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Bezeichnung der Erfindung: Dry analytical element having a reaction zone and a reagent zone
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : G01N 33/52

ENTSCHEIDUNG / DECISION

vom / of / du 29 August 1989

Anmelder / Applicant / Demandeur : Eastman Kodak Company

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Articles 54, 56, 111(1)

Schlagwort / Keyword / Mot clé : "Novelty (yes)"
"Inventive step (yes)"

Leitsatz / Headnote / Sommaire

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Case Number : T 376/86

D E C I S I O N
of the Technical Board of Appeal
of 29 August 1989

Appellant : Eastman Kodak Company
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Decision under appeal : Decision of Examining Division 2.1.07. 061 of the European Patent Office dated 2 June 1986 refusing European patent application No. 81 401 127.6 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
R. Schulte

Summary of Facts and Submissions

I. European patent application 81 401 127.6, filed on 15 July 1981 and published on 27 January 1982 with publication No. 44 775, was refused by the decision of the Examining Division of 2 June 1986. The decision was based on Claims 1-7, filed during the examination proceedings. Claim 1 reads as follows:

"1. A dry analytical element for the analysis of an aqueous fluid containing albumin and, possibly, interferents for the analysis of the albumin wherein the element includes

A. a dry reaction zone for receiving the aqueous fluid,

B. a dry reagent zone that is impermeable to albumin and the interferents, and comes into fluid contact with the reaction zone when the element comes into contact with the aqueous fluid,

and is characterized in that said dry reagent zone contains a chromogenic albumin indicator capable of interacting with the analyte and the interferents to produce a detectable response, and a polymeric release means, impermeable to the analyte and the interferents and responsive to contact of the aqueous fluid with the element, for continuously releasing the chromogenic albumin indicator from the reagent zone to the reaction zone at a rate sufficient to produce a detectable analyte response corresponding to:

(1) the interaction of the indicator with the analyte and

(2) reduced interaction of the indicator with the interferents."

Claims 2-7 are dependent sub-claims, relating to preferred embodiments of the above cited main claim.

II. The ground for refusal was that the subject-matter of Claims 1-7 was not novel within the meaning of Article 54 EPC and hence the said claims were not regarded as relating to a patentable invention in accordance with Article 52(1) EPC.

In its decision the Examining Division stated that a dry analytical element for the analysis of an aqueous fluid containing albumin which includes a reaction zone for receiving the aqueous fluid and a reagent zone which is impermeable to albumin and interferents and comes into fluid contact with the reagent zone when the element comes into contact with the aqueous fluid was disclosed in the citation US-A-4 132 528 (citation A). It was also disclosed in citation (A) that the reagent zone contained a chromogenic albumin indicator, namely: a biuret reagent, which interacts with the analyte and the interferents to produce a detectable response, and the reagent zone comprised a polymeric release means exemplified by the material mentioned at page 22, lines 31-34 in the present application (cf. the "alkaline protective polymer" mentioned in citation (A) and in particular the material of Example 1 of this document).

Thus, all technical features of Claim 1 were known. The functional term of Claim 1: "... for continuously releasing ..." would have applied in the specific example of those materials disclosed in citation (A) because of the same technical features.

Difference in the wording of what was referred to as a "biuret reagent" and the feature of Claim 1 "chromogenic

albumin indicator" was held to be merely of semantic character and did not state a technical difference, because both substances acted in both the present application and in citation (A) the same way.

III. Notice of appeal against this decision was filed on 16 June 1986 and the appeal fee was paid at the same day. A Statement of Grounds was filed on 1 October 1986.

IV. The arguments put forward by the Appellant in the notice of appeal can be summarised as follows:

The decisive difference between the features of the dry analytical element disclosed in citation (A) and that of the present application was that it was recognised in the present case that for the reduction of the interferents problem encountered with chromogenic albumin indicators a continuous release of the indicator was necessary. It so happened that one of the polymers described in citation (A) was capable of continuously releasing chromogenic albumin indicators. The continuous feature, however, did not apply to the materials disclosed in citation (A) insofar as the chromogenic indicator used there, namely the biuret reagent, comprising copper, would immediately be released from the reagent layer, whereas the chromogenic albumin indicator bromcresol green (BCG) was released continuously. This had been conclusively shown in the data submitted to the Examining Division on 28 November 1984. Citation (A) did not disclose any specific materials that continuously released the reagent. Nor was there any appreciation that if such release could have been accomplished, any improvement would have resulted.

In searching for a suitable binder for a chromogenic albumin indicator, there were many possible binders that

would not have released the indicator continuously. One skilled in the art would not even be led to citation (A) for a useful binder.

V. During oral proceedings which were held on 29 August 1989 Appellants emphasised that the main claim on file was novel over citation (A) because it was not recognised in that document that a clinical assay for albumin with chromogenic dye indicators, in order to be correct, must, at least to a certain extent, avoid binding with proteins other than albumin (e.g. globulins) and thus required that the problem of interferents be taken into account.

Solutions to reduce the action of interferents in conventional wet systems had been proposed and were discussed in the present application. These conventional methods, however, were inoperative or inapplicable in dry systems. It had been shown by the Appellants during the examination proceedings that the polymeric release means APY-50, as described in citation (A), was not a release means in the context of this reference and biuret was not a chromogenic albumin indicator in the sense of the present application. It was a part of the common general knowledge of the skilled person that this distinction, rather than being semantic, reflected a difference of nature well recognised in the art.

In support of a broad main claim which included the general terms "polymeric release means" and "chromogenic albumin indicator", and in response to a communication issued by the Board, experimental data were submitted which showed determination of albumin where two comparative dry analytical elements were used which differed only with regard to the character of the dry reagent zone. In one case the polymer APY-50 was used, in the other case an agarose layer. The comparative data

showed clearly that use of the APY-50 polymer ensured a reproducible and specific determination of albumin, whereas use of an agarose as the dry reagent zone apparently did not. Rather, the albumin determination was inaccurate by unspecific interactions with interferents.

Further evidence was submitted that continuous release of the chromogenic albumin indicator and thus specific determination of albumin is possible when using as dry reagent zone the polymeric release means APY-50 in combination with the chromogenic albumin indicators cresol red, bromphenol blue, indigo carmine or bromcresol purple. Further additional data showed that the chromogenic albumin indicator BCG in combination with polymeric release means, defined as APY-90, APY-70, APY-25 or hydroxyethylcellulose were also suitable to provide a continuous release of the chromogenic indicator and thus ensures the specific determination of albumin.

The Appellants argued strongly that the subject-matter of Claim 1 was also inventive over the prior art. There was nowhere any hint that the problem of a specific albumin determination unchallenged by any interferents could be solved by providing a dry reagent zone comprising the essential feature of a combination of a release means and a chromogenic albumin indicator which ensures continuous release of the chromogenic albumin indicator.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be granted on the basis of the rejected claims.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. The subject-matter of the refused patent application is a dry analytical element for the analysis of albumin contained in an aqueous fluid.

3. As already recognised by the Examining Division, the closest state of the art is citation (A), which relates to a dry analytical element for the analysis of protein materials contained in an aqueous liquid comprising a reagent layer which is substantially impermeable to proteins, e.g. albumin, and a chromogenic protein indicator, namely a biuret reagent composition and further a spreading layer in which the dissolved materials of the biuret reagent composition interacts with the protein contained in the aqueous liquid (column 12, lines 35 to 41 and 58 to 64).

The principle of the dry analytical element described in both citation (A) and the present application is that a reagent zone comprises a chromogenic protein indicator which is released, upon contact with aqueous fluid containing a protein to be determined, into a reaction zone where the indicator and the protein interact and the result of the interaction can be determined by a colour response.

4. In the description of the present application it is stated on page 6, lines 6-13 that the dry analytical element of the state of the art as described in citation (A) has disadvantages as the reagent employed determines total protein quantitively, because the biuret composition interacts indiscriminately with albumin as well as with

other proteins. The dry analytical element disclosed in citation (A) can only determine total protein by virtue of the reagent employed.

5. Starting from citation (A), the objective technical problem underlying the present application can be seen in providing an improved dry analytical element for selectively determining albumin contained in an aqueous fluid.

6. The solution proposed lies in a reagent as claimed in Claim 1 whereby, instead of the biuret reagent of the known dry analytical element, a chromogenic albumin indicator is selected which, in combination with a suitable reagent zone, is continuously released into the reaction zone, so that there is an interaction of the indicator with albumin, and a reduced interaction of the indicator with the interferents. The examples of the description and the experimental data filed by the Appellants during the examination proceeding and the oral proceedings before the Board show that the problem was indeed solved by this proposal. Whereas a biuret composition contained in a polymeric release means described in citation (A) is released within 30 seconds almost completely, namely to 97%, only 65% of the BCG is released from the reagent layer in the first 30 seconds. This shows that the polymeric release means in question, polymer APY-50, does not continuously release biuret, but does continuously release BCG. Further additional data show that the important and decisive continuous release of a chromogenic albumin indicator is not restricted to one single combination of a certain reagent zone and chromogenic albumin indicator. Rather, there are further combinations of both features easily available in the state of the art and easily to be tested. In absence of evidence to the contrary, the Board is satisfied that by

the continuous release of a chromogenic albumin indicator from a suitable reagent zone, an improved determination of albumin in an aqueous fluid is possible, due to reduced interaction of the indicator with the interferents.

7. There is no doubt that the decisive feature of continuous release of the chromogenic albumin indicator from the reagent zone to the reaction zone at a rate sufficient to produce a detectable analyte response corresponding to the interaction of the indicator with the analyte and reduced interaction of the indicator with the interferents is not disclosed in citation (A). This was even not contested by the Examining Division in its decision. The Examining Division, however, held that this functional feature would also apply in the specific instance of those materials disclosed in citation (A); that identical technical means provided identical functions, even if these functions were not recognised earlier; and that since there was no technical difference between a biuret reagent and a chromogenic albumin indicator, the differences emphasised by the Appellants were only of semantic character.

In the Board's opinion, citation (A) does not disclose a dry analytical element for the specific determination of albumin. Rather, the only chromogenic indicator described in this citation is a biuret reagent which certainly is not specific for the determination of albumin, but rather is useful in a quantitative determination of proteins in general. It was further convincingly demonstrated by the Appellants that the technical means disclosed in citation (A), namely a certain polymer and a biuret reagent did not solve the above defined problem because the means disclosed in citation (A) did not provide a continuous release of the chromogenic albumin indicator

from the reagent zone into the reaction zone. Thus, the Board considers the subject-matter of Claim 1 to be novel over citation (A).

8. The fact that a decisive feature in the claim is worded in functional terms is not in conflict with patentability of the claim. In the decision T 68/85 "Synergistic Herbicide", O.J. EPO 1987, 228, the Board already decided that functional features defining a technical result are permissible in a claim, if, from an objective viewpoint, such features cannot otherwise be defined more precisely without restricting the scope of the invention, and if those features provided instructions which are sufficiently clear for the expert to reduce them to practice without undue burden.

9. In the Board's opinion, the prerequisites mentioned in the above decision are fulfilled in the present case. As to the first prerequisite (impossibility of more precise definition) the exact structure and interaction between the polymeric release means and the chromogenic albumin indicators are not known and thus cannot serve as a basis for a definition of the structure of this feature.

As to the second prerequisite (that the technical teaching of the chosen definition has to be clear and repeatable), evidence has been provided by the Appellants during the proceedings as described in detail above.

10. The Examining Division did not have occasion to decide whether the patent disclosed any inventive step within the meaning of Article 56 EPC of Claim 1 in question. The Board, however, examined the inventiveness of its own motion, based on Article 111 EPC. The question is, whether, with regard to the state of the art, it was obvious to a person skilled in the art to select certain

combinations of a polymeric release means and a chromogenic albumin indicator for a continuous release of this indicator in order to improve the known dry analytic elements for the analysis of albumin in an aqueous fluid.

11. In citation (A), which has been discussed in detail above with regard to novelty, there is no indication whatsoever that a specific albumin determination could be possible by providing means which continuously release the chromogenic albumin indicator. Actually, the problem underlying citation (A) is different from that of the present application. When incorporating the biuret reagent composition or other highly basic compounds into dry analytical elements, one encounters the problem that many compounds capable of providing highly alkaline conditions undergo rapid deterioration of their initially high pH generating capacity. Therefore, the desired reaction between the analyte and the reagent composition, which requires a highly alkaline environment, either can no longer take place or is substantially inhibited. In citation (A) alkaline protective polymers for the use in dry analytical elements are proposed. It is, however, essential to note that the biuret technique provides a total protein estimation in an analyte. For a more specific or even exclusive determination of albumin, being only one of the total proteins in a sample to be analysed, new techniques have to be developed. Citation (A) does not deal with any of those techniques, let alone a proposal to provide means which continuously release a chromogenic albumin indicator which is more specific to albumin than the biuret reagent.

12. In the present patent application the problems arising with regard to a more specific albumin determination are discussed. For example, on page 2, line 28 to page 4, line 35 several attempts are described how to minimise

interferents of the albumin determination by other proteins contained in the aqueous liquids to be analysed. According to Gustafsson, J.E.C., Clin. Chem., 22: 616, 1976, a measurement of the absorbence of the solution twice after the serum is mixed with BCG reagent, namely immediately and at 60 minutes, may increase a selective determination of albumin. The disadvantages of this method are discussed in detail. This method was further developed by Webster (Clin. Chem., 23: 663, 1977) whereby the first measurement "immediately" after the aqueous liquid is mixed with BCG was improved to 30 seconds. This method is still bound to the use of an arbitrary constant as a correction factor. The problem of non-specificity of the BCG-based albumin assay was further disclosed by Ingwersen and Raabo (Clin. Chem., Acta, 88: 545, 1978). Although this method permits a reading to be taken up to one minute after initiation of the assay in solution, the Appellants found that when BCG indicator is used in dry analytical elements in amounts suggested by Ingwersen, severe interference from competing proteins, such as globulins, is encountered. Thus, the prior art discussed in the patent application provides evidence that the skilled persons were aware of the problem of specific determination of albumin but the suggested methods neither solved the problem, nor had any skilled person proposed a development of an assay which hints in any way at a continuous release of the chromogenic albumin indicator from a polymeric release means.

13. Even a combination of the knowledge of citation (A), i.e. the use of a dry analytical element comprising the reagent and reaction zones for the determination of total protein with the knowledge of the above discussed prior art, does not obviously lead to the idea of providing means for the continuous release of a chromogenic albumin indicator from the reagent zone to the reaction zone at a rate sufficient

to produce a detectable analyte response corresponding to the interaction of the indicator with the analyte and reduced interaction of the indicator with the interferents.

14. Other references cited in the search report are less relevant than those discussed above, and therefore no detailed evaluation is necessary.

15. Thus the dry analytical element of Claim 1 involves an inventive step.

16. Claims 2 to 7 are directly or indirectly dependent on Claim 1, and refer to preferred embodiments of Claim 1. There are no objections to these claims.

Claims 1 to 10 on file are therefore patentable.

Order

For these reasons, it is decided that:

1. The decision of the Examining Division is set aside;

2. the case is remitted to the First Instance with the order that a patent be granted on the basis of the following documents:

Claim 1 filed by letter dated 4 June 1985 and amended by letter of 6 December 1985,
Claims 1 to 7 filed by letter dated 4 June 1985,
description pages 1 to 8, 11, 13, 15 to 26 as originally filed,

pages 9 to 10, 12, 14 and 27 filed by letter dated 4 June 1985.

The Registrar: The Chairman:

M. Beer P. Lançon