BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 19 March 2004

Case Number: T 0881/01 - 3.3.4

Application Number: 93107171.6

Publication Number: 0568959

IPC: C12Q 1/40

Language of the proceedings: EN

Title of invention:
Stable, single liquid liquid alpha-amylase reagent

Patentee:
Modrovich, Ivan E.

Opponent:
Roche Diagnostics GmbH

Headword:
Alpha-amylase reagent/MODROVICH I.E.

Relevant legal provisions:
EPC Art. 54(3), 56

Keyword:
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0881/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.1.1
of 19 March 2004

Appellant: (Opponent)
Roche Diagnostics GmbH
Patentabteilung
D-68298 Mannheim (DE)

Representative:
-

Respondent: (Proprietor of the patent)
Modrovich, Ivan E.
96 Nathalie Way
Camarillo CA 93010 (US)

Representative:
Grünecker, Kinkeldey,
Stockmair & Schwanhäusser
Anwaltssozietät
Maximiliamstrasse 58
D-80538 München (DE)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 28 May 2001 rejecting the opposition filed against European patent No. 0568959 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: S. C. Perryman
Members: M. Wieser
A. L. L. Marie

Summary of Facts and Submissions

I. The appeal lies from the decision of the Opposition Division, whereby the opposition against the European Patent No. 568 959, which had been opposed by the Appellants under Article 100(a) on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) had been rejected and the patent was maintained unamended pursuant to Article 102(2) EPC.

II. Claim 1 as granted read:

"1. A single liquid alpha-amylase reagent composition comprising an aqueous solution of at least one substrate which is hydrolyzed when mixed with body fluid containing alpha-amylase to yield directly or indirectly by a reaction involving alpha-amylase a detectable label to the reaction mixture, the rate of detection of such detectable label being proportional to the amount of alpha-amylase present in the sample and at least one exo-enzyme to cooperate with the alpha-amylase in the formation of such detectable label, said substrate being present in a concentration sufficient to prevent the substrate from limiting the rate of hydrolysis thereof, said reagent composition being stable against substrate and enzyme degradation for at least 6 months at 2 to 10°C, wherein the exo-enzyme comprises alpha-glucosidase from *Bacillus Stearothermophilus* in an amount sufficient to complete the assay within 10 minutes at an assay temperature of 37°C."

III. The Opposition Division decided that claim 1 was novel over document

(4) EP-A-0 541 083

which belonged to the state of the art under Article 54(3) EPC. The decisive part of the reasoning of the Opposition Division was as follows (last two paragraphs of Section 2.2):

"According to claim 1 of the Patent "said reagent composition is stable against substrate and enzyme degradation for 6 months"; in the light of the description on page 5, line 18, this implies a **substrate concentration** of "2 mg/ml of Ethylidene Blocked Substrate (Boehringer Mannheim)" and an "**extremely clean**" alpha-glucosidase, cf. page 6, line 41 to 42.

D4 does not mention, the features which are implied by the phrase of claim 1 "said reagent composition being stable against substrate and enzyme stability [sic] for 6 months at 2 to 10°C", i.e. does not mention a substrate concentration according to the Patent on page 5, line 18/an "extremely clean" alpha-glucosidase; compare in D4 on page 5, line 26 to 27 and the "á-glucosidase standard product" of D4 on e.g. page 4, lines 35 to 36. Thus, "after mixing" of solution A with solution B according to D4 all the features of the single liquid reagent of claim 1 of the Patent are not disclosed and thus, the subject-matter of claim 1 of the Patent would be novel over D4."

IV. Moreover, the Opposition Division decided that the subject-matter of claim 1 was based on an inventive step in the light of the disclosure in the following documents:

(1) WO-A-89/00 600

(3) Biochimica et Biophysica, 787, 1984, pages 281 to 289

Document (1), disclosing a single liquid alpha-amylase reagent composition, was considered as closest state of the art. The reagent of document (1) did not contain alpha-glucosidase from *Bacillus Stearothermophilus*, but a pair of exo-enzymes, preferably glucoamylase and either alpha-or beta-amylase, and a polyol to retard the degradation of the enzymes. Said reagent was stable for at least six months and preferably for at least one year at about 2 to about 8°C (page 4, lines 4 to 7).

