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Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : The stabilization of working reagent solutions containing NADH, NADPH, and/or enzymes, and the use of such stabilized reagents in enzyme or substrate assays

Klassifikation / Classification / Classement : C12Q 1/00

ENTSCHEIDUNG / DECISION

vom / of / du 29 July 1988

Anmelder / Applicant / Demandeur : American Monitor Corp.

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Reagents

EPÜ / EPC / CBE Article 123(2) EPC

Schlagwort / Keyword / Mot clé : "Support for ranges of values"
"Amendments"

Leitsatz / Headnote / Sommaire

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Case Number : T 21/86 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 29 July 1988

Appellant : American Monitor Corp.
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USA

Representative : Speidel, Eberhardt
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Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 3 June 1985 refusing European patent application No. 79 103 451.5 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon
Members : G. Szabo
R. Schulte

Summary of Facts and Submissions

I. European patent application 79 103 451.5 filed on 17 September 1979 and published on 2 April 1980 with publication number 9222, was refused by the decision of the Examining Division of the European Patent Office dated 3 June 1985. The decision was based on Claims 1 to 6, filed on 14 September 1984. The main claim was worded as follows:

"1. Aqueous working reagent solutions for an assay to measure enzymes or substrates which are detected by the oxidation of NADH or NADPH, characterised by

(a) a first aqueous working reagent solution containing less than about 1 millimolar NADH and including a base selected from the group consisting of an amine base and a strong base, said base being present in an amount which is less than about 75 millimolar and is just sufficient to adjust the pH of the solution to between about 7.9 and 10, thereby providing prolonged stabilization of the NADH or NADPH in the working reagent solution, and

(b) a second aqueous working reagent solution containing one or more enzymes and including one or more salts having cations selected from the group consisting of sodium, potassium, rubidium, ammonium, lithium, and basic amines, and anions selected from the group consisting of glycerol monophosphate, ethylene glycol monophosphate, sulfate, sulfonated organic acids, carbonate, phosphate, borate, dicarboxylic acids, monocarboxylic acids, dicarboxylic amino acids,

alpha-glycerophosphate and beta-glycerophosphate, the concentration of the cations or anions of said salt(s) being less than about three equivalents per litre, thereby providing prolonged stabilization of the enzyme(s) in the second working reagent solution." (emphasis added).

II. The sole ground for refusal was that the requirement in Claims 1 to 5 for "less than 1 millimolar NADH" in component (a), had no support in the documents as filed, in particular in pages 27 to 32. The examples demonstrated values from 0.26 to 0.62 millimolar. The wider range of 1 millimolar or less in the claims could not be taken from those figures. The amendments were therefore unallowable under Article 123(2) EPC.

It was also stated in the decision that the range of "less than about three equivalents per litre" for the concentration of ions was inconsistent with the disclosure which had specified a "range greater than 2.3 but less than 3.0 equivalents per litre" in former Claim 34, which was limited to the assay for SGOT. The omission of the lower limit was therefore also new matter and inadmissible.

III. The Appellant filed an appeal against the decision on 5 August 1985 together with the payment of the fee. A Statement of Grounds was also submitted at the same time and supplemented on 30 September 1985. A new set of Claims 1 to 6 was filed on 9 September 1987, in reply to a Communication from the Board dated 7 May 1987. Claim 2 of these claims was further amended on 13 December 1987.

IV. In view of the Appellant's compliance with the requests from the Board, most of the earlier arguments about the issues originally prevailing before the first instance

became superfluous. Amended Claims 1 and 2 read as follows:

"1. Aqueous working reagent solution for an assay to measure enzymes or substrates which are detected by the oxidation of NADH or NADPH, characterized by

(a) a first aqueous working reagent solution containing 0.26 to 0.62 millimolar NADH and including a base selected from the group consisting of an amine base and a strong base, said base being present in an amount which is less than about 75 millimolar and is just sufficient to adjust the pH of the solution to between 7.9 and 10, thereby providing prolonged stabilization of the NADH or NADPH in the working reagent solution, and

(b) a second aqueous working reagent solution containing one or more enzymes and including one or more salts having cations selected from the group consisting of sodium, potassium, rubidium, ammonium, lithium and basic amines, and anions selected from the group consisting of glycerol monophosphate, ethylene glycol monophosphate, sulfate, sulfonated organic acids, carbonate, phosphate, borate, dicarboxylic acids, monocarboxylic acids, dicarboxylic amino acids, alpha-glycerophosphate and beta-glycerophosphate, the concentration of the cations and anions of said salt(s) being between 0.2 and 2.8 per litre, thereby providing prolonged stabilization of the enzyme(s) in the second working reagent solution.

2. Aqueous working reagent solution for an assay for SGOT to measure enzymes or substrates which are detected by the oxidation of NADH or NADPH, characterized by

(a) a first aqueous working reagent solution containing 0.26 to 0.62 millimolar NADH and including a base selected from the group consisting of an amine base and a strong base, said base being present in an amount which is less than about 75 millimolar and is just sufficient to adjust the pH of the solution to between about 7.9 and 10, thereby providing prolongated stabilization of the NADH in the working reagent solution, and

(b) a second aqueous working reagent solution containing the enzyme(s) malate dehydrogenase and/or lactate dehydrogenase and including one or more salts having cations selected from the group consisting of sodium, potassium, rubidium, ammonium, lithium, and basic amines, and anions selected from the group consisting of glycerol monophosphate, ethylene glycol monophosphate, sulfate, sulfonated organic acids, carbonate, phosphate, borate, dicarboxylic acids, monocarboxylic acids, dicarboxylic amino acids, alpha-glycerophosphate and beta-glycerophosphate, the concentration of the cations and anions of said salt(s) being greater than 0.5 but less than 3.0 equivalents per litre, thereby providing prolongated stabilization of the enzyme(s) in the second working reagent solution."

V. The Appellant requested that the decision be set aside and the patent be granted on the basis of the submitted amended claims.

Reasons for the Decision

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

2. The issue originally forming the basis of refusal by the Examining Division under Article 123(2) EPC, i.e. inadequate support from the documents originally filed for the amended claims on file, was effectively disposed of by the Appellant by the further amendments incorporated in the claims.

3. In particular, new Claims 1 to 5 are now restricted to a range containing 0.26 to 0.62 millimolar NADH concentrations in component (a). The limits of the range has been taken from Examples, in particular VII.A.1.(a) and (c), as extremities disclosed in this respect. These could be taken to support the corresponding claimed range, since the particular values were generally independent from the specific choice of other features (cf. "Lead alloys", T 201/83, OJ EPO 1984, 481).

4. Furthermore, the concentration of cations or anions is specified in Claim 1 for compound (b) as values between 0.2 and 2.8 per litre, which is based on the aggregate of original Claims 24 to 26, wherein the individual ranges were 1.0 to 2.0, 2.0 to 2.8 and 0.2 to 1.0, respectively.

5. As regards the new independent Claim 2, this is now relating to an aqueous working solution "for an assay for SGOT" specifically, and comprises the same component (a) as Claim 1. The component (b) contains, on the other hand, specified enzymes MDH and/or LDH, i.e. malate dehydrogenase and/or lactate dehydrogenase, as originally recommended for the same purpose in Claims 17 and 18 as filed, and

other components already suggested for the purpose, including "cations and anions of said salt(s) being greater than 0.5, but less than 3.0 equivalents per litre". This range is based on Claims 34 to 36 in the original set, all dependent on Claims 17 and 18, wherein again an aggregate covering the same range has been disclosed, i.e. 2.3 to 3.0, 0.5 to 1.0, and 1.0 to 2.3, respectively. The combination of three claims covering consecutively the three parts of the total range without a gap is not extending the content of the application as filed. The rest of the subsidiary Claims 3 to 6 contain only subject-matter specifically mentioned in the Examples, including Example VII.D.2. for the assay. Thus, the issue of inadequate support has been eliminated.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The application is remitted to the Examining Division for further examination on the basis of the claims on file.

The Registrar: The Chairman:

F.Klein P.Lançon