Internal distribution code:

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

Datasheet for the decision of 9 August 2021

Case Number: T 0580/19 - 3.3.01

Application Number: 10187310.7

Publication Number: 2320237

IPC: G01N33/74, G01N33/68

Language of the proceedings: EN

Title of invention:
Procalcitonin for the diagnosis of bacterial infections and guidance of antibiotic treatment in patients with acute stroke or transient ischemic attack

Patent Proprietor:
B.R.A.H.M.S GmbH

Opponent:
Radiometer Medical ApS

Headword:
Procalcitonin for diagnosis of infections / B.R.A.H.M.S.

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 100(b)

Keyword:
All requests - sufficiency of disclosure (no)

Europäisches Patentamt
European Patent Office
Office européen des brevets

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 0580/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 9 August 2021

Appellant: (Opponent)	Radiometer Medical ApS Akandevej 21 2700 Bronshoj (DK)
Representative:	Huenges, Martin Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	B.R.A.H.M.S GmbH Neuendorfstrasse 25 16761 Hennigsdorf (DE)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 December 2018 rejecting the opposition filed against European patent No. 2320237 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	S. Albrecht
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 320 237 ("the patent") is based on European patent application No. 10187310.7. The patent was granted with 12 claims.

Claim 1 as granted reads as follows:

"1. An *in vitro* method for diagnosing a bacterial infection of a patient who has suffered from an acute stroke or from a transient ischemic attack, comprising the steps of:

(i) determining the level of Procalcitonin (PCT) or a fragment thereof of at least 12 amino acids in length in a sample obtained from a patient earlier than 72 hours after the onset of acute stroke or transient ischemia attack using a PCT detection assay with a functional assay sensitivity of below 0.06 ng/mL;
(ii) determining whether said patient has a bacterial infection or not by comparing said determined PCT level with a predetermined threshold level."

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC (lack of novelty and lack of inventive step), Article 100(b) EPC and Article 100(c) EPC.

III. The opponent's ("appellant's") appeal is against the opposition division's decision to reject the opposition.

IV. In its statement setting out the grounds of appeal, the appellant requested that the decision under appeal be

set aside and that the patent be revoked in its entirety.

The appellant also submitted the following evidence, *inter alia*:

D19: Declaration by Jacob de Haan dated 16 April 2019 and curriculum vitae of Jacob de Haan

V. In its reply to the statement setting out the grounds of appeal, the patent proprietor ("respondent") requested that the appeal be dismissed. As an auxiliary measure, the respondent requested that the patent be maintained in amended form on the basis of one of the sets of claims in auxiliary requests 1 to 4, originally filed by letter of 20 October 2017 and re-filed with the reply to the statement setting out the grounds of appeal (letter of 1 October 2019).

The respondent also requested that document D19 not be admitted into the proceedings.

VI. The board issued a summons to oral proceedings in accordance with the corresponding requests of the parties.

VII. In a communication pursuant to Article 15(1) RPBA issued on 25 June 2021, the board drew the parties' attention to the points to be discussed during the oral proceedings.

VIII. By letter dated 9 July 2021, the respondent maintained its previous requests and filed a further set of claims as its fifth auxiliary request ("auxiliary request 5").

IX. On 9 August 2021, oral proceedings were held in the presence of both parties; the board decided not to admit document D19 into the proceedings. At the end of the oral proceedings, the chairwoman announced the board's decision.

X. The appellant's written and oral submissions, insofar as they are relevant to the present decision, may be summarised as follows:

Claim 1 of the main request required that the claimed *in vitro* method enabled the diagnosis of a bacterial infection in a patient at early time points after an acute stroke ("AS") or a transient ischemic attack ("TIA"). The experimental data disclosed in Tables 1 and 2 of the patent, however, showed that the claimed method resulted in a significant number of false negatives, i.e. AS and TIA patients incorrectly identified as not having a bacterial infection. Such results were not meaningful and did not allow a physician to make a treatment decision. As a consequence, the aforementioned experimental data from the patent cast serious doubts on the suitability of the claimed method for diagnosing a bacterial infection in a patient at early time points after an AS or a TIA. Sufficiency of disclosure was therefore to be denied for the main request. The same conclusions applied to auxiliary requests 1 to 5.

XI. The respondent's written and oral submissions, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant's criticism of the experimental data provided in the patent was without merit.

The appellant had failed to recognise the added value of the claimed method over the prior art. Indeed, prior to the claimed invention, the skilled person, who in the case at hand was a treating physician, did not have any diagnostic methods at their disposal that could detect bacterial infections in AS or TIA patients earlier than 72 hours after the onset of an AS or a TIA. Furthermore, the guidelines on AS management in place on the filing date of the patent advised against the prophylactic use of antibiotics in AS and TIA patients.

In contrast to this, the claimed method enabled the early detection of bacterial infections in at least some AS and TIA patients, as evidenced by the experimental data disclosed in Tables 1 and 2 of the patent. In this manner, the claimed method constituted an additional tool which provided the treating physician with a better basis for antibiotic treatment than before, i.e. it increased the likelihood that AS and TIA patients with bacterial infections were adequately treated.

