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D E C I S I O N
of 5 February 2004

Case Number: T 1101/00 - 3.3.4

Application Number: 92913443.5

Publication Number: 0608235

IPC: C12Q 1/56

Language of the proceedings: EN

Title of invention:
Method for the diagnosis of blood coagulation disorders

Patentee:
DAHLBÄCK, Björn

Opponents:
Bio Merieux S.A.
Scripps Research Institute
Akzo Nobel N.V.
Baxter Aktiengesellschaft
Dade Behring Marburg GmbH
Dade Behring Inc.
Roche Diagnostics GmbH
Diagnostica Stago

Headword:
Blood coagulation disorders/DAHLBÄCK

Relevant legal provisions:
EPC Art. 108, 113(1), 123(2)(3), 84, 83, 54, 56

Keyword:
"Appeal by appellant III - admissible"
"Opportunity to present comments - in opposition - (yes)"
"Added subject-matter and extension of the scope of protection - (no)"
"Clarity of claims - (yes)"
"Sufficiency of disclosure - (yes)"
"Novelty - (yes)"
"Inventive step - (yes)"

Decisions cited:
T 0284/94, T 0694/92

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1101/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 February 2004

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 1 September 2000 concerning maintenance of European patent No. 0608235 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
V. Di Cerbo

Summary of Facts and Submissions

I. European patent 0 608 235, based on PCT application WO/93/10261, with the title "Method for the Diagnosis of Blood Coagulation Disorders" was granted on the basis of 31 claims.

II. Notices of opposition were filed by eight parties requesting revocation of the patent on the basis of Article 100(a)(b) and (c) i.e. for lack of Novelty (Article 54 EPC) and inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and extension of the subject matter of the claims beyond the content of the application as filed (Article 123(2) EPC).

III. The patent was maintained by the Opposition Division on the basis of a main request with amended claims pursuant to Article 102(3) by a decision dated 1 September 2000.

IV. Notices of appeal against this decision were filed by opponent (1)(appellant I), opponent (2) (appellant II), and opponent (7) (appellant IV) on 26 October 2000, 10 November 2000 and 9 November 2000 respectively; also the statements of grounds were filed.

Opponent (5) (appellant III) filed a notice of appeal on 23 November 2000 and submitted that the decision of the opposition division was not notified to them in accordance with Rule 78(1) EPC. Opponent (5) had only learned from the communication by the registry of the board forwarding the appeals of the other appellants that the decision of the opposition division had

already been notified. After having contacted the registrar of the board a copy of the decision of the opposition division was sent to them via fax, received on 22 November 2000.

The appeal fee was paid on 23 November 2000 and the grounds for this appeal were filed on 20 March 2001.

All grounds for the appeals were answered by the patentee (respondent).

V. The board issued a communication pursuant to Article 12 of the Rules of Procedure of the Boards of Appeal concerning the admissibility of the appeal filed by appellant III and expressed a non-binding opinion that the statements of appellant III in the appeal that they had not received the decision of the opposition division in accordance with Rule 78(1) EPC seemed to be well founded.

VI. Oral proceedings took place on 5 February 2004 which were attended only by appellant III and the respondent. During oral proceedings the respondent submitted a new main request with 23 claims, claims 1 and 13 of which read:

"1. An in vitro method for diagnosing in a human **thromboembolic diseases caused by**, or for determining the risk of a human to acquire manifestation of, a blood coagulation disorder designated APC resistance and recognized by an abnormally low anticoagulant response to exogenous activated Protein C (abbreviated APC) even in presence of normal levels of functional Protein S, Factors V_a and $VIII_a$, which are normally

degraded by APC, and absence of lupus anticoagulants, said method comprising determining for a plasma sample comprising coagulation factors and derived from said human, the anticoagulant activity of exogenous APC by measuring the substrate conversion rate obtained for a coagulation enzyme, the activity of which is influenced by APC, by the following steps:

(i) incubating said plasma sample with

(1) exogenous APC, or exogenous Protein C together with current exogenous reagents to transform the exogenous Protein C to APC, **wherein the concentrations used in the final assay medium being 25 ng/mL-10 µg/mL for human APC, 10 ng/mL-50 µg/mL for non-human APC, and 5 ng/mL-5 µg/mL for bovine APC used in combination with 100 ng/mL-20µg/mL bovine protein S;**

(2) an exogenous Reagent (I), which at least partially activates the blood coagulation system of said sample and is selected in a manner known per se to cause activation of a coagulation factor used for the measurement in step (ii);

(3) components that are necessary for efficient reaction of the activated coagulation factors introduced in step (i)(2), *i.e.* phospholipid(s) and Ca^{++} salt **giving a Ca^{2+} concentration of 0.5-30 mmol/L in the final assay medium**; and, if desired,

(4) an exogenous substrate for an enzyme, the activity of said enzyme being influenced by APC;

(ii) directly measuring said substrate conversion rate obtained in (i), and

(iii) comparing the conversion rate measured in step (ii) with a standard value obtained from samples

from normal individuals, which samples have been subjected to steps (i) and (ii) under the same conditions as the plasma sample from said human, in which method a substrate conversion rate obtained for a plasma sample in step (ii), that is higher than the standard value indicates that said human suffers from or runs the risk of acquiring manifestation of said disorder."