The Opposition Division defined the problem to be solved as being the provision of a stable reagent not requiring the use of a polyol. Although it was acknowledged that document (3) disclosed a stable exo-enzyme from *Bacillus Stearothermophilus* exhibiting both alpha-amylase and glucoamylase activity, it was decided that a skilled person would not have combined the teaching in prior art documents (1) and (3) in order to arrive at the subject-matter of claim 1 of the patent in suit.

V. The submissions by the Appellants (Opponents) may be summarised as follows:

Document (4) disclosed a reagent composition comprising all components of the composition according to claim 1, which therefore inherently had the same stability. The conclusion drawn by the opposition division, based on the finding that the stability feature in claim 1 of the patent implied that the claimed composition contained a specific amount of substrate and an extremely clean alpha-glucosidase, was wrong, as these features were not part of claim 1. Moreover, the amounts of substrate contained in the reagents according to examples 2, 3 and 4 of document (4) were in the same range as in claim 1. With regard to the purity of the used alpha-glucosidase, the patent in suit referred in several passages to the fact that the enzyme was obtained from Toyobo Co., Ltd., Osaka, Japan, i.e. the applicant of document (4).

Document (1) was considered to be the closest state of the art. In the light of the underlying problem, namely to provide a reagent having improved stability, the skilled person would have modified the reagent of document (1) by adding the enzyme disclosed in document (3) and would have arrived at the claimed subject-matter in an obvious way.

VI. No submissions have been made on behalf of the Respondents (Patent Proprietors).

VII. The Appellants requested that the appealed decision be set aside and the patent be revoked. Oral proceedings were requested as an auxiliary measure.

Reasons for the Decision

Novelty (Article 54 EPC)

1. The Board comes to the same result as the Opposition Division on the question of lack of novelty of claim 1 of the patent in suit over document (4), but for different reasons.

2. The Opposition Division has interpreted (see point III above) the feature of claim 1 of "said reagent composition being stable against substrate and enzyme degradation for at least 6 months at 2 to 10°C" as requiring the presence of certain features mentioned in the description. This is not a legitimate form of claim interpretation under the EPC, and seems not to be in accordance with the description itself.

2.1 According to Article 84 EPC the claims define the matter for which protection is sought. Likewise Article 69(1) EPC first sentence states that the extent of protection conferred by a European patent or a European patent application shall be determined by the terms of the claims. While it is true that Article 69(1) EPC second sentence states that the description and drawings shall be used to interpret the claims, this does not make it legitimate to read into the claim features appearing only in the description and then relying on such features to provide a distinction over prior art. This would not be to interpret claims but to rewrite them. The preparatory material available on the discussions leading up to the European Patent

Convention, shows that the effect of Article 69 EPC and its Protocol on Interpretation was always only considered in relation to extending the extent of protection conferred beyond the strict literal meaning of the terms of the claims, and never for excluding what on the clear meaning was covered by the terms of the claims. Certainly in proceedings before the EPO, where the Patentee has the opportunity of cutting down his claims to accord with stricter limits given in the description, the scope of a claim should not be cut down by implying into it features which appear only in the description, as this would deprive claims of their intended function.

Applying this to the present case, the Board considers it inconsistent with proper claim interpretation to read into claim a particular substrate concentration, and thereby distinguish over document (4).

3. Claim 1 requires that the claimed reagent composition is stable against substrate and enzyme degradation for at least 6 months at 2 to 10°C. Document (4) does not state that that the liquid reagent has such stability. In fact document (4) contains no discussion of long term stability, and the liquid composition of Example 4 as described is used immediately. There is nothing in document (4) which would allow the Board to do anything more than conjecture what the stability of the liquid composition of Example 4 might be.

4. On the other hand, the patent in suit suggests a variety of techniques for stabilizing the assay reagent, *inter alia*, filtering the substrate to remove alpha-amylase producing microorganisms, and optionally

filtering the enzymes, or using a polyol to stabilize the enzyme.

5. The Appellants have filed no evidence as to the experimentally determined stability of a liquid composition made following the information in Example 4. In the absence of evidence that such liquid composition has the stability required in claim 1, the chain of proof for lack of novelty is incomplete, so that a case of lack of novelty of claim 1 over document (4) has not been made out.

Inventive step (Article 56 EPC)

6. Document (1), disclosing a single liquid alpha-amylase reagent composition, is considered to be the closest state of the art.