This advantage came at the price of having a certain rate of false negatives; however, this disadvantage existed in any diagnostic method, as no diagnostic assay exhibited a sensitivity and a specificity of 100%. Instead, these two elements had to be weighed against each other, as indicated in paragraph [0060] of the patent. If, as in this case, the aim was to protect as many AS and TIA patients as possible from bacterial infection, the treating physician would select a relatively low PCT cut-off value to decrease the false negative rate. In addition, they could resort to using the claimed method together with other clinical parameters contributing to the diagnosis and treatment

of patients, such as "the gold standard" criteria disclosed in paragraph [0061] of the patent.

Hence, contrary to the appellant's opinion, the experimental data in the patent did not constitute verifiable facts raising serious doubts that the claimed invention could be carried out. Accordingly, the appellant's objection under Article 100(b) EPC in respect of the main request and any of the auxiliary requests had to fail.

XII. The parties' final requests, insofar as they are relevant to the present decision, were as follows:

The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant also requested that document D19 be admitted into the proceedings.

The respondent requested that the appeal be dismissed and the patent be maintained as granted, i.e. that the opposition be rejected. As an auxiliary measure, the respondent requested that

(a) the patent be maintained in amended form on the basis of one of the sets of claims in auxiliary requests 1 to 4, originally filed by letter dated 20 October 2017 and re-filed with the reply to the statement setting out the grounds of appeal, or on the basis of the set of claims in auxiliary request 5, filed with letter dated 9 July 2021;

(b) that document D19 not be admitted into the proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of document D19 into the appeal proceedings (Article 12(4) RPBA 2007)

In the oral proceedings, the board decided not to admit document D19 into the proceedings. In view of the outcome of the appeal proceedings, detailed reasoning on the admission of this document is not necessary.

Main request (patent as granted)

3. Sufficiency of disclosure (Article 100(b) EPC)

3.1 In accordance with the established case law of the boards of appeal, a successful objection based on insufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts, that the invention is disclosed sufficiently clear and complete for it to be carried out by a person skilled in the art.

3.2 In the case at hand, the invention defined in claim 1 as granted relates to an *in vitro* method for the purpose of diagnosing a bacterial infection in an individual patient who has suffered from an acute stroke (AS) or from a transient ischemia attack (TIA) (see point I. above).

3.3 The attainment of this purpose, i.e. the detection of the presence of a bacterial infection in such an AS or TIA patient, is a functional technical feature of this claim. This was not contested by the respondent.

3.4 The parties were, however, in dispute as to whether the experimental data disclosed in Tables 1 and 2 of the patent cast serious doubts on the suitability of the claimed *in vitro* method for the purpose recited in claim 1.

3.5 These data stem from a clinical study disclosed in Examples 1 and 2 of the patent. In this study, procalcitonin (PCT) concentrations were determined in blood samples from two groups of patients using an ultra-sensitive PCT detection assay with a functional assay sensitivity ("FAS") of 0.007 ng/mL.

3.5.1 In the first group (i.e. patients admitted to hospital within the first 12 hours of the onset of AS or TIA symptoms, herein designated as "Group A"), concentrations of PCT were measured at baseline (on admission to hospital, i.e. 0 to 12 hours), on day 1 (24 to 36 hours), on day 3 (72 to 84 hours) and on day 5 (120 to 132 hours) after admission.

3.5.2 In the second group (i.e. patients admitted to hospital within the first 24 hours of the onset of AS or TIA symptoms, herein designated as "Group B"), concentrations of PCT were measured at baseline (on admission to hospital, i.e. 0 to 24 hours), on day 1 (24 to 48 hours), on day 3 (72 to 96 hours) and on day 5 (120 to 144 hours) after admission.

3.6 Subsequently, different PCT cut-off values were selected to determine the corresponding sensitivity and specificity. The results are reported in paragraph [0060] of the patent as well as in Table 1 for Group A and in Table 2 for Group B (see paragraph [0062] of the patent).

3.7 As correctly noted by the respondent in point B.2.1.6 of its letter dated 9 July 2021, sensitivity measures the proportion of true positive patients, i.e. patients who are correctly diagnosed as suffering from a disease (here, the percentage of patients who are correctly identified as having a bacterial infection). Specificity measures the proportion of true negative patients, i.e. patients who are correctly diagnosed as not suffering from a disease (here, the percentage of patients who are correctly identified as not having a bacterial infection).

3.8 It is also common general knowledge that, in order to reduce the number of false negatives, the predetermined PCT threshold level or cut-off value can be selected to be relatively low. In contrast, if a low rate of false positives is sought (i.e. patients suffering from AS or TIA who are incorrectly diagnosed with a bacterial infection), this threshold level or cut-off value can be selected to be higher (see point V.1.1.2.3 of the reply to the statement setting out the grounds of appeal).

3.9 Coming back to the data reported in Tables 1 and 2 of the patent, the board observes the following.

(a) Within the first time period (i.e. 0 to 12 hours after admission to hospital for Group A and 0 to 24 hours after admission to hospital for Group B), the highest sensitivity values are obtained with a PCT cut-off value of 0.03, amounting to 22.7% for Group A and to 29.2 % for Group B.