Emphasis in bold by the board shows the features introduced compared to granted claim 1.

"13. The method of claim 1, wherein the Reagent (I) is
(a) the components necessary to activate the blood coagulation system of the sample via the intrinsic pathway, such as an APTT reagent, a contact activator, Factor IX_a, Factor XI_a, Factor XII_a and/or kallikrein, and/or
(b) the components necessary to activate the blood coagulation system via the extrinsic pathway, e.g. tissue thromplastin,

and the components according to (i)(1), (i)(3) and (i)(4) are added simultaneously with or, where appropriate, after Reagent (I) has been allowed to incubate with the sample for a sufficient time to activate the intrinsic or extrinsic pathway."

Compared to claim 13 as granted the only amendment is that the phrase " ... *the intrinsic* ***and/or*** *extrinsic pathway.*" was changed to "... *the intrinsic* ***or*** *extrinsic pathway.*"

Claims 2 to 12 and 14 to 23 are all directly or indirectly dependant on Claim 1 and identical to the claims as granted.

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

(1) L. Amer et al., Thrombosis Research, 1990, Vol. 57, pages 247 to 258

(2) B. Dahlbäck and M. Carlsson, Thrombosis and Haemostasis, 1991, Vol. 65, page 658, abstract 39

(3) C.A. Mitchell et al., The New England Journal of Medicine, 1987, pages 1638 to 1642

(5) WO 91/02812

(6) E.M. Faioni et al., Thrombosis and Haemostasis, 1991, Vol. 66(4), pages 420 to 425

(12) M. Blombäck and N. Egberg, Haemostasis and Thrombosis, 1987, pages 967 to 981

(19) R.M. Bertina et al., Nature, 1994, Vol. 369, pages 64 to 67

(27) B. Dahlbäck, Advances in Genetics, "Thrombophilia", 1996, pages 135 to 175

(29) J. Svensson and B. Dahlbäck, New England Journal of Medicine, 1994, Vol. 330, pages 517 to 522

(31) P.W. Majerus, Nature, 1994, Vol. 369, pages 14 to 15

(51) R.M. Bertina et al., Thrombosis and Haemostasis, 1995, Vol. 74(1), pages 449 to 453

(60) I. Walker, "Guidelines on the Investigation and Management of Thrombophilia", J. Clin. Pathol., 1990, Vol. 43, pages 703 to 710

(63) H. Greiling and A.M. Gressner, "Lehrbuch der Klinischen Chemie und Pathobiochemie", Schattauer editor, Stuttgart, New York, 1987, pages 752 and 753

(65) J. Malm et al., British Journal of Haematology, 1988, Vol. 68, pages 437 to 443

(68) Deutsche Norm DIN 58 939

VIII. The arguments submitted in writing and during oral proceedings by the appellants may be summarised as follows:

Procedural matters
Article 113(1) EPC

Appellant I submitted that the amendments to the claims carried out by the respondents during oral proceedings before the opposition division should be declared inadmissible since they were modifications of the understanding of the invention and the parties to the proceedings had not sufficient time to analyse, consider and discuss them which amounted to a violation

of Article 113(1) EPC. This was even acknowledged by the opposition division in point 6.2 of the reasons for the decision.

Rule 57(a) EPC

Appellant II argued that, if the addition of the words "*thromboembolic diseases caused by*" did not extend the scope of claim 1 (see below under Article 123(3) EPC), then there did not appear to be any reason for inserting them. Therefore claim 1 was not allowable under Rule 57(a) EPC.

Article 84 EPC

All the causes for the blood coagulation disorder were essential for the method as now claimed and had, therefore, to be included in the claim in order to render it allowable under this Article.

Article 123(2) EPC

The following objections under this provision of the EPC were raised:

(i) The concentrations mentioned in part (i)(1) of claim 1 were originally disclosed only in the context of the addition of exogenous APC, and not in the context of the addition of exogenous Protein C with the reagents necessary to convert the Protein C to APC in the final assay and further not in the context of both the extrinsic and intrinsic pathway.

(ii) The introduction of the feature "*absence of lupus anticoagulants*" in claim 1 amounted to including subject matter in the claim which was not originally disclosed. It was a feature taken out of a specific example of the specification (WO/63/10261, page 3, lines 32 to 37) in which all those causes were excluded which were said not to be responsible for APC resistance. To exclude solely lupus anticoagulants from the claim leaving out all the other factors mentioned in the example was, according to decision T 284/94, not admissible under Article 123(2) EPC. The reason why the respondents did not want to exclude from the claim among other factors also FV, namely that it turned out later that actually a mutation of this factor was the cause of APC resistance, could not remedy the fact that a restriction of the claim by an unallowable selection was made.

(iii) The change of the words " ... *to acquire the disorder* ..." as used in the claims of the application as filed into " ... *to acquire manifestation of a blood coagulation disorder* ..." in claim 1 also violated Article 123(2) EPC because the expression "manifestation" has to be understood as a genetically inherited manifestation which furthermore implied an outbreak of the disease which is different to the understanding of the expression "acquire" without a reference to "manifestation".

