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**Datasheet for the decision
of 1 April 2014**

Case Number: T 1474/12 - 3.3.02

Application Number: 05820913.1

Publication Number: 1831699

IPC: G01N33/68

Language of the proceedings: EN

Title of invention:

DETERMINATION OF NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN
(NGAL) AS A DIAGNOSTIC MARKER FOR RENAL DISORDERS

Patent Proprietor:

Antibodyshop A/S

Opponents:

Getica AB
Alere San Diego, Inc.

Headword:

DIAGNOSTIC MARKER/ANTIBODYSHOP

Relevant legal provisions:

EPC Art. 83, 100(b)

Keyword:

Sufficiency of disclosure - (no)

Decisions cited:

Catchword:



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Case Number: T 1474/12 - 3.3.02

**D E C I S I O N
of Technical Board of Appeal 3.3.02
of 1 April 2014**

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Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted on 21 May 2012
revoking European patent No. 1831699 pursuant to
Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: K. Giebeler
R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 831 699, based on European patent application No. 05820913.1 (published as WO 2006/066587) and entitled "Determination of neutrophil gelatinase-associated lipocalin (NGAL) as a diagnostic marker for renal disorder", was granted with 17 claims.

II. Claim 1 as granted reads:

"A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of
i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of bodily fluid from the human being,
ii) comparing said concentration with a predetermined cutoff value, said cutoff value being 250 ng/mL or a higher value, such as a value between 250 ng/mL and 525 ng/m, chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder."

Claims 2-17 as granted are dependent on claim 1.

III. The patent was opposed by four parties on the grounds of Article 100(a) EPC (lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC)), Article 100(b) EPC and Article 100(c) EPC.

IV. In a decision posted on 21 May 2012, the opposition division decided that the claimed invention of the sole

request before it did not fulfil the requirement of sufficiency of disclosure (Articles 83 and 100(b) EPC) and revoked the patent.

V. The following documents are mentioned in the present decision:

D10: Bewick et al., Critical Care (2004) 8:508
D18: Mishra et al., Lancet (2005) 365:1231
D26: Bennett et al., Clin J Am Soc Nephrol (2008) 3:
665
D38: Zweig and Campbell, Clin Chem (1993) 39: 561
D61: Table A parts 1, 2 and 3: Analysis of the data
presented in Table 2 of the Patent
D72: Alere Triage NGAL Product Insert; dated 2011,
downloaded 2012
D73: Ray et al., Anesthesiology (2010) 112:1023
D74: Youssef and El-Shal, Iran J Kidney Dis (2012)
6:355
D75: Appendix originally filed by Opponent 1 with
letter dated 29 January 2012
D76: Haase et al., Am J Kidney Dis (2009) 54:1012
D77: Cai et al., Clin J Am Soc Nephrol (2010) 4:2229
D78: EP 2 128 625 A2

VI. The appellant (patent proprietor) lodged an appeal against the decision of the opposition division. With the statement of grounds of appeal, it submitted a new main request and seven auxiliary requests as well as new evidence (documents D72 to D75).

VII. With their replies to the appeal, respondents (opponents) 1, 2 and 4 requested that the appeal be dismissed; they furthermore requested that the appellant's main request and auxiliary requests 1-3 and 5-7 not be admitted into the appeal proceedings.

Respondent 4 submitted further evidence (documents D76 to D78).

- VIII. The board summoned the parties to attend oral proceedings to be held on 15 October 2013 and issued a communication in which it gave its preliminary opinion.
- IX. With letter of 13 September 2013, the appellant filed a new main request and auxiliary requests 1 to 10.
- X. Claim 1 of the **main request** reads as follows:

"A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of

i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of urine, plasma or serum from the human being,

ii) comparing said concentration with a predetermined cutoff value, said cutoff value being 250 ng/mL or a higher value, such as a value between 250 ng/mL and 525 ng/m, chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder."

- XI. Claim 1 of **auxiliary request 1** reads as follows:

"A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of

- i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of urine, plasma or serum from the human being,
- ii) comparing said concentration with a predetermined cutoff value, said cutoff value being a value between 250 ng/mL and 525 ng/m, chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder."

XII. Claim 1 of **auxiliary request 2** reads as follows:

"A method of diagnosing, monitoring or determining the likelihood of a renal disorder, wherein the renal disorder is a disorder that may cause acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of

- i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of urine, plasma or serum from the human being,
- ii) comparing said concentration with a predetermined cutoff value, said cutoff value being 250 ng/mL or a higher value, such as a value between 250 ng/mL and 525 ng/m, chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder."

XIII. Claim 1 of **auxiliary request 3** reads as follows:

"A method of diagnosing, monitoring or determining the likelihood of a renal disorder, wherein the renal disorder is a disorder that may cause acute renal

failure, acute tubular necrosis or acute tubulointerstitial nephropathy in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of

i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of urine, plasma or serum from the human being,
ii) comparing said concentration with a predetermined cutoff value, said cutoff value being a value between 250 ng/mL and 525 ng/mL, chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder."

- XIV. Respondent 2 submitted further submissions with letter of 15 September 2013.

- XV. The first oral proceedings before the board took place on 15 October 2013. At the end of the oral proceedings, the debate on the main request in relation to Articles 83, 84 and 123(2) EPC was closed. Furthermore, it was announced that auxiliary request 1 was admitted into the proceedings and that the proceedings would be continued in writing.

- XVI. On 11 November 2013, the board summoned the parties to oral proceedings to be held on 1 April 2014 and issued a communication.

- XVII. With letter of 5 March 2014, respondent 1 withdrew its opposition.

- XVIII. With letter of 31 March 2014, respondent 3 withdrew its opposition.

XIX. The second oral proceedings before the board took place on 1 April 2014.

During these oral proceedings, the appellant withdrew auxiliary requests 4-10 filed with letter of 13 September 2013. The appellant furthermore withdrew its submission that the opposition division had committed a procedural violation.

XX. The submissions made by the appellant, as far as they are relevant to this decision, may be summarised as follows:

Admissibility of auxiliary requests 1-3

These requests should be admitted into the proceedings because they had been filed in response to the decision of the opposition division and thus could not have been presented earlier. Said requests did not represent any "fresh case", but related to the same subject-matter as had been discussed during the first-instance proceedings. The requests had been known to all parties since the filing of the grounds of appeal.

Admissibility of documents D72, D74, D76 and D77

Documents D72 and D74 should be admitted into the proceedings in view of their high relevance. Document D72 was a recent study published by respondent 4, which confirmed the applicability of the cutoff value of 250 ng/mL, even for the case that different NGAL antibodies and a different measurement technique than those of the patent in suit were used, and document D74 showed that a cutoff value of 250 ng/mL was also suitable for the diagnosis of chronic kidney disease.

Documents D76 and D77 should not be admitted into the proceedings because these documents could have been filed earlier and did not show anything new compared to the documents already on file.

Sufficiency of disclosure (Article 83 EPC) - main request

Contrary to the conclusions reached by the opposition division in its decision, the claimed invention was sufficiently disclosed with respect to both (1) the cutoff value of 250 ng/mL or higher and (2) the range of renal disorders to be diagnosed. Furthermore, the opposition division was correct in stating that the patent was sufficiently disclosed with respect to (3) the point in time that the samples are taken and (4) the method of determining the concentration of human NGAL.

The invention of the patent in suit was based on the finding that the NGAL levels were much higher in patients with kidney disease than in patients with other diseases. Using the data of Table 2 of Example 6 of the patent in suit, the skilled person would be able to rank the patients according to their NGAL levels and calculate the diagnostic parameters of sensitivity, specificity, positive predictive value, negative predictive value and accuracy. By proceeding in this way, the skilled person would arrive at the tables shown in document D61, using the raw data of the patent in suit and common general knowledge only. From the tables of document D61, it could be seen that the cutoff value of at least 250 ng/mL provided a good balance of sensitivity and specificity, and that increasing the cutoff value would increase the specificity at the expense of sensitivity. Depending on

the risk for a particular patient and the desired sensitivity and specificity, the medical practitioner would be able to choose a suitable cutoff value. The invention would not require 100% sensitivity and specificity.

The statements in paragraphs [0038] and [0039] of the patent in suit would not neutralise the teaching of the patent if properly read; the skilled person would understand the statements in paragraphs [0038] and [0039] to mean that cutoff values below those specified in the second sentence of each of said paragraphs would not be diagnostic to those sensitivities and specificities specified in the third sentence of each of said paragraphs.

