currents and pharmacological results were as expected when the normalized seal resistance was above 50 Mohm; when the average seal resistance was below ~30 Mohm the technique generally failed. This was believed to be due to the poor cell quality and was an uncommon occurrence (< 2% of runs). From this last sentence, it was concluded that if 2% of the experimental runs failed, 98% of the runs had to be successful. There was neither in the patent nor in the prior art any motivation for a skilled person to seek borderline experimental situations to implement the invention disclosed in the patent and identified in the patent to fail.

It was known that if the ensemble current of the whole cell was altered by high leakage currents, masking the ion channel currents and reducing the signal-to-noise ratio, two different leakage subtraction methods could be adopted to isolate the ion channel currents, thereby obtaining an accurate measurement (see patent [0104] and [0105]). A system for performing electrophysiological measurements on membranous samples was disclosed in document D2. It was capable of forming high-resistance electrical seals, on the order of tens of M Ω to 1 G Ω , through appropriate selection and processing of the substrate material, aperture geometry, and attention to the way in which the biological membrane interacts with the substrate, while keeping the leak current very small (see [0053], [0108], [0163]). Given that the claimed invention was understandable, and contained the technical effect, the sufficiency of disclosure of the claimed invention had to be assessed under Article 83 EPC in the light of the

description (see decision T 862/11 of 17 March 2015, headnote).

The Case Law of the Board of Appeal Sixth Edition; July 2010; section II.A.4.2, established that:

It suffices for the disclosure of an invention that the means intended to carry out the invention are clearly disclosed in technical terms which render them implementable and that the intended result is achieved at least in some, equally realistic, cases (decision T 487/91 of 22.01.1993).

The occasional failure of a process as claimed did not impair its reproducibility if only a few attempts were required to transform failure into success, provided that these attempts were kept within reasonable bounds and did not require an inventive step (decision T 931/91 of 20.04.1993).

The reproducibility was not impaired if the selection of the values for various parameters was a matter of routine and/or if further information was supplied by examples in the description (decision T 107/91 of 06.12.1993).

Paragraph [0143] of the patent stated that "when the average seal resistance is below ~30 Mohm the technique generally fails." This was believed to be due to poor cell quality and was an uncommon occurrence (< 2% of runs). The occasional failure of an individual run could be accordingly avoided when a high percentage of seals was achieved. "After the cells are optimized and a sufficient density of cells is added to each well, the aforementioned seal rate is not difficult to achieve." Finally, the low percent value of

unsuccessful runs meant that the system had a 98% success rate in all other measurements, where currents on the order of pA / nA were detected. The system and method of claims 1 and 16 were outperforming (see post-published documents D22 to D25).

The condition that "at least one of the apertures is sealed by the at least one membranous sample, and another of the apertures is unsealed" did not define a range but a minimum requirement of claims 1 and 16. Since the patent described how the system could be optimized and how the method could provide useful measurement results, a system configured or a method operated so that the measurement failed had to be construed as an uncommon occurrence (see patent [0143]).

The skilled person would have adapted parameters as a matter of routine or based on information provided in the examples of the patent to reproduce the invention without undue experimentation. The occasional failure of a process does not affect its reproducibility, if a few attempts are sufficient to transform the failure into success (see decision T 931/91) or when the means for achieving the effect are disclosed in implementable technical terms and are realized at least in some equally realistic cases (see decision T 487/91).

The rate of successful measurements in the parallel patch-clamp mode (PPC) was reported to be higher than in the single aperture mode, which conversely meant that some unsuccessful measurements existed too (see patent, Fig. 15). Thus, the skilled person could not conclude from a few unsuccessful measurements, which were also observed for prior art methods - known to be

sufficiently disclosed - that the methods were not feasible.

- X. The appellant requested that the decision under appeal be set aside and the patent be revoked. It further requested that documents D35 and D36 be admitted into the proceedings.
- XI. The respondent requested that the appeal be dismissed, or alternatively, that the decision under appeal be set aside and the patent be maintained upon the basis of one of its auxiliary requests 4, 12, 4b, 5, 1, 2, 3, 6 to 11 and 13 to 16, in that order, all these requests, with the exception of 4b, having been filed during the opposition proceedings and again with the respondent's reply to the statement of grounds of appeal. The respondent further requested that documents D20 to D22 and D26 to D36 not be admitted into the proceedings, that documents D23 to D25, Annex A and Annex B be admitted into the proceedings and that document D37 be admitted into the proceedings if document D36 was admitted.

Reasons for the Decision

Admission of documents D20 to 34 into the appeal proceedings

1. Documents D20 to D25 had been admitted into the opposition proceedings (see decision under appeal, item 2). Since the EPC provides no legal basis for excluding, in appeal proceedings, documents that had already been admitted into the first-instance proceedings based on proper legal principles, no decision on their admission was needed (decisions T 1852/11, reasons 1.3; T 1201/14, reasons 2; T 1525/17

reasons 4.3). They were already in the appeal proceedings.

2. Documents D26 to D34, on the other hand, were not admitted into the opposition proceedings (see decision under appeal item 3). The appellant provided no arguments why the opposition division exercised its discretion according to the wrong principles. Thus, the board saw no reason to overrule the way in which the first instance exercised its discretion.

Admission of documents D11a, D35 and D36

3. Document D11a is an excerpt from a textbook in the field of electrophysiology. It was submitted in response to the respondent's views adopted in its reply to the statement of grounds of appeal. Evidence of common general knowledge to provide, in case of dispute, a better and unbiased understanding of the state of the art is in general acceptable. Thus, document D11a was admitted into the proceedings.
4. As for documents D35 and D36 and their annexes, the board indicated at the beginning of the oral proceedings that their admission would be discussed during the proceedings if needed. This was not the case.

Main request (claim as granted)

Sufficiency of disclosure (Article 100(b) EPC)

5. The patent is directed to a method and a system for high-throughput-analysis of membranous samples having ion channels. Claim 1 relates to a system for high-throughput-analysis of membranous samples having ion channels in a chamber having apertures, wherein at

least one of the apertures is sealed by the at least one membranous sample, and another of the apertures is unsealed.

6. The finding in the decision under appeal that the technical information provided in the patent enabled the skilled person to carry out the invention as claimed (see pages 7 and 8 of the decision), was contested by the appellant relying on paragraphs [0143], [0153] and Fig.17 of the patent. Although the experimental procedures in the patent provided sufficient guidance how to put into practice the claimed system or method (see patent paragraphs [0155] to [0165]), appellant contested that the skilled person was guided to select only conditions allowing successful measurement of currents through the membranes, in either parallel patch clamp or single aperture mode, and would have naturally avoided less favourable conditions. It contested also that there were no verifiable facts or experimental evidence which substantiated that the skilled person could not perform the invention across the entire scope claimed.

7. Article 83 EPC stipulates that the invention shall be disclosed in the patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. According to the established case law of the boards of appeal, this requires that the application as a whole taking common general knowledge into account must disclose at least one way of performing the invention such that the skilled person is in a position to perform the claimed invention readily and without undue burden across substantially the whole range claimed.

7.1 The criteria for determining sufficiency of disclosure are the same for all inventions, irrespective of the way in which their technical features are defined, whether it be by way of structure or by function. In both cases the requirement of sufficient disclosure can only mean that the whole subject-matter that is defined in the claims, and not only a part of it, must be capable of being carried out by the skilled person without the burden of an undue amount of experimentation or the application of inventive ingenuity (see decision T 0435/91 of 9 March 1994, point 2.2.1).

8. The patent discloses at least one way to carry out the invention as set out in claim 1. This was not disputed.

It was however disputed whether or not the patent, alone or in combination with the general knowledge, provides information which enables the skilled person to obtain substantially all the embodiments falling within the ambit of the claims.

8.1 The board, with a mind willing to understand what claim 1 covers, excluding illogical or technically meaningless interpretations, considers that claim 1 relates to a system suitable for high-throughput-analysis of membranous samples having ion channels providing meaningful ion channel analysis results.

8.2 Thus, the wording of claim 1 imposes the functional limitation that the system is suitable for the stated purpose. At the same time claim 1 defines essential structural features needed to obtain the desired functional result. The system of claim 1 comprises an undefined number of sample wells having any number of apertures ("... having a plurality of apertures") being

sealed, partially occluded or completely open, with the limitation that at least one of the apertures is sealed by the at least one membranous sample and another of the apertures is unsealed. Thus, the structural definition of claim 1 covers any system comprising a sample well having at least one aperture open and another one closed by a membranous sample, irrespective of the number of apertures existing in the partition.

It is important to note that the claimed system is not the instrumental set up per se but the set up comprising at least one compartment (well) with at least one aperture sealed by a membranous sample and another unsealed, i.e. the system in use.

- 8.3 The subject-matter of claim 1 extends unequivocally to systems for high-throughput-analysis of membranous samples having ion channels comprising inter alia a partition (40) with at least two or ten apertures (42) fluidly and electrically coupling the extracellular and intracellular chambers, wherein at least one of the apertures is sealed by the at least one membranous sample, and another of the apertures is unsealed.
- 8.4 More specifically, it embraces systems having a partition with two apertures wherein one aperture is sealed by the at least one membranous sample while the other aperture is unsealed. This system has a seal rate of 50%. It embraces also systems having a partition with ten apertures wherein nine apertures are sealed by the at least one membranous sample while one aperture is unsealed. This system has a seal rate of 90%.
9. The patent mentions that, for successful runs, there is no way to directly determine the percentage of apertures that remain open or partially occluded by

debris. Two models were proposed to address this issue (see paragraphs [0143], [0153], FIG. 17). Both are based on data obtained with partitions having 64 apertures. The first model assumes that there are only two populations of seals at the recording sites, one being successful seals (120 Mohm) and the other completely open holes (3 Mohm). The second model assumes two other populations of seals at the recording sites, again the successful seals (120 Mohm), and the other partially occluded holes (assumed to be 10 Mohm). The models suggest that for meaningful measurements the seal rates must be of 88% or greater, once a cell line is optimized. This represents for the first model a ratio of 3% of the holes being completely open (or 2 out of 64 holes) and for the second model a ratio of 12% or less of the holes partially occluded (or 7 out of 64).

9.1 Applying the prediction of percentage of open apertures onto the two systems described above having a partition with two apertures, wherein one aperture is sealed by the at least one membranous sample while the other aperture is unsealed, results in a seal rate of 50%, or alternatively having a partition with ten apertures, wherein nine apertures are sealed by the at least one membranous sample while the other aperture is unsealed, results in a seal rate of 90%, both resulting in a mean seal resistance falling outside of the "functional PPC range" area, defined in Figure 17. This implies that both systems fall under the complementary "non-functional PPC range" area.

9.2 The lower curve of Figure 17 represents the mean seal resistance value attributed to a system comprising good seals, having a resistance value of 120 MΩ or more, and all the remaining apertures completely open, having a

resistance value of 3 MΩ. The upper curve of Figure 17 represents the mean seal resistance value attributed to a system comprising good seals, having a resistance value of 120 MΩ or more, and all the remaining apertures being partially occluded, having a resistance value of 10 MΩ. The resistance values for good seals and open holes selected in the patent are commonly accepted values in the art (see e.g. document D2, [0142]; 150-200 Mohms and 3 Mohms, respectively).

- 9.3 Given that the systems described above with two or ten apertures have a seal rate of 50% and 90% (x-axis), their mean seal resistance value remains always lower than 30 Mohm according to Figure 17, which prevents the systems from providing useful results. As explicitly stated in the patent, such systems generally fail.
- 9.4 Since the patent states that systems comprising sample wells having an average seal resistance below about 30 Mohm generally fail, systems suitable for high-throughput-analysis of membranous samples having ion channels, on the basis of the information contained in the patent specification and taking into account the common general knowledge must have a high sealing rate to bring about the desired effect.
- 9.5 Thus, there is a clear teaching in the patent that not all the embodiments falling under claim 1 are suitable to perform high-throughput-analysis of membranous samples having ion channels, i.e. provide meaningful results. Therefore, the subject matter of claim 1 encompasses a host of possible systems which may not enable high-throughput-analysis of membranous samples having ion channels.

9.6 Even if the board accepted that the skilled person would have been motivated and could have optimized and selected adequate parameters to avoid, in practice, non-functional systems, the skilled person has no instructions how to readily implement a working system with two apertures where one aperture is unsealed. As for ten apertures, there is no guidance how to make it work with at least one of the apertures unsealed. Hence, claim 1 covers systems with two or ten apertures having a mean seal resistance of less than 30 Mohm, described to generally fail, which can by no means be optimized or improved to render them functional. These illustrative examples are just a few of many embodiments that are non-functional and fall under the scope of protection of claim 1. Thus, any system ranging between two and ten apertures per sample wells, in line with this rationale, fails as well.

9.7 In addition, the claims are not limited to systems having a high average seal resistance and thus suitable for automatically and accurately recording electrophysiological signals with high throughput and high resolution. They encompass also systems having sample wells with an average seal resistance below about 30 Mohm, and/or a low signal to noise ratio. The patent provides no technical guidance how they can be made operational other than by discarding them and instead selecting systems comprising sample wells having an average resistance above 30 Mohm, and thus limiting the ratio of sealed and unsealed apertures to 88% or more.

9.8 The board does not agree with the respondent that the reported failure rate of 2% of the experimental runs means that 98% of the systems covered by claim 1 provide meaningful results. The result of an

experimental run depends on many parameters inter alia the type of cells or membrane, the ion channel, the concentrations or density of cells per sample well, the number of apertures per sample well, the aperture diameter, the voltage step and its duration etc... (see patent e.g. paragraph [0161]). The experimental runs described in the patent do not encompass substantially all embodiments falling under claim 1.

9.9 Even if the board followed the respondent's view that the skilled person was motivated and could have optimized non-functional embodiments by increasing the ratio of sealed to unsealed apertures, the patent states explicitly that there is no way to directly determine the percentage of apertures that remain open or partially occluded by debris (see [0143]). Thus, the skilled person is not in a position to readily generate a system having partitions with ten apertures wherein only one single aperture is unsealed.

9.10 For all these reasons, the board considers that the patent does not disclose a technical concept fit for generalisation, thus the majority of the systems encompassed by claim 1 are not available to the skilled person. A teaching how the non-functional embodiments can be made functional is not at the disposal of the person skilled in the art even after reading the patent.

9.11 Thus, the non-functional systems of claim 1 are not the result of an occasional failure that can be tolerated and turned into a success without undue burden, but of a systematic occurrence in systems comprising sample wells with an average seal resistance less than about 30 Mohm. The decisions T 487/91, T 931/91 and T 107/91, cited supra by the respondent, are thus not applicable.

9.12 The board concludes that claim 1 includes many embodiments which are not operable under any circumstances. Hence, the patent does not disclose the invention as defined in claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out by the skilled person over the whole scope claimed (Article 100(b) EPC).

Auxiliary request 4 (Version 2)

10. Claim 1 of auxiliary request 4 differs from claim 1 of the main request in that the system is further characterized by the feature: "each extracellular chamber (33) includes at least 10, 50, 64, 100 or 1000 apertures (42)." Claim 15 of auxiliary request 4 differs from claim 16 of the main request in that the method of high-throughput analysis of membranous samples (44) having ion channels comprises: providing a system (30) including a multi-compartment structure ... "wherein the extracellular chamber (33) includes at least 10, 50, 64, 100 or 1000 apertures (42);".

11. Auxiliary request 4 was first filed with the patentee's reply to the communication in preparation of oral proceedings before the opposition division. The appellant had no objections against its admission.

11.1 The appellant raised objections under Articles 123(2), 83 and 84 EPC. After having heard the parties at the oral proceedings the board concluded that auxiliary request 4 did not contravene Articles 123(2) and 84 EPC. In view of the board's negative conclusion on the issue of sufficiency of disclosure (see below), no purpose is served in providing detailed reasons on these issues.

Sufficiency of disclosure Article 83 EPC

12. Claims 1 and 15 define the system and the method by the same features as the respective claims of the main request except for a limitation of the number of apertures to at least 10 in each extracellular chamber.

13. Appellant argued that all the previous objections with regard to amended claim 1 equally applied. Claim 1 still included systems having partitions without defining the minimal ratio of sealed to unsealed apertures and therefore encompassed many non-workable embodiments.

14. The respondent asserted that the calculation and the conclusion drawn in paragraph [0143] of the patent were based on a system having 64 apertures and not on 10 apertures per sample well. It was questionable whether the conclusion drawn with regard to the average resistance for 64 apertures could be extrapolated to a system having 10 apertures. The leak or ion channel current contribution measured in a system comprising sample wells having partitions with 10 apertures could not be assumed to be identical to the current in a system comprising sample wells having a partition with 64 apertures.

15. The board is not convinced by the respondent's assertion that the models for assessing the PPC average seal resistance described in the patent is limited to systems having a partition with only 64 apertures. This assertion is not supported by any evidence.

First, the two models made it possible to assess the average seal resistance based on the proportion of

"successful" seals, partially occluded holes, and completely open holes within the parallel circuit. The first model consisted of only two populations of seals at the recording sites, one being successful seals (120 Mohm) and the other completely open holes (3 Mohm), while the second model consisted of only two populations of seals one being successful seals (120 Mohm), and the other partially occluded holes (10 Mohm). The average seal resistance in each chamber normalized to a per-aperture value - 50 to 110 Mohm - was for a 64 aperture substrate usually lower than for a single aperture substrate for a successful experimental run. Given the two models, the assigned resistances per hole and the observed resistance value ranging between 50 to 110 Mohm, it was possible to predict that up to 3% and up to 12% of the number of apertures were open or partially occluded in the first and second model respectively. These values corresponded to a number of 2 open holes and 7 partially occluded holes in a sample well with 64 holes. There was neither an explicit nor an implicit disclosure in paragraphs [0143], [0153] that the models had to be limited to systems comprising a partition with 64 apertures per sample well only.

Second, the mean seal resistance values were clearly shown in Figure 17 and its corresponding legend to depend only on the ratio of sealed to unsealed apertures or the number of sealed to partially occluded apertures, irrespective of the total number of apertures per sample well. Thus, in light of paragraphs [0143], [0153] and Figure 17 and its legend, the number of open and sealed as well as partially occluded and sealed apertures, is independent from the absolute number of apertures in the partition.

- 15.1 Since the limitation to a higher number of apertures in auxiliary request 4 does not exclude from the scope of the claims the vast number of embodiments explicitly mentioned in the patent to fail, the situation remains the same as for the main request. Auxiliary request 4 still covers many embodiments which are not operable under any circumstances and thus fails to meet the requirements of Article 83 EPC.

Auxiliary request 12

Admission of auxiliary request 12 and request for remittal to the opposition division

16. Auxiliary request 12 was first filed with the patentee's reply to the communication in preparation of oral proceedings before the opposition division. The appellant had no objections against its admission.
17. The respondent requested that the case be remitted to the opposition division as otherwise it would be deprived of the opportunity to have the matter reviewed by two instances.
18. It is established case law that parties do not have a fundamental right to have their case examined at two levels of jurisdiction. Article 111(1) EPC, second sentence, leaves it to the board's discretion to decide on an appeal either by exercising any power conferred on the department of first instance or by remitting the case to that department. Since the opposition division had already examined and decided upon the essential issues concerning the patentability of the claimed subject-matter, the board sees no need to remit the case to the opposition division.

Sufficiency of disclosure Article 83 EPC

19. Claims 1 to 15 of the main request relating to systems have been deleted in this auxiliary request. Claim 1 of auxiliary request 12 differs from claim 16 of the main request in that the method of high-throughput analysis of membranous samples (44) having ion channels comprises: providing a system (30) including a multi-compartment structure ... "wherein the extracellular chamber (33) includes at least 10, 50, 64, 100 or 1000 apertures (42); "... .

20. Claim 1 defines the method of high-throughput analysis by "providing a system ..., dispersing a plurality of membraneous samples ... such that the membraneous samples seal at least one of the apertures ... while another of the apertures is unsealed ...".

Thus, the claim still encompasses many embodiments with an insufficient number of apertures sealed.

21. The respondent argued that the step of "... detecting a resulting ensemble current and/or voltage across the extracellular and intracellular chambers (33, 37) through all the apertures (42) of the partition (40), wherein a portion of current travels through **the** unsealed aperture; ..." (emphasis added) as defined in claim 1 implied one unsealed aperture only.

22. The board is not convinced by the respondent's interpretation of "the" unsealed aperture as one single unsealed aperture (see claim 1, line 25). First the method according to claim 1 comprises the step of "... dispersing ... such that the membranous samples seal at least one of the apertures (42); applying electrical voltage and/or current between the extracellular and

intracellular chambers (33, 37) while another of the apertures is unsealed; ... " and "... applying a leak subtraction data acquisition protocol to the detected ensemble current to account for leak current through the unblocked apertures (42) ..." (emphasis added). This wording does not support the respondent's argument. Thus, the method of claim 1 is not limited to methods using a system comprising a partition with at least 10 apertures per sample well with only one unsealed aperture while all the others are sealed. Respondent's argument finds also no support in the patent which explicitly states that it was not possible to generate directly a system comprising sample wells having a partition with ten apertures where only one single aperture is unsealed (paragraph [0143]).

- 22.1 Since the proposed amendment does not exclude the vast number of embodiments explicitly mentioned in the patent as non-working, the situation remains the same as for the main request. Auxiliary request 12 still covers many embodiments which are not operable and thus fails to meet the requirements of Article 83 EPC.

Auxiliary request 4b

23. Auxiliary request 4b, filed at the oral proceedings, differs from auxiliary request 4 previously on file in that independent claims 1 and 16 were amended to a system wherein each extracellular chamber (33) includes at least 64 apertures.
24. The respondent submitted that it should be admitted. The amendments were proposed in response to the board's interpretation of the subject matter of the main request and auxiliary request 12. The board's view was never discussed before.

25. The appellant objected to the admission of auxiliary request 4b, as it was both, formally new and late-filed in appeal proceedings, and not clearly allowable.
26. The admission of auxiliary request 4b filed during oral proceedings is at the board's discretion (Articles 13(1) and 13(2) RPBA 2020).
27. The board decided not to admit it into the appeal proceedings for the following reasons:
First, auxiliary request 4b was submitted at a very late stage, i.e. during oral proceedings in appeal. Second, it re-introduced product claims 1 to 15 deleted in preceding auxiliary request 12 and was thus non-convergent. Third, the board concluded that the subject-matter of the main request and auxiliary requests 4 and 12 was insufficiently disclosed, because the system and the method using it encompassed systems with an average seal resistance below ~30 Mohm that were described as non-working in the patent. Since claims 1 and 15 of auxiliary request 4b were not limited to a system and a method using a system with an average seal resistance above ~30 Mohm, the board considered, given the conclusion drawn for the preceding requests, that auxiliary request 4b is not clearly allowable.

*Auxiliary requests 1 to 3, 5 to 11 or 13 to 16
Sufficiency of disclosure Article 83 EPC*

28. All of auxiliary requests 1 to 3, 5 to 11, and 13 to 16 propose amendments unsuitable to overcome the problem of insufficient disclosure. The claimed subject matter is not limited to embodiments readily available to the skilled person. None of the proposed amendments defines

a ratio between sealed and unsealed apertures in the partition of the sample well of the systems used. Thus, the subject matter of these auxiliary requests does not substantially differ from the systems and/or methods according to claims 1 or 16 of the main request or of auxiliary requests 4 and 12. The objections with regard to sufficiency of disclosure set out above for claim 1 of the main request, or auxiliary requests 4 and 12 equally apply to the systems and/or the methods of auxiliary requests 1 to 3, 5 to 11 or 13 to 16, which in consequence do not sufficiently disclose the claimed subject matter.

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:



L. Malécot-Grob

B. Stolz

Decision electronically authenticated