(iv) In claim 1 of the new request in step (iii) it is now said: "... *under the **same** conditions as the plasma sample from said human*," whereas in claim 1 as originally filed the conditions were qualified as "*identical*". The "same" however was not the same as

"identical" and amounted to an extension of the subject matter as originally filed.

(v) Finally, the deletion of the word "*and*" in claim 13 of the new main request from the former expression "*and/or*" in the context of activating the extrinsic/intrinsic pathway changed the subject matter of this claim in an unallowable way.

Article 123(3) EPC

Claim 1 as granted covered methods for diagnosing in a human, or determining the risk of a human acquiring a blood coagulation disorder designated APC resistance. Claim 1 as amended now after grant covered methods for diagnosing thromboembolic diseases caused by APC resistance, rather than APC itself. Accordingly, claim 1 now covered methods of diagnosis which were not covered by the granted claims whose scope was, thus, extended contrary to the requirement of Article 123(3) EPC.

Article 83 EPC

Since the blood coagulation disorder was only vaguely identified and its cause unknown, it was not possible to identify the persons, the plasma of which had to be excluded from the "normal pooled plasma". Thus, the plasma of individuals carrying a defective FV_a could have been included in the normal pooled plasma, because of the erroneous teaching of the patent in suit on the non-involvement of this factor in APC resistance, which was only corrected in post-published document (19). Furthermore, in the claimed method the plasma from

"normal" individuals was used as a reference. However, the patent in suit did not disclose a way of determining whether a person fulfilled this criterion other than by comparison with plasma from a "normal" individual which in turn was the very subject matter of the claim to be identified. This kind of circular teaching did not enable the skilled person to carry out the invention.

The assays required for the determination of normal levels of functional Protein S, functional FVIII and the absence of lupus antibodies were insufficiently described in the patent in suit, but even if they were, their reliability was questionable, since, in the case of the determination of a potentially defective FVIII, the results given in the patent in suit were in contradiction with those disclosed in document (2), although both had been achieved using the same assay.

The prevalence of APC resistance in the population of individuals with a healthy appearance was not described in the patent in suit, but only in post-published documents (31) and (51). Furthermore, in document (27) the distinction between normal and pathologically APC resistant individuals was said on page 159, even in 1992, i.e. after the priority date of the patent in suit, to be a major problem, as a certain percentage of apparently healthy individuals were found to be APC resistant. In post-published document (29), individuals with an abnormally low APC ratio were not excluded from the group of healthy individuals for the determination of the standard value. Since both documents emanated from the laboratory of the respondent, they showed that not even this group used after the priority date of the

patent in suit a standard value obtained after exclusion from the normal pooled plasma of the plasma of healthy individuals showing nevertheless an abnormally low response to exogenous APC.

Article 54 EPC

The disclosure of documents (1), (2), (3) and (5) was novelty destroying for the subject matter as claimed since they all described a method for determining a blood coagulation disorder. The feature in claim 1 relating to blood samples from normal individuals to be used for comparison and the concentration ranges were not suited to distinguish what was claimed from the prior art documents since firstly the claim did not exclude pooled normal plasma as used in the prior art and it was anyway a matter of routine to determine a standard value as shown *inter alia* in document (63); secondly the concentration ranges were so broad that any use of the respective substances in the prior art fell under these ranges.

Article 56 EPC

The teaching of document (1) or (2) were considered to render the claimed subject matter obvious for the skilled person if the problem to be solved was a modification of the assays described therein. The close relationship of Article 83 and Article 56 applied in this case because either it was obvious to depart from these documents and to arrive at the claimed subject matter by routinely improving the assays described in the mentioned documents or if it was not, then the patent specification did not provide the skilled person

with the information necessary to carry out the invention. This was so because the "standard value" necessary to get the comparative data for arriving at the desired information whether or not there was APC resistance or a prevalence for it could either not be achieved because the selection of comparative samples from "normal" individuals always could contain samples from undetected APC resistant individuals (Article 83 EPC) or if it was feasible to get standard or reference values as was e.g. described in document (63), then the method as claimed was obvious (Article 56 EPC). Again here was a circular teaching because one first had to know that the standard samples did not contain blood from individuals which suffered from APC resistance before it could be used as standard to test on APC resistance. To establish this "standard value" however, was the alleged invention as claimed. In particular document (2) disclosed the same method by quantifying the sensitivity and showed also the inheritance of APC resistance.

Adaptation of the description

The sentence on page 6, lines 27 to 29 of the patent specification had to be deleted or amended because according to Article 69 EPC the claims were to be interpreted in the light of this sentence and then the scope of claim 1, first restricted, was again extended.

IX. The arguments submitted by the respondents can be summarised as follows:

Rule 57(a) EPC

The argument put forward by appellant II that the amendment "*thromboembolic diseases caused by*" in claim 1 of the new main request was not caused by the oppositions was wrong because it was the opponents who emphasised the necessity to insert into the claim the cause of the coagulation disorder.

Article 84 EPC

To insert into the claim all other potential causes for APC referred to in the specification, and discarded therein as irrelevant, into claim 1, as demanded by the appellants would not add clarity to it. The wording of the claim provided for a simple, very successful and reliable way for the diagnosis of the blood coagulation disorder under consideration and was clear and concise as required by the law.

Article 123(2) EPC

All the objections raised by the appellants (see section VIII above under the heading Article 123(2) EPC points (i) to (v)) were answered (see also reasons for the decision point 7).

Article 123(3) EPC

The insertion of the term "*thromboembolic diseases caused by*" served to identify the invention more clearly and did not amount to an extension of the scope of the claim because it merely specified the disease.

Article 83 EPC

The patent in suit disclosed the claimed method by stating that the plasmas of healthy individuals had to be separately tested to define the standard value and that a substrate conversion rate higher than the standard value was indicative of APC resistance, so that the skilled person was not only provided with the method to be used, but also with a criterion to interpret the results obtained. Therefore, the knowledge of the true cause for APC resistance was not required for the performance of the claimed method and the determination of the standard value. The prevalence was described in the patent in suit by reference to the study carried out on 100 patients with diagnosed thrombosis, which showed that 10% of them exhibited APC resistance, despite being negative in other commonly used blood coagulation assays.

Assays for the determination of normal levels of functional Protein S, FVIII and for the absence of lupus anticoagulants were mentioned in the patent in suit and were routine assays at the priority date of the patent in suit.

Article 54 EPC

None of the documents (1), (2), (3) or (5) mentioned the concentration ranges of claim 1 or taught to separately test the plasmas of healthy individuals to determine the standard value.

Article 56 EPC

Documents (1), (2) and (3) each reported on the results of blood coagulation tests relating to the effect of Protein C which tests had been carried out on one patient only in each case. The objective technical problem to be solved in the light of these isolated studies was the provision of a general *in vitro* test for diagnosing in a human thromboembolic diseases caused by or determining the risk of a human to acquire manifestation of a blood coagulation disorder designated APC resistance in a more accurate way. The solution defined by the special combination of features mentioned in claim 1 could not be deduced from documents (1) or (2), each of them being considered as the closest prior art, since they did not give any hint to increase the sensitivity of the known methods, the prevalence of APC resistance, the inheritability of APC resistance or that patients suffering from APC resistance showed negative results in hitherto commonly used blood coagulation assays.

Adaptation of the description

The sentences on page 6, lines 27 to 29 of the patent in suit did not modify the understanding of claim 1 and did not need to be amended or deleted.

X. The appellants requested that the decision under appeal be set aside and that European patent No. 0 608 235 be revoked.

The respondent (patentee) requested that the decision under appeal be set aside and the patent be maintained

on the basis of claims 1 to 23 and amended description filed at the oral proceedings.

Reasons for the Decision

Procedural matters

Admissibility of the appeal of appellant III

1. The board refers to the facts set out in section IV above. The decision of the opposition division was not notified to opponent (5) in accordance with Rule 78(1) EPC. The opposition file shows that the pertinent advice of delivery carrying the address of opponent (5) had been signed by an unidentified person in Nottingham (UK). In such a case Rule 82 EPC applies which governs the case of irregularities in the notification. Accordingly, given that a copy of the decision of the opposition division was received according to the evidence provided by appellant III on 22 November 2000, the decision of the opposition division shall be deemed to have been notified on that day which is established by the board as the date of receipt. The appeal was filed on 23 November 2000 and the appeal fee paid at the same day. The statement of grounds was filed on 20 March 2001 and, thus, the requirements of Article 108 EPC are fulfilled and this appeal is admissible.

Article 113(1) EPC

2. Appellant I alleges that in the oral proceedings before the opposition division not sufficient time was provided to consider adequately the amended claims

submitted by the Respondent which resulted in a denial of the right to be heard contrary to the provision of the above-mentioned article of the EPC. As evidence the statement in the decision under appeal in point 6.2 was quoted.

3. The board firstly observes that the minutes of the oral proceedings before the opposition division do not provide evidence that amendments in the claims in the newly filed request by the patentee were not sufficiently discussed. Rather to the contrary it can be concluded from page 1, last three paragraphs to page 2, first four paragraphs of the minutes that the opposition division invited all parties to the proceedings to discuss the newly filed requests in particular in the framework of Article 123(2) EPC. In this context no objection was raised by opponent (1) against the admissibility of the new request or a request for a delay or a break of the oral proceedings was filed in order to have more time to study the new request.

4. Secondly, in paragraph 6.2 of the decision under appeal it is stated in relation to inventive step that the amendments made by the patentee in the claims of the request under consideration render many objections raised by the opponents during the written proceedings of little relevance. In the board's view this can hardly be seen as an evidence that the opposition division have violated the right to be heard.

Rule 57(a) EPC

5. The logic of the statement of appellant II (see section VIII above) seems to be that the wording in claim 1 of the new main request " ... *thromboembolic diseases caused by* ..." either violated the requirements of Article 123(3) EPC or, if not, the amendment is against Rule 57(a) EPC, i.e. this amendment was not caused by the objections raised in the oppositions. In other words, appellant II seems to argue that the respondent is in a trap: a certain feature was required to be in the claim and if the respondent reacts accordingly, and thus there would be no case of Rule 57(a) EPC because the amendment was carried out in a reaction to objections by the appellants, it is argued that it now violates Article 123(3) EPC. In the board's view there is no violation of Rule 57(a) EPC since, as maintained by the respondent (see above section IX), the amendment under consideration was a reaction to the oppositions insisting that the cause of the disease has to be in the claim. Moreover the amendment does not violate Article 123(3) for the reasons given below in point 8.

Article 84 EPC

6. The board agrees to the respondent's position (see section IX above) that the steps to be carried out in the method as claimed are defined in a clear way and any addition of features excluding what was found not to be the cause for APC resistance would, if anything, render the claim more unclear. In particular the incorporation of e.g. FV into the claim would not add clarity because it was accepted by the respondent that the inventor erred in assuming that this factor was not

the cause of the APC resistance. However, the knowledge of the correct molecular/physiological mechanism underlying the invention is not necessary for the claimed method and to incorporate into a claim something which turned out later to be wrong seems to be just the opposite of what one would think of in the framework of clarity.

Evidently no case of lack of clarity can be made out for the concentration ranges in the claim.

Article 123(2) EPC

7. The appellants argued that there was added matter introduced by a number of amendments in claim 1 (see section VIII above) which the board answers as follows in the same order:

(i) The concentration ranges in claim 1 are taken identically from the specification in method A (page 8, lines 16 to 31) and the objection raised by the appellants seems not to be against the ranges as such. They rather argue that it is claimed now that the ranges referred to added exogenous APC or exogenous Protein C together with exogenous activators of it to produce APC to be in "*the final assay medium*" and for this there was no basis in the application as filed. The board agrees that there is no *expressis verbis* disclosure of this context but is nonetheless convinced that for the skilled person there is an implicit but clear and unambiguous teaching, as required by the established case law of the boards of appeal, that in Method A it has to be the concentration of APC in the final assay which matters. This is so because it is

only this substance which is the one to be tested in the given context and it is the very aim of the method as claimed to test the effect of APC in a given coagulation system and it is, therefore, the only sensible and technically meaningful understanding of the ranges given in Method A as now claimed.

As far as there were objections raised that the concentration ranges were not disclosed in relation to both the extrinsic and intrinsic pathway the board observes that the concentration ranges are disclosed on page 8, lines 16 to 32 of the application as filed in relation to "combination A", which is an embodiment of the intrinsic pathway. They are also used in the other combinations mentioned and, in particular, in "combination E" which is an embodiment of the extrinsic pathway.

(ii) The incorporation into the claim of the words "*and absence of lupus anticoagulants*" while keeping in the claim "*even in the presence of normal levels of functional Protein S, Factors V_a and $VIII_a$*", was, as argued by the appellants, a kind of "selection invention" unallowable under Article 123(2) EPC. However, the board observes that on page 13, lines 36 to 37 of the application as filed it is said that "*The ATP-time together with values for ATIII and Protein S were normal and the patient had no indication of the presence of lupus anticoagulants.*" On the basis of this the board cannot see a violation of the requirement of this provision of the EPC in the sense of an unallowable selection. The attention drawn by appellant III to decision T 284/94 of 25 November 1998 as support for their argument does not help his case. There, a

special feature from a preferred embodiment was taken into the claim without all other elements to characterize the invention. This is quite a different technical situation from the one in the present case, where the mentioning of those elements which tested "normal" were not taken out from a particular example or a preferred embodiment. Only in these cases the established case law for which decision T 284/94 is representative requires to include all technical features closely connected.

(iii) The argument by the appellants that the phrase in the claim under consideration " ... *for determining the risk of a human to acquire manifestation of* ..." was not originally disclosed and thus amounted to added matter does not convince the board. While it is agreed that there is in this field a difference between an "inherited" and an "acquired" disease (see e.g. document (63)) and also that the word "manifestation" is not *expressis verbis* mentioned in the application as filed, the board, however, observes that it is said on page 1, lines 2 to 4 that the method is appropriate for screening and diagnosis of throboembolic diseases, e.g. hereditary thrombophilia and on page 5, lines 7 and 8 that " ... *the individual from which the sample derives is classified as suffering from the disorder* ...". From this it follows clearly and unambiguously, as required by the established case law in the case of an implicit disclosure, that the disorder, whether inherited or acquired, is recognisable by its manifestation.

(iv) The change of the word "*identical*" in claim 1 of the application as originally filed to the word "*same*" in claim 1 of the new main request is allowable under

this provision of the EPC because these words are technically the "same/identical" in the context of the claimed method. Both mean that the samples to be compared have to be treated such that the claimed aim is arrived at, namely to distinguish them or not, as the case may be, to be able to establish whether there is a disorder or not. It is evident for the skilled person when carrying out comparative test that this precondition has to be fulfilled notwithstanding the fact that there may be some sophisticated nuances between the meaning of the words "identical" and "same".

(v) The deletion of the word "*or*" in the expression "*and/or*" in claim 13 of the new main request results in a meaning which is the same as the expression "respective" in this context in originally filed claim 3 and is, thus, allowable under this provision of the EPC.

It follows that none of the numerous objections raised by the appellants convince the board and claims 1 and 13 of the new request fulfil the requirement of Article 123(2) EPC.

Article 123(3) EPC

8. The beginning of claim 1 of the new main request now reads: "An in vitro method for diagnosing in a human **thromboembolic diseases caused by**, ... a blood coagulation disorder designated APC resistance ..." instead of: "An in vitro method for diagnosing in human ... a blood coagulation disorder designated APC resistance ..." as in the claim as granted. The phrase

in bold type was introduced by the respondent into the claim as an answer to the respective objection raised by the appellants (see also point 5 above). Compared with claim 1 as granted the disease which is to be diagnosed by the claimed method is defined and this disease is said to be caused by APC resistance. Appellant I, however, argues that now other/more diseases to be diagnosed are covered by a claim by this definition than by the granted claim because now diseases "caused by" are to be assayed rather than APC resistance itself. The board finds it difficult to see the convincing power in this argument when considering this in the light of the whole disclosure of the patent in suit which teaches how to find APC resistance in a patient whatever the pathway in the complicated part of the coagulation system here at stake may be, given that it is both in the granted claim and now the manifestation of the APC resistance in the symptom of a thromboembolic disease which matters. Thus, there is no violation of Article 123(3) EPC.

Article 83 EPC

9. Not even appellant III contested in the oral proceedings that the method steps as such in claim 1 which are correspondingly described in the patent specification can be put into practice as required by Article 83 EPC requiring that the invention must be described in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

10. Rather it was argued that the claim has to be judged under this article in close connection with the requirement of inventive step (Article 56 EPC). If the

skilled person was able to carry out the invention despite the poor description which had to be combined with common general knowledge then it was for the same skilled person with the help of common general knowledge obvious to modify the teaching in the prior art to arrive at the claimed method. The key feature which, according to the appellants, renders the claim unworkable under Article 83 EPC is the alleged "circular teaching" in view of the determination of the standard value. In fact claim 1 requires under step (iii) that the conversion rate measured in step (ii) has to be compared with a standard value. However, it is said that these values have to be obtained from samples from normal individuals, which samples have been subjected to steps (i) and (ii) under the same conditions as the plasma sample from the human to be tested. That is to say, the "control" first has to be identified as a reliable standard with the method steps (i) and (ii) to be used as comparison in the method step (iii). While the board accepts that this is "a method within a method" to define a standard value it fails to see how this can be a basis for the argument that the claimed method cannot be carried out. It was the inventor who found out that the standard values derived from blood samples of individuals whose appearance is healthy first have to be tested with the method he invented whether they are suited as standards because of a possibly "hidden" prevalence of the disease. This was, until the invention was made, not known. While the arguments of the appellants may have a certain bearing on the question of how the inventor himself might have detected the prevalence, they do not succeed in convincing the board that this renders the method unworkable which now advises the reader what to

do because it is stated in the application and in the claim how to establish the standard value. It is exemplified in the "Experimental Part" from page 6, line 32 to page 8, line 40. A criterion is also indicated in order to distinguish healthy individuals from those showing APC resistance, namely a higher substrate conversion rate for an enzyme, the activity of which is influenced by APC. Finally, in the "Experimental Part" of the patent in suit the method of claim 1 is shown to lead to the identification of APC resistance in the patient studied, as well as in ten of 18 of his relatives and in 10% of 100 patients with diagnosed thrombosis which were, nevertheless, found negative in other blood coagulation assays (page 8, lines 13 to 16 of the patent in suit), in view of which they would have been considered as "healthy" individuals. This result provides the skilled person with the prevalence of APC resistance in the "healthy" or "normal" population, which is hence not deduced from post-published documents (31) and (51), as argued by the appellants.

11. In the above context of the balance between the requirements of sufficiency and inventive step it was also argued by the appellants that there is no disclosure in the patent in suit that the samples used from "normal" individuals may not be pooled plasma samples, i.e. a mixture of many blood samples collected from individuals, which would not be suited to exclude in the steps (i) and (ii) of the claimed method to sort out the "hidden" unsuited samples. The board agrees that pooled plasma may not be suited to establish the standard value necessary for the method to be carried out but also is convinced by the respondent's

argumentation that the wording in step (iii) of the claimed method "*comparing the conversion rate measured in step (ii) with a standard value* ***obtained from samples from normal individuals ...***" does give the skilled person the information that the samples for obtaining the comparative values have to be individual ones because this is the only sensible way to read this phrase in the context of what is disclosed in the patent specification to be the aim of the invention, and steps (i), (ii) and (iii) in claim 1 advise the skilled person how to achieve the standard value. This position is *inter alia* supported by document (68), filed by appellant III to support a different argument, which describes the concepts, requirements and preparation of so-called reference plasmas and without exception defines these as pooled plasmas which is seen by the board as evidence that it was standard to use pooled plasma and to name it so.

12. When arguing against inventive step appellant III draws attention to the disclosure of document (60) and derives from it that in particular in cases where the cause of a disease is unknown or the method used is new the skilled person in the field of coagulation diagnosis would determine the samples of patients separately. The board, however, is unable to see this disclosure in document (60) but rather sees support for the opinion stated above in the statement on page 704, left hand column, second paragraph und the heading "Protein C Deficiency", lines 9 to 11: "*Laboratories must establish their own normal ranges for the particular assay method they are using ...*" since apparently in the prior art the term "normal" was used for "pooled" plasma.