Sufficiency of disclosure (Article 83 EPC) - auxiliary requests 1-3

The methods claimed in auxiliary requests 1-3 were sufficiently disclosed for the same reasons as set out for the main request. The upper limit of 525 ng/mL for the cutoff value introduced into claim 1 of auxiliary request 1 had the consequence that lower sensitivities were excluded. Concerning auxiliary request 2, there was no evidence on file showing that a cutoff value of 250 ng/mL would not work for the disorders specified in claim 1. The patients with renal affection of Example 6 of the patent in suit would have predominantly acute renal disorder, because patients with chronic renal failure would not normally enter an intensive care unit, although this was also possible.

XXI. The submissions of the respondents, as far as they are relevant to this decision, may be summarised as follows:

Admissibility of auxiliary requests 1-3

These requests should not be admitted into the proceedings because they could have been presented earlier and thus constituted an abuse of procedure.

Admissibility of documents D76 and D77

Document D76 had been filed in direct reply to the grounds of appeal, which stated that the cutoff value had "excellent discriminating properties". The document was a meta-analysis and disclosed that different research groups had arrived at different NGAL cutoff values. Therefore, the document should be admitted into the proceedings in view of its relevance.

Document D77 had been filed in direct reply to the decision of the opposition division and should be admitted into the proceedings in view of its relevance.

Sufficiency of disclosure (Article 83 EPC) - main request

The claimed invention was insufficiently disclosed with respect to (1) the cutoff value of 250 ng/mL or higher, (2) the range of renal disorders to be diagnosed, and in particular with respect to the diagnosis of chronic renal failure, (3) the point in time that the samples are taken and (4) the method of determining the concentration of human NGAL.

Concerning the cutoff value, the wording of claim 1 required that it resulted in 100% specificity and 100% sensitivity; otherwise the claimed method would not discriminate between a renal and a non-renal disorder

and the cutoff value would not exclude NGAL concentrations associated with non-renal disorders. However, the data of Table 2 in Example 6 of the patent in suit showed that a cutoff value of 250 ng/mL did not exclude all non-renal patients. In order to find a suitable cutoff value, the skilled person would have to test a large number of non-renal patients, which would represent a research programme and hence an undue burden. Furthermore, claim 1 was directed to three different types of method, i.e. a method of diagnosing a renal disorder, a method of monitoring a renal disorder, and a method of determining the likelihood of a renal disorder. Each of said methods required a different cutoff value, which the skilled person could not establish without undue burden.

In the patent in suit, paragraph [0017] referred to "an acceptable degree of specificity", without specifying what such acceptable degree was. Therefore, the skilled reader would understand from paragraphs [0038] and [0039] that for urine a specificity of 89.3% and for plasma a specificity of 96.3% represented "an acceptable degree of specificity", i.e. lower specificities were not acceptable. The skilled person would trust the statements in paragraphs [0038] and [0039] that cutoff values below 329 ng/mL for urine and 355ng/mL for plasma were not diagnostic for renal disorders, and this teaching was in contradiction to the general part of the patent in suit.

According to the appellant's own calculations, the cutoff value of 250 ng/mL provided only 64% specificity for plasma and 80% specificity for urine. Therefore, the cutoff value of 250 ng/mL had no acceptable discriminating power and was entirely arbitrary. The appellant had in fact stated in its grounds of appeal

that when selecting the cutoff value of 250 ng/mL "it was initially decided that the criteria for an acceptable lower limit for a cutoff value should be that it gave an accuracy of $\geq 80\%$, together with $\geq 70\%$ or the closest approach thereto for the 4 diagnostic performance measures: sensitivity, specificity, and positive and negative predictive values"; however, the patent in suit provided no guidance whatsoever on this decision-making process.

Sufficiency of disclosure (Article 83 EPC) - auxiliary requests 1-3

The introduction of an upper limit for the cutoff value in claim 1 of auxiliary request 1 did not overcome any of the objections under Article 83 EPC. The same applied to the patient group specified in claim 1 of auxiliary request 2, because the data of Example 6 and in particular the statements in paragraphs [0038] and [0039] applied to patients with acute renal disorders. There was no teaching in the patent in suit that different cutoff values should be used for the diagnosis of acute and chronic renal disorders.

