BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: T 594/89 - 3.3.2

Application No.: 83 108 933.9

Publication No.: 0 103 288

Title of invention: Multilayer analytical element

Classification: C12Q 1/28

D E C I S I O N
of 18 July 1991

Proprietor of the patent: Fuji Photo Film Co., Ltd.

Opponent: Eastman Kodak Company

Headword: Analytical element/FUJI

EPC Art. 56

Keyword: "Inventive step (yes) - not foreseeable improvement - additional unexpected advantage"

Headnote

Case Number : T 594/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 July 1991

Appellant : (Opponent)
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Decision under appeal :
Interlocutory decision of the Opposition Division of the European Patent Office dated 9 August 1989 concerning maintenance of European patent No. 0 103 288 in amended form.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : A.J. Nuss
M.K.S. Aúz Castro

Summary of Facts and Submissions

I. European patent No. 0 103 288 was granted with ten claims on European patent application No. 83 108 933.9.

II. The Appellant (Opponent) filed a notice of opposition against the European patent requesting revocation of the patent on the ground that its subject-matter was not patentable within the meaning of the terms of Articles 52-57 EPC.

Eight documents were cited in support of the opposition of which the following remain relevant in this appeal.

(I) US-A-4 322 496
(VI) US-A-4 098 574
(VIII) "Interferographs" (Science Enterprises, Inc., 1987).

III. In its interlocutory decision, the Opposition Division decided to maintain the patent in amended form with the text as notified to the parties in the communication pursuant to Rule 58(4) EPC issued on 3 August 1988.

In its decision the Opposition Division accepted the technical problem as stated in column 2, lines 5 to 20 of the patent in suit and took the view that according to Claim 1 this problem was solved by incorporating in one of the layers of an analytical element such as previously described in US-A-4 292 272 (cited in the description of the patent in suit and hereinafter referred to as document (IX)), a specific water-soluble monocarboxylic acid or a salt thereof. However, none of the opposed documents referred to this problem. In document (I) several specific acids like glycolic and oxalic acid were used to act as inhibitor against undesired enzymes. Other

related acids such as methoxyacetic acid were stated to be ineffective as inhibitors. In view of the difference in the problem and the solution found to it, this citation did not therefore render obvious the subject-matter of the patent in suit.

In document (VI) acids or buffers such as dimethylglutaric acid were used to solve the problem of apparent reduction of measured glucose concentrations in blood containing sodium fluoride as a preservative. However, as shown by Table 3 of the patent in suit these substances were less effective than the claimed ones and even inferior to a composition free of added acid. Document (VIII) neither provided adequate nor sufficient information to establish that only at very high levels of hemolysate any interference was likely to be observed. In these circumstances, the existence of catalase interference stated in the patent in suit could not be denied. Therefore, this attack upon inventive step also failed.

In addition, the results in Table 3 of the patent in suit showed a distinct effect and clearly were not of random distribution as would be expected by results showing experimental error of an unspecified nature. Therefore, the Opponent's view that these results seemed to be purely the result of experimental error could not be accepted either.

IV. The Appellant lodged an appeal against the said decision.

The arguments of the Appellant both in the written procedure and at the oral proceedings on 18 July 1991 may be summarised as follows.

The Respondent (Proprietor of the patent) had failed to establish the existence of a general problem of catalase

interference with all the analytical elements of the type claimed. Moreover, document (VIII) described tests carried out on EKTACHEM DT60 and EKTACHEM 700, both commercial analysers, with elements including all of the components of the present patent claims, except for the monocarboxylic acid, supporting the non-existence of interference with hemolysed samples. Hence, no difference could come from hemolysis caused by ruptured red blood cells in a sample or by adding hemolysate from an outside source. In confirmation of these arguments, the Appellant had filed a statement of the Head of the Clinical Diagnostics Center in the Research Laboratories of the Appellant's company, Dr. Sundberg, which expressed the opinion that if a clinical determination exhibited any significant amount of interference from hemolysis, that either method (i.e. the test procedure according to document (VIII) or to the patent in suit) would illustrate this. However, without having to contest the data provided in the patent in suit, it was likely that the Patentee's catalase problem was due to the particular type of element used in the patent in suit. Since the present claims were not limited to an element producing the effect of decreased interference due to hemolysed samples, they should be considered to go beyond the problem that was solved. Moreover, in accordance with common practice in wet chemistry tests, a man skilled in the art could easily have incorporated a well known acid-like acetic acid or a salt thereof into a dry multilayer element of the type described in document (VI) in order to adjust the pH or as part of a buffer composition. The activity of enzymes being generally known to be pH dependent, it was indeed already normal practice to adjust the pH at an optimum value. Therefore, if left unchallenged, the present claims might be interpreted to include any element comprising such a well-known acid or buffer, in spite of the fact that such an element would not necessarily provide the