13. A further argument put forward by the appellants for lack of sufficient disclosure is that documents (27) and (29) are publications where the inventor is one of the authors and not even he, quite a while after the priority date, did apply the method as claimed. The reasons why a patented method may not have been applied in a later study may be so manifold that the board cannot see convincing evidence in this line of argumentation but observes that in document (27) on page 158, last paragraph, it is said: "*In September 1991 the APC-resistance test was ready for use in the routine laboratory ...*" The priority date of the patent in suit is November 1991 and it seems to be more likely than not that the inventor referred to his invention. Furthermore, on page 159 second full paragraph it is stated: "*A major problem at the time was distinguishing between a normal and a pathological APC-resistance as several apparently healthy individuals were also found to be APC resistant. We now know that approximately 10% of the Swedish population has the factor V gene mutation which causes APC resistance, but this was of course not easily envisioned in the early days of the assay.*" While in particular this passage was quoted by the appellants to show that the inventor erred in the patent in suit when excluding factor V as cause for the APC resistance (which, however, as stated below in point 15 has also no negative consequence for the requirements of Article 83 EPC) the mention of the early days of **the** assay is, if anything, for the board rather support for the view that the inventor in his later publication has used the method of claim 1 than evidence against.

14. It was further submitted by the appellants that the tests for the normal level of all other factors being involved in the blood coagulation cascade here in question were not disclosed sufficiently and even if, they were not reliable. In the patent specification it is indicated as to how to carry out these determinations with reference to common assays (page 2, lines 52 to page 3, line 2 and lines 8 to 14 and page 6, line 48 to page 7, line 1). Even if, as argued, there was a contradiction as to the potential defect of FVIII in the patent in suit and document (2), both using the same assay, this does not amount to an insufficient disclosure because, in the board's view, these tests were known and used by the skilled person at the priority date of the patent in suit as shown by the coagulation profile disclosed in Table 1 of document (1), the disclosure of document (12) from page 971 (left column) to page 977 concerning the determination of various proenzymes, cofactors, activators or inhibitors of the blood coagulation system and the teaching of document (65) on the determination of Protein C, Protein S (page 438, right column to page 411) and of Factors VII, IX and X (page 422, left column). In document (5) assays for the determination of Factors V, VII, VIII, IX, X and XI are disclosed from page 13, line 23 to page 16 line 3.

15. Finally, the method can be carried out without the molecular/physiological/genetic understanding for the APC resistance. Whether or not the claimed method is suited to find out the molecular reason for the disease is not the question here but rather whether it can be reliably applied in order to establish a coagulation disorder related to APC resistance whatever the reason

for it may be. It is the result of the comparison of the coagulation time data to be established with the claimed method in step (4)(iii) which provides the desired information of whether or not an individual to be tested suffers from APC resistance or the risk to acquire thromboembolic diseases caused by APC resistance and the board is convinced that this result can be achieved by following the method steps claimed.

Article 54 EPC

16. The board agrees with the line of argument by the respondent against the appellant's objections raised against the novelty of the *in vitro* method of claim 1 of the new main request, namely that none of documents (1), (2), (3) or (5), although all of them are describing a method for determining a blood coagulation disorder, discloses the concentration ranges in paragraphs (i)(1) and (i)(3) of the claim for exogenous APC or Protein C together with current exogenous reagent to transform the exogenous Protein C to APC with which the plasma sample is to be incubated and the Ca-concentration in the final assay. Already for this reason alone novelty is to be acknowledged and there is no need to answer all other lines of arguments under this provision submitted by the appellants, with the exception, however, of an argument raised by appellant III, namely that the ranges were so broad that virtually every application of APC or Protein C together with an activator in a method for testing on a blood disorder and Ca-concentrations as disclosed in the relevant documents fell necessarily under these broad ranges and were, thus, novelty-destroying. Appellant III seems here to argue with reference to the

case law of the boards of appeal on, albeit implicit, nonetheless clear and unambiguous, and thereby novelty-destroying disclosure in a piece of prior art. The board fails to see the clear and unambiguous disclosure of ranges. To find a lack of novelty would go against a plethora of decisions and thus the established case law of the boards of appeal, which acknowledge novelty if and when an undefined area in a prior art document is specified by defined elements - in the present case the concentration ranges - in a claim under consideration.

17. Therefore, no case has been made out for lack of novelty and thus the requirement of Article 54 EPC is met by the subject matter of claim 1 of the new main request.

Article 56 EPC

18. The parties consider the disclosures of documents (1) and (2) as equally suited to represent the closest prior art for the application of the problem-solution approach. The board agrees.

19. Document (1) describes the identification of an inhibitor of the Protein C anticoagulant pathway in the plasma of a patient with systemic lupus erythematosus and a history of recurrent deep vein thrombosis. A modified prothrombin time assay is described on pages 248 and 250 in the respective last paragraphs and a comparison of the patient's plasma with "normal pooled plasma" was made. The activated Protein C-mediated prolongation of the clotting time observed in normal plasma was not observed in this patient's plasma. In the discussion on page 255 it is speculated what the

reason for the observed inhibition of the activated Protein C coagulation time might be and it is stated that "... *our modified prothrombin time assay may be of considerable value as a sensitive prognosticator of thromboses in patients with lupus-anticoagulants and/or anticardiolipin antibody.*"

20. Also the disclosure of document (2) relates to a single patient with multiple thrombosis. The functional Protein C assays carried out reveal no clear picture but it is said that the results " ... *did not suggest the presence of a strong inhibitor.*" (line 14 of the single page of this document). In lines 16 and 17 it is further stated that: "*This was a strong indication against an inhibitor of immunoglobulin type.*"

21. On the basis of this prior art the problem to be solved can be seen in an improvement of the assay. In view of the experimental part of the patent in suit the board is satisfied that the claimed method solves this problem.