XXII. The final requests of the parties were:

The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or, alternatively, on the basis of one of auxiliary requests 1-3, all filed with letter of 13 September 2013.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.
2. *Admissibility of the main requests and of auxiliary requests 1-3*
 - 2.1 The main request and auxiliary requests 1-3 were filed one month before the first oral proceedings.
 - 2.2 According to Article 12(2) of the Rules of Procedure of the Boards of Appeal (RPBA), the statement of grounds of appeal and the reply thereto must contain the party's complete case. Any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion, which is to be exercised in view of inter alia the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy (Article 13(1) RPBA). Amendments sought to be made after oral proceedings have been arranged are not to be admitted if they raise issues which the board or the other party cannot reasonably be expected to deal with without adjournment of the oral proceedings (Article 13(3) RPBA).
 - 2.3 The claims of the main request are identical to the claims of the sole request on which the opposition division took its decision, and these claims had already been filed by the appellant with the grounds of appeal as "auxiliary request 4". Therefore, the main request does not constitute an amendment to the appellant's case under Article 13(1) RPBA and is admissible. In fact the respondents have not objected to the admissibility of this request.

- 2.4 The claims of auxiliary request 1 differ from the claims of the main request in that an upper limit of 525 ng/mL is defined for the predetermined cutoff value. Claim 1 of this request is identical to claim 1 of "auxiliary request 5" filed by the appellant with the grounds of appeal. This claim had not been presented in the first instance proceedings, but the board sees it as an attempt to overcome reasons given in the opposition division's decision, stressing that the cutoff value "is not limited at all by an upper value" (page 6, lines 10-11, of the decision). Therefore, this request is admitted into the proceedings.
- 2.5 Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it states the feature of dependent claim 9 of the main request, namely that the renal disorder is a disorder that may cause acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy. Claim 1 of auxiliary request 2 is identical to claim 1 of "auxiliary request 6" filed by the appellant with the grounds of appeal. No decision was taken by the opposition division on this claim. However, the board considers the claim to be a fair attempt to address the finding in the opposition division's decision that the patent in suit is not sufficiently disclosed with respect to the diagnosis of chronic renal failure (page 9 of the decision). Therefore, this request is admitted into the proceedings.
- 2.6 Claim 1 of auxiliary request 3 combines the limitations introduced into claim 1 of auxiliary requests 1 and 2. In view of the considerations set out above with respect to the admissibility of auxiliary requests 1

and 2, the board considers it appropriate to admit auxiliary request 3 into the proceedings.

3. *Admissibility of documents D72, D74, D76 and D77*

- 3.1 Document D72 was submitted by the appellant with its grounds of appeal. The appellant referred to this document in order to support its argumentation that, contrary to the findings in the opposition division's decision, the value of 250 ng/mL was a suitable cutoff, even when different antibodies than those mentioned in the patent in suit were used.

In view of its *prima facie* relevance and in view of the fact that the respondents did not object, the board decided to admit the document into the proceedings.

- 3.2 Document D74 was submitted by the appellant with its grounds of appeal in order to show that the opposition division's finding in its decision that a cutoff value of 250 ng/mL was not suitable for the diagnosis of chronic renal failure was wrong. According to the appellant, the document disclosed a mean level of urinary NGAL of 350 ng/mL in patients with chronic kidney disease.

In view of the *prima facie* relevance of the document with respect to the issue of NGAL levels in patients with chronic renal diseases and in view of the fact that the respondents did not object, the board decided to admit it into the proceedings.

- 3.3 Document D77 was submitted by respondent 4 with its response to the grounds of appeal in order to support its position that the opposition division's finding in its decision that the claimed invention was

sufficiently disclosed with respect to the method of determining the concentration of NGAL was wrong.

In view of the *prima facie* relevance of the document for the issue of calibration of NGAL measurements, the board decided to admit it into the proceedings.

- 3.4 Document D76 was submitted by respondent 4 with its reply to the grounds of appeal. The document is a meta-analysis and refers *inter alia* to documents D18 and D26.

The board considered that document D76 was no more relevant than said documents already on file and decided **not** to admit it into the proceedings.

Main request

4. *Amendments (Articles 84 and 123(2) EPC)*

- 4.1 Claim 1 differs from claim 1 as granted in that the expression "sample of bodily fluid" is replaced by the expression "sample of urine, plasma or serum".
- 4.2 Respondent 4 submitted that the expression "sample of urine, plasma or serum" could be interpreted as either "sample of urine or plasma or serum" or as "sample of urine and (plasma or serum)", and was thus unclear, contrary to Article 84 EPC. Moreover, according to respondent 4, the claimed subject-matter when relating to a "sample of urine and (plasma or serum)" was not disclosed in the application as filed, contrary to Article 123(2) EPC.
- 4.3 The skilled person would read the expression "sample of urine, plasma or serum" in the context of the patent in

suit as meaning "sample of urine or plasma or serum"; there is no teaching in the patent in suit to use a mixture of a urine sample with a plasma/serum sample when determining the concentration of NGAL in the context of the claimed method, nor would the skilled person be inclined to use such sample mixtures in view of his/her common general knowledge. Therefore, the amendment in question does not give rise to a lack of clarity under Article 84 EPC. Furthermore, the amendment is directly and unambiguously derivable from the application as filed, notably from claims 16 and 17 or from page 9, lines 3 and 33, and thus complies with Article 123(2) EPC.

5. *Sufficiency of disclosure (Article 83 EPC)*

5.1 According to Articles 100(b) and 83 EPC, the claimed invention must be disclosed in the European patent and in the European patent application in a manner sufficiently **clear** and **complete** for it to be carried out by a person skilled in the art.

5.2 Claim 1 concerns a "method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being, wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of urine, plasma or serum from the human being, ii) comparing said concentration with a predetermined cutoff value, said cutoff value being 250 ng/mL or a higher value, such as a value between 250 ng/mL and 525 ng/mL, chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the

kidney, wherein a concentration above the cutoff value is indicative of a renal disorder".

Claim 1 thus encompasses three different kinds of method, (1) a method of diagnosing a renal disorder, (2) a method of monitoring a renal disorder, and (3) a method of determining the likelihood of a renal disorder; the following considerations will focus on alternative (1), a method of diagnosing a renal disorder.

- 5.3 In order to carry out the claimed diagnostic method, the skilled person has to be able to perform step ii) of comparing the concentration of NGAL in the sample as determined in step i) with a **predetermined cutoff value**, said cutoff value being 250 ng/mL or a higher value, **chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney, wherein a concentration above the cutoff value is indicative of a renal disorder**. Hence one of the questions arising in the context of sufficiency of disclosure with respect to the patent in suit is whether the skilled person trying to carry out the claimed diagnostic method would be in a position to choose a cutoff value which fulfills the requirements specified in claim 1, without undue burden and without needing inventive skill, taking account of the disclosure of the patent in suit and his/her common general knowledge only. Choosing a correct cutoff value is crucial for the claimed diagnostic method, because it is only if the cutoff value used excludes lower concentrations of NGAL associated with conditions that are not affecting the kidney and the concentration of NGAL above the cutoff value is indeed indicative of a renal disorder that the claimed diagnostic method will discriminate between a renal disorder and a condition

that is not affecting the kidney, as required by claim 1.

5.4 In order to find out how suitable cutoff values are to be chosen, the skilled person would turn to the description of the patent in suit.

5.4.1 It is stated therein that "for the concentration of NGAL to be specifically indicative of renal disorder, it must exceed a cutoff value set to exclude those lower concentrations of NGAL that may result from infective or inflammatory states or carcinomas that do not give rise to renal injury" (paragraph [0015]). It is further stated that "[t]he cutoff level below which the urinary level of NGAL cannot be diagnostic of renal injury with an acceptable degree of specificity because such a level can be found in healthy individuals or those suffering from inflammatory, infective or cancerous conditions is preferably a level of 250 ng/mL or more, such a value between 250 ng/mL and 525 ng/mL, such as 275 ng/mL, or 300 ng/mL, or 325 ng/mL, or 350 ng/mL, or 375 ng/mL, or 400 ng/mL, or 425 ng/mL, or 450 ng/mL, or 475 ng/mL, or 500 ng/mL. In another embodiment, the cutoff value used is a value of 1 µg/mL or a higher value. Preferably, the positive predictive value for the urinary cutoff value is 80% or more, such as 85% or more, e.g. 90% or more. Alternatively, or in addition, the negative predictive value for the urinary cutoff is preferably 80% or more, such as 85% or more, e.g. 90% or more." (paragraph [0017]). Further, it is stated that "[t]he cutoff level for the NGAL concentration in plasma or serum is similar to that for urine" (paragraph [0019]).

Said passages thus teach that in order to be diagnostic of renal injury, the cutoff value should have an

acceptable degree of specificity and is to be chosen from the range of 250 ng/mL or higher for urine, plasma and serum.

5.4.2 Among the six examples of the patent in suit, Example 6 is the only one which addresses the issue of cutoff values. This example is of prime importance for the present decision. It is entitled "Diagnostic power with respect to renal disorder of urine and plasma NGAL determinations in unselected adult patients admitted to intensive care" and contains a detailed study of 60 patients that were admitted to a hospital intensive care unit and that were classified (independently of the NGAL data) into those with and without a renal affection; their plasma and urine NGAL concentrations were determined and are shown in Table 2 together with the patients' clinical classification. Example 6 further reports on the statistical evaluation of the clinical data. Receiver operating characteristic (ROC) curves were plotted for the urine and plasma NGAL values (paragraph [0037]); the ROC curves are shown in the figures. Based on these evaluations, the inventors conclude that with respect to urinary NGAL values, "the cutoff value below which the concentration of urinary NGAL is **not diagnostic** of renal disorder was determined to be between 370 ng/mL and 329 ng/mL. With a cutoff in this range the diagnostic sensitivity was 96.9%, the diagnostic specificity was 89.3%, the positive predictive value was 91.2% and the negative predictive value was 96.2%" (paragraph [0038]; emphasis added by the board). With respect to plasma NGAL values, "the cutoff value below which the concentration of plasma NGAL is **not diagnostic** of renal disorder was determined to be between 436 ng/mL and 355 ng/mL. With a cutoff in this range the diagnostic sensitivity was 84.8%, the diagnostic specificity was 96.3%, the positive

predictive value was 93.1% and the negative predictive value was 83.9%" (paragraph [0038]; emphasis added by the board).

Said passages of Example 6 thus teach that on the basis of the evaluation of the clinical data of 60 patients admitted to a hospital intensive care unit, the cutoff value to be used in a diagnostic method should be at least 329 ng/mL for urine and at least 355 ng/mL for plasma, because lower cutoff values are not diagnostic of renal disorders.

A skilled person would thus derive from Example 6 that not any cutoff value within the range of 250 ng/mL or a higher value, as referred to in claim 1, would be suitable for use in the claimed method. In particular, the skilled person would understand from Example 6 that cutoff values such as 250 ng/mL, 275 ng/mL, 300 ng/mL or 325 ng/mL for urine and 250 ng/mL, 275 ng/mL, 300 ng/mL, 325 ng/mL or 350 ng/mL for plasma would **not** be diagnostic and hence not suitable for use in the claimed method, this being in contrast to the teaching of paragraphs [0017] and [0019] in the general part of the patent in suit, which disclose these specific cutoff values as preferred embodiments.

- 5.5 The appellant has submitted that in order to choose suitable cutoff values, the skilled person would use the data of Table 2 of Example 6 to provide the tables shown in document D61 as Table A, parts 1 to 3. In these tables, the data of Table 2 are listed in order of increasing NGAL concentration, either for both urine and plasma (part 1) or for plasma (part 2) or urine (part 3), and the diagnostic parameters of sensitivity, specificity, positive predictive value, negative predictive value and accuracy are shown. The necessary

calculations of the statistical parameters would be within the skilled person's common general knowledge as represented for instance by documents D10 or D38. Using the tables of document D61, the skilled person would be able to choose suitable cutoff values depending on the desired sensitivity and specificity. It could be seen from document D61 that a cutoff value of 250 ng/mL corresponded to a specificity of 80% for urine and 64% for plasma; any cutoff value within the range of 250 ng/mL or a higher value would in principle be suitable for use in the claimed method.

According to the appellant, the skilled person reading paragraphs [0038] and [0039] of the patent in suit would understand that the cutoff values referred to therein represented the mathematically obtained "optimal value", which would not necessarily be the best to use in the real world and which applied only if the mentioned sensitivities and specificities were desired.

5.6 The respondents have disputed that the data of the tables of document D61 were a direct consequence of the data of Table 2 of the patent in suit. However, this issue need not be addressed in this decision, because the board is not convinced by the appellant's arguments for other reasons.

5.7 The board agrees with the appellant that statistical methods for assessing the performance of a diagnostic test and involving the calculation of the parameters of sensitivity, specificity, positive predictive value, negative predictive value and accuracy, as well as receiver-operating characteristic (ROC) curves, formed part of the skilled person's common general knowledge at the priority date of the patent in suit. However,

the board considers that the skilled person trying to carry out the claimed invention would not apply his/her common general knowledge in the way suggested by the appellant, i.e. by re-evaluating the data of Table 2 and providing tables as in document D61. The reasons for this are as follows: Firstly, there is no teaching in the patent in suit that the data of Table 2 of Example 6 should be further evaluated in order to allow the selection of suitable cutoff values. Secondly, and even more importantly, the data of Table 2 have already been evaluated in the patent in suit by the inventors, who reached the conclusion that cutoff values below 329 ng/mL for urine and 355 ng/mL for plasma are not diagnostic for renal disease (see point 5.4.2 above). A skilled person reading Example 6 would not recognise any apparent reason why the inventors' conclusion with respect to the cutoff values specified in paragraphs [0038] and [0039] should be wrong, and would thus not start re-evaluating the very same data that gave rise to these conclusions.

The board furthermore takes the position that the skilled person might envisage that cutoff values below 329 ng/mL for urine and below 355 ng/mL for plasma would give rise to sensitivities and/or specificities lower than those stated in paragraphs [0038] and [0039], but would trust the inventors' conclusions based on the data of Table 2 that such cutoff values are "not diagnostic" of renal disorder. Therefore, the skilled person would not try to modify or extend the teaching in Example 6 concerning cutoff values, or give the inventors' conclusions a meaning different from that explicitly stated in the patent in suit.

5.8 In view of the fact that the general part of the patent in suit teaches the use of cutoff values different from

those taught in Example 6, and considering that the patent in suit does not provide the skilled person with sufficient information on how a cutoff value that complies with the requirements set out in claim 1 is to be chosen, the board judges that the skilled person cannot carry out the claimed invention. In order to find out how to choose suitable cutoff values, the skilled person would have to collect and evaluate additional clinical data, which would represent a research project and hence an undue burden.

Therefore, the requirement of sufficiency of disclosure is not complied with.

- 5.9 Consequently, the appellant's main request must be refused pursuant to Article 83 EPC.

Auxiliary requests 1-3

6. *Formal matters*

In view of the board's negative findings with respect to sufficiency of disclosure (Article 83 EPC) in relation to auxiliary requests 1-3 as set out below, the issues of Articles 84 and 123(2) EPC and of Rule 80 EPC in relation to said requests are not dealt with in the present decision.

7. *Sufficiency of disclosure (Article 83 EPC)*

- 7.1 Claim 1 of **auxiliary request 1** differs from claim 1 of the main request in that the predetermined cutoff value is a value between 250 ng/mL and 525 ng/mL instead of being 250 ng/mL or a higher value. However, this introduction into claim 1 of an upper limit for the predetermined cutoff value cannot cure the lack of

sufficient disclosure as to how a cutoff value which fulfills the requirements specified in the claim is to be chosen, and the reasons set out in points 5.1 to 5.8 above in relation to the invention claimed in the main request apply *mutatis mutandis* to the invention claimed in auxiliary request 1.

7.2 Claim 1 of **auxiliary request 2** differs from claim 1 of the main request in that the renal disorder is a disorder that may cause acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy. Having regard to the disclosure of the patent in suit, there is no additional teaching as to how to choose a cutoff value which excludes lower concentrations of NGAL associated with conditions that do not affect the kidney and where a concentration above the cutoff value is indicative of any of the specified renal disorders referred to in claim 1 of auxiliary request 2. Therefore, the board must conclude that the invention of the claims of auxiliary request 2 is not sufficiently disclosed for the same reasons as set out in detail for the main request in points 5.1 to 5.8 above.

7.3 Claim 1 of **auxiliary request 3** differs from claim 1 of the main request in that it combines the limitation of claim 1 of auxiliary request 1 relating to the upper limit of the cutoff value with the limitations of claim 1 of auxiliary request 2 relating to the nature of the renal disorder. However, these limitations fail to overcome the lack of sufficiency of disclosure concerning the issue of how a suitable cutoff value as specified in claim 1 is to be chosen in the light of the patent in suit combined with common general knowledge, see the reasons given in points 5.1 to 5.8 in relation to the main request above.

8. In view of the above, none of the claim requests fulfills the requirement of sufficiency of disclosure (Article 83 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



N. Maslin

U. Oswald

Decision electronically authenticated