alleged effect. Furthermore, some of the acids described in the patent in suit as being suitable for increasing the optical density were also examples of those substances which could serve for adjusting the pH of the layers of the claimed analytical element. Although Table 3 of the patent in suit showed some insignificant improvement of the optical density of the formed colour when using the claimed acids, these results could at most be regarded as a direct consequence of usual routine pH optimisation carried out by the man skilled in the art. Under these circumstances hundreds of tests would have been required in order to establish statistical significance. No comparison test could actually be provided because there was no problem to be solved. Therefore, even if there were results which could be considered as unexpected, the claims should be limited to analytical elements for which such a result was obtained, viz. those comprising a fibrous, anisotropically porous spreading layer consisting of water-washed fabrics as disclosed in document (IX). At least Claim 1 should specify that a buffer (system) could be present in a layer other than the support layer to adjust the optimum pH of the peroxidase.

V. The Respondent argued that the Opposition Division was right to note the absence of any suggestion in the prior art. Neither document (VIII), published after the priority date of the patent in suit, nor the statement of Dr. Sundberg could provide arguments against the patentability of the claimed subject-matter in connection with the problem of interference caused by catalase. According to document (VIII) many of the tested analytical systems were influenced greatly by hemolysate found in the serum specimens and most of the figures revealed that hemolysate had an effect on analytical results. In particular, glucose determination on EKTACHEM showed that hemolysis caused a decrease in measured values. As to the statement

of Dr. Sundberg, it was obvious that without revealing the facts on which this declaration was based, it could only reflect Dr. Sundberg's personal opinion. Consequently, the problem of catalase interference by hemolysis really existed. As shown in Table 3 of the patent in suit, the addition of the specific compounds claimed had the effect of clearly increasing the optical density of the formed colour.

As to the spreading layer used in the analytical element, there was no reason to assume that only water-washed fabric would be suitable in the present case as suggested by the Appellant. On the contrary, there could be no doubt on the basis of the description of the patent in suit that many other porous spreading layers could be used as well. In view of the explanations provided in the description of the patent in suit, it was also not necessary to mention in the main claim the possibility of adjusting the optimum pH of the peroxidase by adding a buffer.

VI. At the end of the hearing before the Board, the Appellant requested that the decision under appeal be set aside and that the European patent No. 0 103 288 be revoked, alternatively that the patent be maintained on the basis of auxiliary requests, whereby Claim 1 as submitted during opposition proceedings (see point III above) was suggested to be amended as follows:

auxiliary request 1: (additional matter to be included highlighted): ... a porous spreading layer consisting of a fibrous, anisotropically porous spreading layer consisting of water-washed fabrics as disclosed in US patent 4 292 272, which are superposed in this order ...;

auxiliary request 2: (additional matter to be included highlighted): ... said support contains besides a buffer

or buffer system which may be present to adjust the optimum pH of the peroxidase, a water-soluble monocarboxylic acid or salt thereof ... .

The Respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Claim 1 as amended during the opposition procedure (see point III above) is supported by Claims 1 to 3 and 6 as originally filed, together with page 10, line 33 to page 11, line 10 of the originally filed patent application (corresponds to Claims 1 to 3 as granted and to subject-matter disclosed in column 6, line 50 to 63 of the patent in suit). By this amendment the monocarboxylic acid is now specified to be selected from the group consisting of formic acid, acetic acid, propionic acid, butyric acid, valeric acid an aromatic-substituted aliphatic monocarboxylic acid, and an aromatic monocarboxylic acid, in conformity with original dependent Claims 2 and 3, whereby at the same time an oxidase is required to be contained in the reagent layer in accordance with the first alternative mentioned in original dependent Claim 6. The amended main claim does not contravene the provisions of Article 123(2) and (3) EPC.

The subject-matter of Claims 2 to 8 stems from Claims 3 to 5 and 7 to 10 as granted (corresponds to Claims 3 to 5 and 7 to 9 as originally filed, and to subject-matter disclosed on page 7, lines 15 to 18 of the original specification). Consequently, they also meet the requirements of Article 123 EPC.

3. The patent in suit relates to a multilayer analytical element.

3.1 At the oral proceedings before the Board, the parties were in agreement with the Board that in the present case the closest state of the art is document (IX). This document had also been considered in the Opposition Division's decision. It relates to a multilayer analytical element of the type claimed, with the difference, however, that none of the layers of the known element contains a monocarboxylic acid as defined in present Claim 1 (see Claim 1 and example 1 of document (IX)). This was not disputed by the parties.

As stated in the patent in suit, it was noted that with this known analytical element the optical density of colour formed in the reagent layer was reduced in the case of using a hemolytic whole blood or hemolytic plasma as a liquid sample, as compared with the case of using a non-hemolytic whole blood or non-hemolytic plasma as the liquid sample. It was further noted that glucose concentration in the former case was lower than in the latter case. Upon further studies, this problem was assumed to arise from interference by catalase or substances having a catalase activity contained in the blood (see column 2, lines 5 to 20).

3.2 In view of the above, the problem underlying the patent in suit is to be seen in providing a multilayer analytical element with increased optical density of the formed colour, when used in quantitative analysis of liquid samples subject to interference arising from hemolytic blood or plasma.

3.3 The solution to this problem is a multilayer analytical element as defined in present Claim 1, i.e. one containing in at least one layer other than the support a monocarboxylic acid selected from the group consisting of formic acid, acetic acid, propionic acid, butyric acid, valeric acid, an aromatic-substituted aliphatic monocarboxylic acid and an aromatic monocarboxylic acid.

3.4 Having regard to the experimental results reported in examples and control examples 2, 8 and 10 of the patent in suit, the Board is satisfied that the problem has been solved by the analytical element as defined in present Claim 1.

4. None of the documents considered in the present proceedings discloses the multilayer analytical element defined by Claim 1; the element claimed must thus be regarded as new. In any event, novelty is no longer in dispute.

5. It remains, therefore, to be considered whether or not the claimed solution to the above indicated technical problem meets the requirements of Article 56 in respect of inventive step.

5.1 None of the documents (I), (VI) and (IX) is concerned with the problem of altered optical density of colour formed in the reagent layer of a multilayer analytical element when used with hemolytic liquids (e.g. blood, plasma) and none of them mentions a monocarboxylic acid of the group as defined in Claim 1. Document (IX) is completely silent as to the inclusion of organic acids in analytical elements (see point 3.1 above), whereas in the other two documents carboxylic acids are added to one of the layers (reagent layer) of the element for a quite different purpose than in the patent in suit, these acids being moreover all

different from those listed in present Claim 1. This becomes plain from the following analysis.

Document (I) is concerned with finding an inhibitor to act against undesired lactate oxidase in enzymatic reagents in which the oxygen present catalyzes the direct conversion of lactic acid or lactate to pyruvate and hydrogen peroxide rather than water. As indicated there, the solution to this problem consists in the use of at least one inhibitor selected from the group consisting of glyoxalic acid, oxalic acid, glycolic acid, and salts thereof to reduce the activity of said oxidase on lactic acid and lactate. The action of these inhibitors is considered quite unique, because tests have demonstrated that many closely related chemical homologues and analogues (e.g. methoxyacetic acid, α- and ß-hydroxybutyric acid) are ineffective as inhibitors (see Claim 1; column 3, line 54 to column 4, line 21; column 7, line 7 to 17; column 8, lines 22 to 58).

Document (VI) relates to a test element useful in performing assays of glucose, especially in biological fluids, and which comprises a spreading layer and a reagent layer. In this citation, the problem consists in the reduction or elimination of assay influence due to fluoride interference as a consequence of the use of sodium fluoride as a preservative and it is solved by buffering the reagent composition to a pH between about 4.5 and 6.0. Buffers that have been found useful include dimethylglutaric acid, succinic acid, malic acid, potassium acid phtalate and mixed phosphate-citrate buffers, whereby 3,3-dimethylglutaric acid is preferred. Although the mechanism for this reduction or elimination is not completely understood, performance of the assay reactions within said pH range provides the desired result.

All this is sufficient to show that the cited documents do not contain any information which could have been used by the man skilled in the art when trying to solve the specific problem he was confronted with in the patent in suit.

5.2 As shown above, there is no prior art document relating to "dry chemistry" techniques in which it is suggested to add to one of the layers of the multilayer analytical element an acid as defined in the patent in suit. Consequently, the Board has no reason to believe that these acids are commonly used in such elements for adjusting the pH or as a buffer. As a matter of fact, in document (I) the buffer used in the reagent layer is a potassium phosphate buffer, pH 7.0 (see column 8, line 46/47), the carboxylic acid having - as already pointed out above - a quite different function (i.e. lactate oxidase inhibitor). As to the buffers disclosed in document (VI) for adjusting pH between a value of 4.5 to 6.0, they are without exception complex chemical compounds, such as aliphatic and aromatic diacids or mixtures of anorganic and organic triacids (phosphate-citrate buffers). All this leads rather to the assumption that pH control agents typically used in "dry chemistry" are not necessarily identical with those readily used in "wet chemistry" and among which acetate buffer is certainly a classical one. Moreover, what is really important is not that the man skilled could have used the said acids in a multilayer analytical element of the type claimed, but whether he would have done so in expectation of some improvement or advantage (see T 2/83, OJ EPO 1984, 265). In the present case, there is no support for the latter.

5.3 Since in the present case, the claimed solution has not been rendered obvious by the state of the art, it is

of no importance for the question of inventive step that, as indicated in the patent in suit, three of the monocarboxylic acids mentioned in present Claim 1 (i.e. acetic acid, propionic acid and butyric acid) may incidentally also be employed for adjusting the pH conditions of the reagent layer, other layers or the porous spreading layer of the analytical element. Moreover, it is quite clear from said patent that it is not essential for carrying out the claimed invention to use a pH control agent or a buffer and even less to use one of the claimed acids for pH control of the different layers of the element, which is supported by the fact that only under certain circumstances it might be preferred to use such agents (see column 9, line 44 to column 10, line 38). Obviously, in none of the examples of the description additional pH control agents or buffers are added, or said to be required, for carrying out the invention.

5.4 Whatever the scientific explanation for the above stated reduced optical density of the formed colour might be, the fact remains that the Respondent has shown in the patent in suit by way of experiment that the inclusion of a monocarboxylic acid, as defined in Claim 1, has the effect to substantially increase the optical density of formed colour (e.g. 0.62 vs. 0.54 and 0.45 vs. 0.41 - respective increase: 14.8% and 9.7% - as documented by example/comparison example 2 and 10). Although these experiments were all carried out with an element having as porous spreading layer a cotton breadcloth (i.e. the one mentioned in example 1 of the patent in suit and which falls under those known from document (IX)), it is clearly stated in the general description part of the published patent specification that the porous spreading layer may be made of a wide variety of anisotropic, fibrous materials or isotropic, non-fibrous materials (see

column 11, lines 26 to 60). The former include for example water-washed fabrics, hydrophillically processed fabrics, fabrics having physically activated surfaces as well as paper, paper filter or non-woven fabrics containing synthetic polymer fibre pulps, whereas the latter include layers made of fine spherical beads which adhere to one another in point-to-point contact whereby a three-dimensional matrix is formed by using a material like brush polymers, diatomaceous earth, microcristalline cellulose, glass etc. (see also document (IX), column 2, lines 56 to 68). Under these circumstances, the Board has no reason to assume that with these porous layers the problem of colour reduction would not exist or could not be demonstrated. According to the jurisprudence of the Boards of Appeal, it is indeed not sufficient in opposition or appeal proceedings to impugn a granted patent with an assertion which is not substantiated (cf. T 219/83, OJ EPO 1986, 211). Without evidence to the contrary the Board therefore cannot accept that in the present case the phenomenon of reduced optical density of formed colour is due to the spreading layer of the analytical element used in the examples of the patent in suit. Consequently, the experimental results indicated in said examples are to be considered as representative for all multilayer analytical elements comprising a porous spreading layer and which fall under the scope of Claim 1.

The above considerations are not altered by the fact that it has been recognised in the patent in suit that there is no reliable scientific explanation for the observed effect of reduced optical density, which is only assumed to arise from interference by catalase or substances having a catalase activity contained in the blood (see column 2, lines 16 to 20). As can be seen from document (VI), the Appellant's own patent, it may indeed occasionally occur

that a technical phenomenon on which an invention is based cannot be properly understood (see point 5.1, penultimate paragraph). In the opinion of the Board this is, however, not necessarily a bar to patentability. What really counts in that situation is the effect as such and not any tentative scientific theory trying to elucidate its origin, even if such theory happened to be wrong, as long as the disclosure can nevertheless be regarded as sufficient for reproducing the invention as such (cf. decision T 418/89 of 8 January 1991, in particular point 3.10 of the Reasons - to be published in OJ). Since in the present proceedings insufficiency of disclosure is not a point at issue, there is no need to further consider this matter.

5.5 In view of its late publication (i.e. 1987), document (VIII) does not form part of the state of the art and is therefore, in conformity with the Appellant's intention, only relevant as supporting evidence for his allegation concerning the non-existence of a general problem of catalase interference with hemolysed samples. However, as already explained in the preceding paragraph, it really does not matter in the present case whether the observed effect arises from catalase interference or not. Apart from this, the information provided in this document fully supports the Respondent's view that many analytic systems are influenced greatly by hemolysate and that most of the figures reveal that hemolysate has an effect on analytical results. In particular, glucose determination on EKTACHEM DT60 and EKTACHEM 700 analysers show a negative bias of up to 5% for the former and one of 3% for the latter (see page 14, right column, first paragraph; page 24, right column, last paragraph; page 34, left column, last paragraph; pages 36 and 37, in particular page 37, left column, penultimate paragraph). All this is perfectly in line with both the statements and the comparative

experimental data contained in the patent in suit (see column 2, line 5 ff.; examples 2 and 8). Consequently, there can be no doubt that the problem underlying the patent in suit (see points 3.1 and 3.2 above) arises from a disadvantageous technical effect which really exists in quantitative analysis of hemolytic samples. This also shows that Dr. Sundberg was in fact right to consider that if a chemical determination exhibited any significant amount of interference from hemolysis, that either method (i.e. the test procedure for hemolysed samples in both the patent in suit and in document (VIII)) would illustrate this.

5.6 As to the results shown in Table 3 of the patent in suit, they relate to experiments carried out in the absence of hemolytic influence, the plasma used being indeed non-hemolytic. These results were obtained in similar conditions as in example 1. The effect shown in these examples does not concern, therefore, the elimination of interference arising from hemolysis discussed in detail in the preceding paragraphs, but an additional effect achieved when using the claimed analytical element in quantitative analysis. With these experiments the Respondent has shown that the claimed elements lead to an overall increase in the optical density of the formed colour when using one of the said acids. As may be seen from Table 1, the higher colour formation efficiency leads to a larger scale of values. This is also mentioned in the patent in suit (see column 3, lines 3 and 4). However, the broadening of the scale necessarily improves the accuracy of measurements.

As indicated in Table 3 of the patent in suit, the purpose of this series of comparisons is to show the influence of various acids and salts, including a control test (blank). The effect of the substances as claimed is distinct

because they lead to an optical density between 0.76 and 0.79, whereas the figures for comparison substances (known pH control agents) and the blank are systematically inferior, with values situated only between 0.71 and 0.73. The increase of the optical density is thus at least 4.1 to 8.2% when using the substances as claimed.

Therefore, in addition to solving the problem of interference caused by hemolysis, the claimed element confers at the same time the advantage of broadening the measurable range which, as is plain from the prior art discussed above, is also unexpected. In the opinion of the Board, this additional advantage cannot but reinforce the non-obviousness of the claimed solution.

6. Accordingly, there are no grounds which prejudice the maintenance of the patent in the form as amended during opposition proceedings. Consequently, the Appellant's main request must be rejected.

7. Since it has been shown in the foregoing paragraphs that the examples of the patent in suit are representative for all multilayer analytical elements comprising a porous layer and which fall under the scope of Claim 1, there is no basis to require that Claim 1 be limited to an element comprising a porous layer such as defined in accordance with Appellant's first auxiliary request (see in particular point 5.4).

It is also clear from what has already been said that in the previous paragraphs, that in the present case a pH control agent or buffer is not an essential feature for solving the problem underlying the patent in suit (see point 5.3 above). There is thus no reason either to require that Claim 1 be amended in accordance with Appellant's second auxiliary request.

Moreover, in the absence of corresponding requests from the Respondent, the Board can only decide upon the patent in the text agreed by the latter (see Article 113(2) EPC). There is thus no need to further consider the Appellant's auxiliary requests.

Consequently, the patent in suit is to be maintained in the form indicated in the communication pursuant to Rule 58(4) EPC, dated 3 August 1988.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P.A.M. Lançon