(b) Within the second time period (i.e. on day 1 after admission to hospital), the highest sensitivity values are again obtained with a PCT cut-off value

of 0.03, amounting to 33.3% for Group A and to 40.9% for Group B.

(c) The sensitivities further increase on days 3 and 5 after admission to hospital for each PCT cut-off value in both groups; however, these time periods do not fall within the scope of claim 1.

3.10 Hence, the highest sensitivity obtained within the time periods falling within the scope of claim 1 is 40.9%

(a) at a selected PCT cut-off value of 0.03,

(b) calculated on the basis of PCT values in samples obtained from patients within 24 to 48 hours of admission to hospital,

(c) using a PCT detection assay with an FAS of 0.007 ng/mL.

3.11 Therefore, the most sensitive method of the *in vitro* diagnostic methods described in Example 2 of the patent is a method in which around 41 out of 100 truly infected AS or TIA patients are correctly identified as having a bacterial infection. Conversely, this means that with the claimed method bacterial infections remain undetected in more than 50% of infected AS or TIA patients. The board also notes that Table 1 of the patent reports sensitivities for *in vitro* methods falling within the scope of claim 1 which are as low as 13.6% for a PCT cut-off value of 0.045 ng/mL and 9.1% for a PCT cut-off value of 0.06 ng/mL (see second column of Table 1, below the heading "0-12h").

3.12 In view of these facts, the board concludes that the claimed *in vitro* method is not suitable for the purpose recited in claim 1.

3.13 The respondent essentially based its case regarding sufficiency of disclosure on the alleged added value of the claimed method over the prior art (see point XI. above).

3.14 On the face of the facts on file, the board has no reason to doubt the respondent's submission that the claimed method represents an additional tool which provides the treating physician with a better basis for antibiotic treatment than before.

3.15 However, the purpose stated in claim 1 is different, i.e. the claimed method must be able to detect the presence of a bacterial infection in a patient who has suffered from an AS or from a TIA (see point 3.3 above). As explained in point 3.11 above, the experimental data disclosed in Tables 1 and 2 of the patent undisputedly show that *in vitro* methods falling within the scope of claim 1 are not able to detect bacterial infections in a large proportion of infected AS and TIA patients. It follows that these data do not support the suitability of the claimed method for the claimed purpose, but instead appear to show the opposite.

3.16 As a consequence, the board cannot be convinced by the respondent's arguments.

Overall conclusion on sufficiency of disclosure

3.17 In agreement with the appellant, the board finds that the experimental data disclosed in Tables 1 and 2 of

the patent show that the claimed *in vitro* method is not suitable for achieving the purpose recited in claim 1. This conclusion has not been convincingly rebutted by the respondent. The board therefore concludes that the appellant's objection of insufficiency of disclosure under Article 100(b) EPC prejudices the maintenance of the patent as granted.

Auxiliary requests 1 to 5

4. Sufficiency of disclosure of auxiliary requests 1 to 3

4.1 Claim 1 of auxiliary request 1 is identical to claim 1 of the main request, with the exception that the predetermined PCT threshold level must be between 0.02 ng/mL and 0.1 ng/mL ("limitation 1").

4.2 Claim 1 of auxiliary request 2 differs from claim 1 of the main request on account of the insertion of the following feature at the end of the claim:

"wherein said patient has a bacterial infection when said determined PCT level is higher than the predetermined threshold level" ("limitation 2").

4.3 Claim 1 of auxiliary request 3 incorporates limitation 1 and limitation 2.

4.4 When comparing the amended subject-matter of claim 1 of each of these three auxiliary requests with the clinical study described in Examples 1 and 2 of the patent ("clinical study"), the following is noted.

(a) All of the predetermined PCT threshold levels (i.e. PCT cut-off values) selected in the clinical study fall within the range specified in claim 1 of each

of auxiliary requests 1 and 3 (see first column of Tables 1 and 2 of the patent).

(b) The clinical study reveals an association between increased PCT concentration and the presence of a bacterial infection (see paragraph [0060] of the patent). This correlation is in agreement with limitation 2 included in claim 1 of each of auxiliary requests 2 and 3.

4.5 Accordingly, the experimental data reported in Tables 1 and 2 of Example 2 of the patent remain relevant for the subject-matter of claim 1 of each of auxiliary requests 1 to 3. Hence, for the same reasons as outlined above for claim 1 of the main request, these data lead to the same conclusion on the sufficiency of disclosure of the invention underlying claim 1 of each of auxiliary requests 1 to 3.

4.6 It follows that auxiliary requests 1 to 3 must also fail for lack of sufficient disclosure under Article 100(b) EPC.

5. Sufficiency of disclosure of auxiliary requests 4 and 5

Claim 1 of each of auxiliary requests 4 and 5 is identical to claim 1 of the main request. Hence, the considerations set out above regarding sufficiency of disclosure of claim 1 of the main request equally apply to claim 1 of each of these two auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated