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**Datasheet for the decision
of 22 December 2010**

Case Number: T 1062/07 - 3.4.01

Application Number: 99962446.3

Publication Number: 1141738

IPC: G01R 33/465, G01N 33/48

Language of the proceedings: EN

Title of invention:

NMR spectroscopic in vitro assay using hyperpolarization

Applicant:

GE Healthcare Limited

Opponent:

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Headword:

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Relevant legal provisions:

-

Relevant legal provisions (EPC 1973):

EPC Art. 83

Keyword:

"Disclosure - enabling - undue burden"

Decisions cited:

-

Catchword:

-



Case Number: T 1062/07 - 3.4.01

D E C I S I O N
of the Technical Board of Appeal 3.4.01
of 22 December 2010

Appellant: GE Healthcare Limited
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Representative: Hammett, Audrey Grace Campbell
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 20 February 2007
refusing European patent application
No. 99962446.3 pursuant to Article 97(1) EPC
1973.

Composition of the Board:

Chairman: B. Schachenmann
Members: F. Neumann
P. Fontenay

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division of 20 February 2007 to refuse the European patent application number 99 962 446.3.
- II. The application was refused on the grounds of lack of clarity and lack of support by the description (Article 84 EPC 1973), insufficient disclosure (Article 83 EPC 1973) and lack of inventive step (Articles 52(1), 56 EPC 1973).
- III. The appellant requested in writing that the decision be set aside and a patent be granted on the basis of claims 1 to 21 of the main request filed with the grounds of appeal dated 20 June 2007, or alternatively on the basis of claims 1-17 of auxiliary request 1 or claims 1-14 of auxiliary request 2, both auxiliary requests filed with the grounds of appeal dated 20 June 2007.

As a further auxiliary measure, oral proceedings were requested.

- IV. The Board issued a summons to oral proceedings and a communication drawing attention to various objections under Articles 84 and 83 EPC 1973 and briefly discussing the questions of novelty and inventive step. In this communication, reference was made *inter alia* to the following documents:

D2: SPOONER P J R ET AL: "Weak substrate binding to transport proteins studied by NMR" BIOPHYSICAL

JOURNAL, DEC. 1998, BIOPHYS. SOC, USA, vol. 75,
no. 6, pages 2794-2800, XP000882271;

D5: ARDENKJAER-LARSEN J H ET AL: "EPR and DNP
properties of certain novel single electron
contrast agents intended for oximetric imaging"
JOURNAL OF MAGNETIC RESONANCE, JULY 1998,
ACADEMIC PRESS, USA, vol. 133, no. 1, pages 1-12,
XP002133854.

V. No reply was filed to the communication of the Board.
Instead, on the day before the date of the oral
proceedings, the appellant informed the Board that he
would not appear.

VI. Claim 1 of the **main request** reads as follows:

*"An in vitro assay method to observe a physical or
chemical change involving a biological species which
comprises:*

*a) using an assay reagent containing an artificially
enriched abundance of at least one NMR active nucleus
selected from ¹³C and/or ¹⁵N to perform an assay, and
b) hyperpolarising the at least one NMR active nucleus
of the assay reagent; wherein steps (a) and (b) are
performed simultaneously or sequentially in either
order, and
c) analysing the assay reagent by NMR for changes to
the chemical and/or physical environment of the at
least one NMR active nucleus;*

*wherein said hyperpolarising step results in a degree
of hyperpolarisation in excess of 0.1% above the
equilibrium population of the excited state."*

The independent claims of each of the first and second auxiliary requests are based on claim 1 of the main request, with the following modifications:

Step (a) of claim 1 of the **first auxiliary request** reads "*using an assay reagent which is an organic compound, said assay reagent containing an artificially enriched abundance of at least one NMR active nucleus selected from ^{13}C and/or ^{15}N to perform an assay,*" and the wording "*and wherein said at least one NMR active nucleus is associated with a bond which is broken during the course of the assay.*" has been added to the end of the claim. The claim is otherwise identical to claim 1 of the main request.

Step (b) of claim 1 of the **second auxiliary request** reads "*hyperpolarising the at least one NMR active nucleus of the assay reagent by polarisation transfer using dynamic nuclear polarisation;*". The claim is otherwise identical to claim 1 of the main request.

VII. The arguments of the appellant, insofar as they are pertinent to the present decision, are set out below in the reasons for the decision.

Reasons for the Decision

1. Reference is made to the transitional provisions for the amended and new provisions of the EPC, from which it may be derived which Articles of the EPC 1973 are still applicable to the present application and which Articles of the EPC 2000 shall apply.

2. The invention

The spectrum of an NMR active nucleus (i.e. a nucleus with non-zero nuclear spin) varies depending on the environment of the nucleus. By observing the spectra of NMR active nuclei present in an assay reagent (test compound), physical or chemical changes within the reagent can be monitored. The invention provides an *in vitro* method for observing such changes in the environment of NMR active nuclei which, in the present case, are either ^{13}C and/or ^{15}N nuclei. The assay reagent is prepared to include an artificially enriched abundance of ^{13}C and/or ^{15}N nuclei. For the analysis of the assay reagent, the polarisation of these nuclei is enhanced over the equilibrium polarisation. This "hyperpolarisation" increases the signal-to-noise ratio and thus improves the sensitivity of the analysis with respect to assay techniques without hyperpolarisation. The increased signal-to-noise ratio means that the time required to obtain usable results is considerably shortened. The invention involves reaching a degree of hyperpolarisation greater than 0.1% above the equilibrium population of the excited state. As an aside it is noted that the examining division held this term to be unclear, but the Board has understood it to mean that the population of spins in the excited state is 0.1% higher (in absolute terms) than the population at the equilibrium polarisation.

3. Sufficiency of disclosure - Article 83 EPC 1973

3.1 Article 83 EPC 1973 sets out that the invention shall be disclosed in a manner sufficiently clear and

complete for it to be carried out by a person skilled in the art. What is important for the purposes of Article 83 EPC 1973 is whether the application disclosed the invention in a manner sufficiently clear and complete for the skilled person - **at the filing date** - to carry it out. Whilst it may be possible to subsequently delete incorrect or misleading material without infringing Article 123(2) EPC, such modification of the application cannot alter the teaching of the originally filed disclosure.

3.2 In the present case, the step of hyperpolarising the active nucleus/nuclei of ^{13}C and/or ^{15}N contained in the assay reagent such that the degree of hyperpolarisation is in excess of 0.1% above the equilibrium population of the excited state is a key feature of the invention. This step is now included in claim 1 of all requests, and was always presented as a crucial part of the invention (see, e.g., page 4, lines 27-29). However, the originally filed application did not disclose the *in vitro* assay method in a manner sufficiently clear for the skilled person to know what specific steps to take in order to achieve this level of hyperpolarisation.

3.3 The Board accepts that various methods are known for hyperpolarising an NMR active nucleus. Indeed, the application discusses a number of methods by which hyperpolarisation may be transferred to an NMR active nucleus in an assay reagent. However, these methods are only discussed in general terms and no specific guidance is given as to how to achieve the desired degree of hyperpolarisation in the target nucleus.

In the letter of 01 September 2006, the appellant explained that neither the Overhauser method of D5 nor the cross-polarisation method of D2 would reach the necessary degree of hyperpolarisation. However, it is not clear whether - and if so, under what operating conditions - any of the methods listed in the description (e.g. the Brute Force, parahydrogen and other DNP methods) are capable of attaining the desired value. Moreover, the sole example contained in the originally filed application (on pages 19 to 20) was deleted after the examining division showed that this specific method would not achieve the required degree of hyperpolarisation.

The indications provided in the original description appear to serve only as a rough framework within which the skilled person could attempt to reach the desired degree of hyperpolarisation, without providing any specific instructions which would lead him directly to an arrangement which would result in success. The Board considers that in view of these very general indications, the skilled person would be faced with undue difficulties in establishing the conditions under which a polarisation transfer resulting in the desired degree of hyperpolarisation in the target nucleus may be achieved.

- 3.4 To be more concrete, from page 9 to the middle of page 11 of the application, hyperpolarisation transfer using a hyperpolarised noble gas is discussed. The Board is satisfied that the skilled person will be conversant with this method of hyperpolarisation transfer and so does not consider it necessary to include all details of the methodology required to

achieve hyperpolarisation of the NMR active nucleus. However, any specific measures to be taken to achieve a degree of hyperpolarisation in excess of 0.1% above the equilibrium population of the excited state are not identified. Page 10, line 19 to page 11, line 17 indicates that the polarisation enhancement factor may be optimised and draws attention to the fact that the extent of polarisation is affected by a whole host of parameters. However, this passage fails to include any concrete guidance as to how to achieve a degree of hyperpolarisation exceeding 0.1% above the equilibrium population of the excited state. In particular, the viscosity of the solvent (which itself depends on the solvent used and the temperature thereof), the concentration of the noble gas in the solution, the pressure of the noble gas, the atoms with magnetic moment in the solvent and the magnetogyric ratio of the solvent all affect the degree of hyperpolarisation attainable. However, the application contains no indication of which specific combination of these various parameters must be adhered to in order to achieve a hyperpolarisation greater than 0.1% above the equilibrium population.

In the absence of any teaching with respect to specific operating conditions, the skilled person has to resort to trial and error to establish how to achieve the desired result.

3.5 From the middle of page 11 to the bottom of page 12 the Brute Force method of hyperpolarisation transfer is discussed. Again, the Board does not doubt that the skilled person would have known at the date of filing how to impart hyperpolarisation to an NMR active

nucleus using the Brute Force method. However, the Board is less certain that the skilled person would have known how to attain the required level of hyperpolarisation. Indeed these doubts are compounded by the fact that page 11, lines 21-24 of the description has subsequently been modified to remove certain operational parameters which would not have led to the required result. Even if the remaining parameters would enable the desired degree of hyperpolarisation to be reached (an issue which the Board consciously refrains from taking a position on), the original disclosure of the Brute Force method cannot be seen to be a sufficiently clear and complete disclosure for it to be carried out by a skilled person. On the filing date of the application, the skilled person was faced with a number of operating parameters but no guidance as to which configurations would succeed in producing the desired degree of hyperpolarisation. As conceded by the appellant, a number of these options would in fact not have succeeded. In order to implement the invention, the skilled person would have had to establish this on his own without any further teaching. Bearing in mind that the invention has always been presented as involving a degree of hyperpolarisation in excess of 0.1% above the equilibrium population of the excited state, the fact that at the date of filing the application, not even the inventor could clearly identify those conditions which would have led to the desired result, the Board does not consider that the implementable operating conditions would belong to the common general knowledge of the skilled person.

3.6 At the bottom of page 12 to the middle of page 13, the description explains that the Dynamic Nuclear Polarisation (DNP) method of polarisation transfer may be employed. Whilst a brief summary of the DNP mechanism is provided, none of the operating parameters necessary to achieve a degree of hyperpolarisation exceeding 0.1% above the equilibrium population of the excited state are outlined. As explained during the written proceedings before the examining division, DNP of the Overhauser type does not result in the desired degree of hyperpolarisation. However, no details are provided in the application which would suggest exactly how the DNP method should be performed to ensure that the polarisation is transferred to the desired degree. Again, it is left to the skilled person to establish the operational set-up which will achieve the desired result.

3.7 The description goes on to discuss parahydrogen induced polarisation and the spin refrigeration method.

Again, the description briefly summarises these techniques, but provides no instructions as to the operating parameters to be selected in order to reach the desired degree of hyperpolarisation.

3.8 The appellant submitted that any of these described methods could be used for assays whereby the particular method selected would depend on the details of the assay. The skilled person simply had to select that method of hyperpolarisation which was most suitable.

The Board does not contest that the skilled person would know which of the various methods would be most

suitable for the specific assay reagents and the Board agrees that the skilled person would be able to impart a certain degree of hyperpolarisation to the NMR active nucleus of the assay reagent. However, on the filing date of the application, the skilled person was confronted with numerous alternatives for achieving hyperpolarisation but none of the descriptions of these methods includes a clear disclosure of the operating conditions required in order to impart the desired degree of hyperpolarisation on the NMR active nucleus. The clarity of disclosure is compromised by the fact that the original application refers to incorrect parameters and operating conditions. This incorrect and misleading information presented the skilled person at the filing date with undue difficulties in establishing the necessary method and configurations to achieve the desired result and consequently the original teaching as a whole cannot be seen to be a sufficiently clear and complete disclosure for it to be carried out by a skilled person.

- 3.9 In summary, at the date of filing the application, the invention cannot be said to have been disclosed in "a manner sufficiently clear and complete for [the invention] to be carried out by a person skilled in the art" and therefore the application does not meet the requirements of Article 83 EPC 1973. As pointed out by the examining division, the description simply lists a number of proposals without providing any clear teaching as to how to achieve the required result. The Board agrees with the conclusion of the examining division that this effectively amounts to no more than the definition of the framework for a potential

research programme to establish which configurations will succeed.

The skilled person, faced with the information of the originally-filed application, is placed under an undue burden to establish the operating conditions under which the desired degree of hyperpolarisation may be achieved.

Even a subsequent deletion of those set-ups which clearly do not enable a degree of 0.1% to be attained does not change the finding that on the filing date of the application, the skilled person was confronted with numerous alternatives but no guidance as to which options would lead him to success.

3.10 **Auxiliary requests:**

Neither of the auxiliary requests overcome the above objection which is concerned with the lack of disclosure of the details required to implement the invention. The modifications made to the respective independent claim of each of the auxiliary requests do not address the problem of lack of disclosure.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

R. Schumacher

B. Schachenmann