The reagent comprises a substrate for alpha-amylase, being an oligosaccharide of at least three glucose units, whose reducing end glucose unit is bonded, by a bond which can be cleaved by alpha- or beta-glucosidase, to an optically measurable label. The non-reducing terminal glucose is bonded to a blocking group which inhibits cleavage by exo-enzymes of the bond between the terminal glucose unit and the adjacent glucose unit (document (1) page 4, line 27 to page 5, line 2). The substrate is present in the reagent in a quantity that is sufficient to prevent it from limiting the rate of hydrolysis thereof (page 5, lines 17 to 20). Upon contact with a biological sample, containing alpha-amylase, the rate of formation of the optically measurable label is proportional to the

concentration of alpha-amylase in the biological fluid (page 4, lines 15 to 20).

The assay comprises a pair of exo-enzymes, i.e. a glucoamylase and either alpha-or beta-glucosidase, depending on the nature of the bond between the label and the reducing end glucose of the substrate. The only example on pages 9 and 10 of the description uses a glucoamylase and an alpha-glucosidase.

In order to remove alpha-amylase producing bacteria, enzymes and substrate are filtered using a filter having a pore size not greater than 0.2 microns, and sterile equipment and distilled or boiled water only are used (page 8, lines 1 to 16). The same measures are taken in the patent in suit (page 4, lines 21 to 28).

In order to retard the degradation of the exo-enzymes, document (1) teaches to add a water soluble polyol, most preferably sorbitol, to the reagent (page 6, lines 16 to 26). The same is described on page 3, line 56 to page 4, line 1 of the patent in suit.

Document (1) states on page 4, lines 4 to 7, that the disclosed reagent is stable for at least six months and preferably for at least one year at 2 to 8°C.

7. In the light of the disclosure in the closest prior art, document (1), the problem to be solved by the patent in suit is considered to be the provision of an alternative single liquid alpha-amylase reagent composition.

The problem is solved by providing the reagent composition according to claim 1, comprising alpha-glucosidase from *Bacillus Stearothermophilus.*

8. Document (3) discloses alpha-glucosidase from *Bacillus Stearothermophilus* ATCC 12016. Stability and catalytic properties of the enzyme are tested at various temperatures, pH values and in the presence of substances, like urea, ethanol and SDS, and the enzyme is found to be very stable (cf page 285 to 286). Moreover it is disclosed that the enzyme exhibits both, alpha-glucosidase and glucoamylase activity (cf abstract, page 286, right column to page 287 and figure 5).

The statement on page 288, left column, of document (3), saying that it is unlikely that the enzyme belongs to a type of glucoamylase, is of theoretical nature and seems to refer to a problem of classification.

9. The Opposition Division has concluded that a skilled person would not have been prompted, in order to solve the underlying problem, to replace three out of four components of the reagent of document (1), i.e. the two exo-enzymes and the polyol, by the enzyme of document (3). Moreover as document (1) disclosed the use of a glucoamylase and either alpha-or beta-amylase, no direct hint could be seen to replace them by an enzyme having glucoamylase and alpha-amylase activity. But in fact claim 1 does not preclude the use of an additional exo-enzyme or a stabilizing polyol. The only difference between what is required by claim 1 and the specific embodiment of document (1) is that the latter suggests using as alpha-glucosidase maltase, while claim 1

requires the alpha-glucosidase from *Bacillus Stearothermophilus.*

10. The Board does not agree with the Opposition Division's conclusion, particularly since the stability of a reagent composition according to document (1) to a great extent depends upon the stability of the contained enzymes. A skilled person, when trying to solve the posed problem and provide an alternative to the reagent of document (1), will consider the question of enzyme stability and has reason to regard the stable enzyme disclosed in document (3) as a possible alternative to the specific alpha-glucosidase of the example of document (1).

Only two enzymes are able to cleave at the reducing end of an oligosaccharide derivative, namely alpha-and beta-glucosidase. In the present case, depending on the bond between the label and the reducing end glucose of the substrate the skilled person will chose either the one or the other. The only example of document (1) makes use of an alpha-amylase, which means that the label is bonded to the reducing end glucose of the substrate by an alpha-glucoside linkage. The skilled person being aware of the problem to be solved in the light of the closest prior art and knowing from the disclosure in document (3) about the stable enzyme from *Bacillus Stearothermophilus* having glucoamylase and alpha-amylase activity would use this enzyme in the reagent composition of document (1) and would thus arrive at the claimed subject-matter in an obvious way.

11. Claim 1, therefore, is not based on an inventive concept and does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

P. Cremona S. C. Perryman