22. The respondent put the emphasis when arguing inventive step on the finding of the inventor not to use pooled plasma as reference but rather separately to test the plasma samples of healthy individuals for APC resistance to define the standard value to exclude undetected disorders which would render the reference unsuitable for carrying out the method. This position was counter-argued by all appellants who in particular submitted that this decisive feature was not originally disclosed and if, then it was equally feasible for the same skilled person to implement this missing teaching

into the prior art documents and thereby to arrive at the claimed method.

23. The answer by the respondent was that without the teaching of the patent in suit of the "prevalence" of the disease and the "sensitivity" of the method the skilled person would not have had the idea of separately testing the plasma of normal individuals for APC resistance to define the standard value.

24. The board has accepted that for the method in the patent in suit as how to establish the standard value by screening individual samples of apparently healthy persons, the requirement of Article 83 is met (see points 9 to 15 above). The board cannot see that this case is one of those where a balanced consideration of the requirement of this article with the establishment of an inventive step mattered. The case law relating to this "balance" (e.g. T 694/92, OJ EPO 1997, 408) relates to situations where the state of the art is very close (Article 56 EPC) and it is then required that the disclosure in the patent provides for sufficient disclosure that all embodiments falling under a given broad claim can be carried out by a skilled person. In the present case, however, quite a different picture is painted to the skilled reader of the disclosure of documents (1) and (2), when unaffected by the knowledge of the invention. The board agrees to the position of the respondent that only with knowledge of the sensitivity and about the prevalence was it possible to arrive at the claimed invention and to read into these documents any hint to the claimed solution would amount to the application of non-allowed hindsight. The board, thus, considers that there is no

hint in these documents to further develop any of the assays used there because the prevalence was not known, so that first the window had to be opened to see the direction to improve any of the assays in the prior art. In this context the board draws attention to the passages quoted from both documents above in points 19 and 20, where there are contradictory speculations stated for the APC resistance (antibody in document (1); no antibody in document (2)) and, seen without hindsight, the skilled person was still in the dark and would certainly not have been in a one way street situation which method to further investigate for providing a reliable method to diagnose APC resistance.

25. The board further observes that the skilled person being confronted with the teaching of document (2) speculating about an antibody as the inhibiting agent would also have taken into consideration the disclosure of document (3) which reports a fatal thrombotic disorder in a patient " ... *with an IgG paraprotein .... The IgG fraction of the patient's plasma completely inhibited the functional anticoagulation activity of activated protein* C." Here, the authors did not even only speculate on the antibody to be the causative agent for APC resistance but seemed to be sure that this was so. In the light of this, in the board's view, the skilled person would have rather further pursued the route to identify the inhibiting antibody.

26. It follows from what is said in points 24 and 25 above that, even if one were to assume that the skilled person could have turned to a modification of the assay described in document (2) which did not draw the

reader's attention to an antibody as inhibiting agent he would not have done it.

27. Finally, the teaching of document (6) which is a study on the anticoagulant activity of Protein C in uremic patients is for the board also indicative for an inventive step. The results of this study are expressed in Figure 1 in the form of a dot plot. This dot plot also includes the values given by 39 normal individuals: the left part of Figure 1 is concerned with APC activity and in the group of the healthy individuals two points are slightly lower than the values given by the other 37 healthy individuals. Although the authors of document (6) were concerned with APC resistance, they have not recognised this result as indicative of the occurrence of a certain amount of APC resistance in healthy individuals. The disclosure of document (6) hence stands in contradiction with the argument of the appellants that the average skilled person would obviously have modified assays of prior art documents to arrive at the claimed invention.

28. Thus, the method of claim 1 of the new main request is inventive. Claims 2 to 23 are dependent claims and, therefore, also inventive. The requirement of Article 56 EPC is fulfilled.

Adaptation of the description

29. The passage in the description which was considered by the appellants as broadening again the scope of claim 1 as now restricted reads: "*In principle the inventive method will detect disorders related to defective interactions between activated Protein C and Factor* V_a,

Factor VIII$_a$. It will also detect the presence of inhibitors of activated Protein C, and abnormalities in hitherto unrecognized interactions and factors influenced by Protein C activation or activated Protein C activity." The board agrees that this sentence informs the reader about what can possibly be achieved with the claimed method in terms of finding out what the molecular basis for APC resistance might be. The board, however, sees this passage in this very context so that it neither adds anything to the claimed method nor misleads the reader even though it turned out only later that actually a defect FV was the reason for the APC resistance. The method may work or not in further identifying the reason for APC resistance but that does not matter as long as the method as claimed can determine an APC resistance as such, whatever the reason for it may be.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 23 and amended description (pages 2 to 8) filed at the oral proceedings

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey