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Datasheet for the decision of 6 December 2006

Case Number: T 0018/02 - 3.3.08

Application Number: 94909609.3

Publication Number: 0689589

IPC: C12N 9/28

Language of the proceedings: EN

Title of invention:
Oxidatively stable alpha-amylase

Patentee:
GENENCOR INTERNATIONAL, INC.

Opponent:
NOVOZYMES A/S

Headword:
Mutant alpha-amylase/GENENCOR

Relevant legal provisions:
EPC Art. 54(3), 56, 83, 84, 87, 89, 114(2), 123(2),(3), 158(1),(2)

Keyword:
"Admission of new evidence (no)"
"New request - admission into the proceedings (yes)"
"Added matter (no)"
"Clarity and sufficiency of disclosure (yes)"
"Priority (yes)"
"Novelty and inventive step (yes)"

Decisions cited:
G 0009/91, G 0002/98

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0018/02 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 6 December 2006

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 13 November 2001 rejecting the opposition filed against European Patent No. 0689589 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: F. Davison-Brunel
Members: M. R. Vega Laso
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 0 689 589 with the title "Oxidatively stable alpha-amylase" was granted on European patent application No. 94 909 609.3, which was filed as international application PCT/US94/01553 on 10 February 1994 claiming the priority of the previous US patent application No. 08/016,395 of 11 February 1993. The international application was published as WO 94/18314.

II. The patent was opposed on the grounds of Article 100(a), in particular lack of novelty (cf. Article 54 EPC) and lack of inventive step (cf. Article 56 EPC), and Article 100(b) EPC. An objection under Article 100(c) EPC raised by the opponent after expiry of the period for filing an opposition (Article 99(1) EPC) was admitted into the proceedings by the opposition division.

III. By a decision announced orally at the end of oral proceedings and issued in writing on 13 November 2001, the opposition division rejected the opposition pursuant to Article 102(2) EPC, on the grounds that none of the grounds for opposition adduced by the opponent prejudiced the maintenance of the patent as granted.

IV. An appeal was filed by the opponent (appellant), who paid the appeal fee and submitted a statement setting out the grounds of appeal. The proprietor (respondent) filed observations to the grounds of appeal. Both parties requested oral proceedings in the event that

the board did not intend to grant their respective requests.

V. The appellant submitted further comments in answer to the respondent's observations.

VI. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) accompanying the summons, the board expressed its preliminary opinion on some of the matters in dispute, in particular matters in connection with Articles 100(b) and (c) EPC, as well as on the issue of novelty. With respect to inventive step, various issues to be discussed at the oral proceedings were identified in the communication.

VII. In reply to the board's communication, the appellant made his submissions. The respondent filed twelve sets of amended claims which were intended to address some of the issues identified in the board's communication.

VIII. On 17 November 2006, the appellant submitted additional observations and documentary evidence via telefax.

IX. Oral proceedings were held on 6 December 2005. At the outset of the proceedings, the board, after hearing the parties, decided not to admit into the proceedings the evidence filed by the appellant on 17 November 2006. The respondent withdrew four of the requests then on file and, after discussion of the remaining requests, filed an amended set of claims (claims 1 to 17) which, upon subsequent withdrawal of all further requests, became his sole request.

X. Amended claims 1, 14 and 17 according to the sole request read as follows (insertions compared to claims 1, 15 and 18 as granted have been emphasized in bold by the board):

"1. A mutant alpha-amylase that is the expression produce[*sic*] of a mutated DNA sequence encoding an alpha-amylase, the mutated DNA sequence being derived from a precursor alpha-amylase which is a *Bacillus* alpha-amylase by substitution or deletion of **a methionine which corresponds in position in the primary structure of the precursor alpha-amylase** to M+197 in *B. licheniformis* alpha-amylase**, wherein the substituent amino acid is selected from the group consisting of alanine, threonine and cysteine**.

14. A detergent composition which comprises a mutant alpha-amylase and one or more additional enzymes wherein said mutant alpha-amylase is the expression product of a mutated DNA sequence encoding an alpha-amylase, the mutated DNA sequence being derived from a precursor alpha-amylase which is a *Bacillus* alpha-amylase by substitution or deletion of **a methionine which corresponds in position in the primary structure of the precursor alpha-amylase** to M+197 in *B. licheniformis* alpha-amylase**, wherein the substituent amino acid is selected from the group consisting of alanine, leucine and threonine**.

17. A method of liquefying a granular starch slurry from either a wet or dry milling process at a pH of from about 4 to about 6 comprising:

(a) adding an effective amount of an alpha-amylase mutant to the slurry;

(b) optionally adding an effective amount of an antioxidant to the slurry; and

(c) reacting to the slurry for an appropriate time and at an appropriate temperature to liquefy the starch;

wherein said alpha-amylase mutant is the expression product of a mutated DNA sequence encoding an alpha-amylase, the mutated DNA sequence being derived from a precursor alpha-amylase which is a *Bacillus* alpha-amylase by substitution or deletion of **a methionine which corresponds in position in the primary structure of the precursor alpha-amylase** to M+197 in *B. licheniformis* alpha-amylase, **wherein the substituent amino acid is selected from the group consisting of threonine and cysteine**."

Dependent claims 2, 3, 5 and 6 corresponded to claims 3, 4, 6 and 7 as granted. Dependent claim 4 differed from claim 5 as granted in that the phrase "*an amino acid at a position equivalent to W138*" had been replaced by "*an amino acid which corresponds in position in the primary structure of the precursor alpha-amylases to W138*".

Independent claims 7, 8 and 9, which corresponded to claims 8, 9 and 10 as granted, were directed to DNA, expression vectors and host cells, respectively.

Independent claim 10 related to a detergent composition and differed from claim 11 as granted in that the phrase "*wherein the substituent amino acid is selected from alanine and threonine*" had been inserted at the end of the claim. Claims 11 and 12 depending on

claim 10 and independent claimed 13, which was directed to a starch liquefying composition, corresponded to claims 12 to 14 as granted. Claims 15 and 16 specified preferred embodiments of the detergent composition of claim 14 and corresponded to claims 16 and 17 as granted.

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

(1): WO 94/02597, published on 3 February 1994;

(P1): Priority document of document (1) corresponding to the Danish patent application No. 0946/92, filed on 23 July 1992;

(P2): Priority document of document (1) corresponding to the Danish patent application No. 1503/92, filed on 16 December 1992;

(3): D. Scott, 1980, in Kirk-Othmer Encyclopaedia of Chemical Technology, John Wiley and Sons, Editors, Vol. 9, pages 173 to 224;

(5): K. Takase, Eur. J. Biochem., 1993, Vol. 211, pages 899 to 902;

(8): E. W. Flick, 1989, in Advanced Cleaning Product Formulations, Noyes Publications, pages 96 to 159;

(9): H. Malmos, 19 March 1990, Chemistry and Industry, pages 183 to 186;

(10): Ullmann's Encyclopedia of Industrial Chemistry, 5th edition, 1987, VCH Verlagsgesellschaft, Vol. A8, pages 362 to 365;

(12): L. Holm et al., Protein Engineering, 1990, Vol. 3, No. 3, pages 181 to 191;

(22): T.V. Borchert et al., 1995, in Progress in Biotechnology 10, Carbohydrate Bioengineering, S.B. Petersen, B. Svensson, and S. Pedersen (Eds.), pages 175 to 179;

(23): D. A. Estell et al., 10 June 1985, The Journal of Biological Chemistry, Vol. 260, No. 11, pages 6518 to 6521;

(A2): Declaration of Carsten Andersen dated 22 August 2001.

XII. The arguments of the appellant, as far as they are relevant to the present decision, can be summarized as follows:

Articles 123(2), 84 and 83 EPC

There was no individualisation in the application as filed of specific alpha-amylases in which a methionine residue corresponding in position to M+197 in *B. licheniformis* alpha-amylase had been substituted by an alanine, threonine or cysteine residue.

Claims 1, 14 and 17, which included the amended feature "*a methionine which corresponds in position in the primary structure of the precursor alpha-amylase to*

M+197 in B. licheniformis alpha-amylase", offended against Article 84 EPC. Many alpha-amylases from *Bacillus* did not have any residue resembling the methionine at position 197 in *B. licheniformis*. Moreover, since the patent did not disclose how positions corresponding in primary structure could be identified, a person skilled in the art would not be able to determine, clearly and reliably, whether or not a given methionine in a precursor alpha-amylase corresponded in position in the primary structure to M+197 in *B. licheniformis*.

Article 87 EPC - Priority

Like in the application as filed, there was no individualisation in the priority application of specific alpha-amylases in which a methionine corresponding in position to M+197 in *B. licheniformis* alpha-amylase had been replaced by alanine, threonine or cysteine. Consequently, the patent did not enjoy the claimed priority, and the relevant date for the assessment of novelty was the filing date.

Article 54 EPC - Novelty

Document (1), which was comprised in the state of the art relevant to the assessment of novelty (Article 54(3) EPC), disclosed mutant *Bacillus* alpha-amylases in which the methionine at position 197 was replaced by any amino acid residue, including alanine, threonine and cysteine, as well as detergent compositions containing such a mutant alpha-amylase together with a protease. The mutant alpha-amylases and the detergent compositions as described in document (1)

were also implicitly disclosed in the previous applications (P1) and (P2), the priority of which was claimed in document (1). Thus, document (1) anticipated the subject-matter of claims 1 and 14.

Article 56 EPC - Inventive step

Document (23) disclosed a general method for increasing the resistance of enzymes to chemical oxidation. Although the specific examples in this document related to the production of oxidatively resistant subtilisin, it was clear from different passages of the document that it provided the skilled person with the more general teaching that the oxidative stability of enzymes *in general* could be increased by replacement of methionine residues with less oxidizable amino acids.

Taking document (23) as the closest prior art, the problem addressed by the invention was how to apply the general teaching in that document to alpha-amylase enzymes. The solution and the incentive for applying the teaching of document (23) to alpha-amylases was evident from document (9).

Alternatively, document (23) could be combined with document (12), from which it could be learnt that there were a limited number of methionine residues common to the alpha-amylases of *B. licheniformis* and *B. amyloliquefaciens*. Since the methionine at position 197 was located in a highly conserved region between alpha-amylases from different B*acillus* species, it was the most obvious for the skilled person to choose for substitution.

The patent provided experimental data only for mutant alpha-amylases derived from the *B. licheniformis* alpha-amylase; however, there was no evidence showing that mutant alpha-amylases derived from other *Bacillus* species could solve the problem of increasing oxidation stability. Thus, the technical problem was not solved throughout the scope of the claims.

XIII. The arguments put forward by the respondent were as follows:

Articles 123(2), 84 and 83 EPC

The application as filed specifically disclosed mutant *Bacillus* alpha-amylases and detergent compositions as claimed in claims 1 and 14. Contrary to the arguments put forward by the appellant in respect of Articles 84 and 83 EPC, a skilled person, applying common general knowledge, was perfectly able to align the amino acid sequence of a given B*acillus* alpha-amylase with that of the *B. licheniformis* alpha-amylase, and identify the methionine residue corresponding in position in the primary structure to the M+197 of *B. licheniformis* alpha-amylase. Methods for genetically engineering proteins by replacing a given amino acid residue by other residues were well known in the art.

Article 54 EPC - Novelty

Since the present claims were entitled to the claimed priority date, document (1) was only citable under Article 54(3) EPC against the novelty of the claimed subject-matter if the same subject-matter was disclosed in the previous applications (P1) and (P2). This was,

however, not the case and, therefore, the teachings of document (1) were not detrimental to novelty.

Article 56 EPC - Inventive step

Only documents relating to alpha-amylases, for instance document (5), could serve as starting point for the assessment of inventive step in the present case. None of the documents on file relevant to assessment of inventive step suggested to replace a methionine corresponding in position in the primary structure to M+197 in *B. licheniformis* alpha-amylase. The examples of the patent showed that the problem of providing mutant *Bacillus* alpha-amylases having improved properties had been solved. Thus, the claimed subject-matter involved an inventive step.

XIV. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 689 589 be revoked.

XV. The respondent (patentee) requested that the patent be maintained in amended form on the basis of his request filed during oral proceedings.

Reasons for the Decision

Admission of late-filed documentary evidence

1. In the present case, the appellant filed in his second reply of 17 November 2006 to the board's communication additional written evidence in the form of an alignment of the amino acid sequences of three alpha-amylases from different *Bacillus* species with the sequence of

the alpha-amylase from *Bacillus licheniformis*. This evidence aimed at supporting the appellant's argument that, since the patent did not disclose how homologous positions or positions corresponding in primary structure could be identified, a person skilled in the art did not know, and could not tell, whether a given *Bacillus* alpha-amylase had a position which was homologous or equivalent to M197 in *B. licheniformis* alpha-amylase. The appellant justified the submission at this late stage of the appeal proceedings arguing that the evidence in question had been prompted by the phrases "homologous to" and "corresponds in position in the primary structure to" which appeared for the first time in some sets of claims filed by the respondent together with his reply to the board's communication.

2. The board cannot accept this argument. In opposition proceedings, the appellant raised and substantiated the ground of opposition under Article 100(b) EPC arguing that the teaching provided in the patent with respect to the feature "*an amino acid at the position **equivalent to** M+197 in B. licheniformis alpha-amylase*" present in, *inter alia*, claim 1 as granted, did not allow the skilled person to carry out the invention over the whole scope of the claim. The phrase "*equivalent to*" is defined in the passage on page 5, lines 17 to 23 of the patent specification as follows:

"*A residue (amino acid) of a precursor alpha-amylase is equivalent to a residue of B. licheniformis alpha-amylase if it is either **homologous** (i.e., **corresponding in position in** either **primary** or tertiary **structure**) or analogous to a specific residue or portion of that residue in B. licheniformis alpha-amylase (i.e., having*

the same or similar functional capacity to combine, react, or interact chemically or structurally)." (emphasis added by the board).

3. In its decision, the opposition division held that the ground of opposition under Article 100(b) EPC did not prejudice the maintenance of the patent in suit. Therefore, in reaction to the reasons given in the appealed decision, the appellant could have filed further evidence in support of the alleged insufficient disclosure of the invention already at the outset of the appeal proceedings rather than three weeks before the date of oral proceedings. One last remark in this respect is also that the appellant's attention was drawn to the "homology problem" once more in the communication sent by the board under Article 11(1) RPBA.

4. Since the evidence at issue was filed late and, as the appellant admitted, has not more relevance than other evidence already on file, in particular document (A2), the board in exercising its discretion under Article 114(2) EPC does not admit this evidence into the proceedings.

Request filed during the oral proceedings

Admission of the new request

5. The respondent's new and sole request filed during the oral proceedings comprises amendments to the claims which were made in direct response to the substantive discussion during the hearing, and represented a serious attempt at remedying deficiencies present in

the previous sets of claims that only became apparent during the discussion.

6. Even if it is true that the new request was filed at a very late stage of the proceedings, it was prompted by the discussion in the oral proceedings on the issue of inventive step in relation to the requests then on file. Contrary to the appellant's view, the board is therefore unable to see in the respondent's behaviour any abuse of the procedure.

7. For these reasons, the board decides to admit the new request into the proceedings.

Rule 57a EPC

8. The amendments introduced into the claims of the new request were occasioned by grounds for opposition specified in Article 100 EPC, in particular by the grounds under Article 100(a) in conjunction with Articles 54(3) and 56 EPC, and under Article 100(b) in conjunction with Article 83 EPC. Thus, the requirement of Rule 57a EPC is met.

Article 123(2) and (3) EPC

9. Amended claim 1 is derived essentially from claim 1 as originally filed in combination with the features of claim 3 (substitution or deletion at a position equivalent to M+197 in *B. licheniformis* alpha-amylase) and claim 4 (an amino acid selected from the group consisting of alanine, threonine and cysteine is substituted for methionine at a position equivalent to +197 in *B. licheniformis* alpha-amylase). The limitation

to a mutant alpha-amylase derived from a precursor alpha-amylase which is a *Bacillus* alpha-amylase has its basis on page 6, second full paragraph of the application as filed. As stated above (see point 2), an amino acid equivalent to a particular residue of *B. licheniformis* is defined in the application as, *inter alia*, an amino acid corresponding in position in the primary structure of the alpha-amylase of *B. licheniformis*.

10. The board does not share the appellant's view that, in the original application, there is no individualisation of specific alpha-amylases in which a methionine corresponding in position to **M+197** in *B. licheniformis* alpha-amylase has been substituted by the amino acids alanine, threonine or cysteine. As a matter of fact, in the paragraph bridging pages 4 and 5 of the application, it is stated that:

> "*Most preferably the methionine to be replaced is a methionine at a position equivalent to position +197 or +15 in B. licheniformis alpha-amylase. Preferred substitute amino acids to replace the methionine at position +197 are alanine (A), isoleucine (I), threonine (T) or a cysteine (C).*"

Isoleucine is also mentioned in this passage as a possible substitute amino acid. However, its exclusion from the claim does not offend against Article 123(2) EPC, as each individual substitute amino acid is to be regarded as representing a separate embodiment for which protection is individually sought.

11. In addition to the passage quoted above, a M197T mutant, ie a mutant in which the methionine at position 197 is substituted by threonine, is specifically disclosed in SEQ ID NO: 36 as well as on page 6, lines 1 and 2 of the application as filed. A M197C mutant with the methionine at position 197 substituted by cysteine is described in the second sentence of the first full paragraph on page 6 of the application as filed.

12. As regards amended claims 10 and 14 (cf. section X above), it is noted that a detergent composition containing a mutant alpha-amylase, in particular an alpha-amylase modified at a position equivalent to M+197 in *B. licheniformis* alpha-amylase was claimed in claim 28 as filed. The choice of alanine, leucine and threonine as substitute amino acids finds a basis in the passage of the application quoted in point 10 above and in claim 4 as originally filed. The feature "*comprising one or more additional enzymes*" is derivable from claim 30 as filed, as well as from the statements in the paragraph bridging pages 15 and 16 of the application.

13. Finally, claim 33 as originally filed is considered to provide the basis for the method of present claim 17, in which a mutant alpha-amylase is used which exhibits the same features as in claim 1 (cf. point 9 above for its basis in the application as filed), except for the substitute amino acid being either threonine or cysteine.

14. No objections under Article 123(2) EPC were raised by the appellant in respect of claims 2 to 9, 11 to 14, 15 and 16.

15. The appellant raised also no objections under Article 123(3) EPC, and the board is satisfied that the amendments introduced into the claims do not extend the protection conferred by the patent. Thus, the requirements of Article 123(2) and (3) EPC are fulfilled.

Article 84 EPC - Clarity

16. Clarity issues (Article 84 EPC) which arise from amendments introduced into the claims either in opposition or in appeal proceedings are to be fully examined (cf. G 9/91, OJ EPO 1993, 408).

17. Upon consideration of the arguments and evidence put forward by the appellant in respect of the feature "*a methionine which corresponds in position in the primary structure of the precursor alpha-amylase to M+197 in B. licheniformis alpha-amylase*" introduced into amended claims 1, 14 and 17, the board considers that his objections in connection with Article 84 EPC are not justified. In the board's view, the fact that no methionine residue corresponding to M+197 in *B. licheniformis* can be found in certain *Bacillus* alpha-amylases (eg in the alpha-amylases of *B. subtilis* or *B. thuringensis*; cf. sequences BSAMYL and A27092 in the sequence alignment included in document (A2)) does not render the feature in question unclear, as there is no doubt that, in order to obtain mutant alpha-amylases falling under the scope of the claims, only a methionine as defined may be substituted or deleted. If such a methionine residue is absent in a precursor alpha-amylase, it is obvious that the teaching of the

patent is not applicable and, consequently, no mutant alpha-amylase as claimed is obtained.

18. As support for his further argument that a methionine residue of a precursor alpha-amylase which corresponds to M+197 in *B. licheniformis* cannot be clearly identified, the appellant referred to documents (A2) and (12). Document (A2), a declaration of Mr Andersen - an employee of the appellant -, includes a protein sequence alignment of the alpha-amylase of *B. licheniformis* with seven *Bacillus* alpha-amylases which were in the public domain at the priority date of the patent. Mr Andersen states that three of these alpha-amylases were relatively homologous with the *B. licheniformis* alpha-amylase and a methionine corresponding to M+197 could be found, whereas the remaining four alpha-amylases were highly divergent from the *B. licheniformis* alpha-amylase and could, in practice, not be aligned. Consequently, no methionine equivalent to M+197 could be found in these alpha-amylases.

19. The board notes that Mr Andersen did not appear to encounter any difficulty either in comparing the amino acid sequences of the various alpha-amylases with that of *B. licheniformis*, or in determining whether or not there is a methionine residue which corresponds in position in the primary structure to M+197 in *B. licheniformis* alpha-amylase. Neither did he expressed any doubt as to whether a particular methionine residue present in the precursor alpha-amylase might or might not correspond to M+197 in *B. licheniformis* alpha-amylase. The mere fact that in some alpha-amylases no methionine residue corresponding

in position in the primary structure to M+197 in *B. licheniformis* alpha-amylase can be found is, as explained above, not prejudicial to the clarity of the claims.

20. It should be noted also that, besides the alpha-amylases from *B. amyloliquefaciens* and *B. stearothermophilus*, Mr Andersen was able to align the amino acid sequence of the alpha-amylase from an alkalophilic *Bacillus* species designated BSAMYG6 (cf. Appendix A of document (A2)) and to determine the methionine residue corresponding to M+197 in *B. licheniformis* alpha-amylase, what seems to contradict the appellant's further argument that a methionine residue corresponding to M+197 in *B. licheniformis* alpha-amylase can be clearly determined solely in the alpha-amylases from *B. amyloliquefaciens* and *B. stearothermophilus*.

21. As it concerns document (12), the appellant pointed to the sequence alignment in Figure 1 as well as to the chapter concerning alignment of alpha-amylase sequences (cf. page 182, right column, half way to the bottom). In Figure 1, the amino acid sequences of ten alpha-amylases from various sources (from pig pancreas to barley), including five *Bacillus* alpha-amylases are compared. It is stated in the document that the alignment of distantly related alpha-amylase sequences was far from obvious because only six blocks of residues were clearly conserved in them. In domain B - where M+197 is located -, very little amino acid homology was said to be found.

22. The board notes that the sequence alignment described in document (12) is a consensus alignment of ten very distant alpha-amylases, which was prepared with the aim of finding potential candidates for the extrapolation of the three-dimensional model for the Taka-amylase A of *Aspergillus orizae* to other alpha-amylases. Having this in mind, the difficulties encountered in the alignment are somehow not surprising; however, they cannot be considered as a clear evidence for any alleged difficulties in the alignment of the amino acid sequences of ***Bacillus*** alpha-amylases. In fact, the alignment in Figure 1, as far as it concerns *Bacillus* alpha-amylases, is perfectly in line with the results reported by Mr Andersen in document (A2), insofar as this alignment allows a person skilled in the art to determine which methionine residue corresponds to M+197 in *B. licheniformis* alpha-amylase, provided that such methionine residue exists in a given *Bacillus* alpha-amylase.

23. Thus, neither document (A2) nor document (12) support the appellant's objection of lack of clarity. Consequently, the board considers that the requirement of legal certainty underlying the provision of Article 84 EPC is fulfilled with regard to the scope of claims 1, 14 and 17. The same applies, *mutatis mutandis*, to claim 10 which, in spite of including a similar feature, was not objected to by the appellant.

Article 83 EPC - Sufficiency of disclosure

24. Since for the reasons given above claims 1, 14 and 17, in particular the feature "*a methionine which corresponds in position in the primary structure of the*

precursor alpha-amylase to M+197 in B. licheniformis alpha-amylase" fulfil the requirements of Article 84 EPC, and given that suitable genetic engineering methods for the deletion or substitution of a particular amino acid residue in a protein were part of the common general knowledge of the skilled person at the priority date, there is no reason to believe that the invention as described in the patent could be carried out only with an undue burden of experimentation. No evidence to the contrary has been submitted by the appellant. Thus, the requirements of Article 83 EPC are considered to be met.

Article 87 EPC - Priority

25. The appellant has contested the validity of the priority claimed in the present patent in respect of the subject-matter of claims 1 and 14. The arguments put forward by the appellant in respect of the previous US application (cf. section XII above) were essentially the same as those put forward in connection with Article 123(2) EPC in respect of the application as filed.

26. As it was the case for the analogous arguments in respect of the application as filed, the appellant's arguments concerning the disclosure content of the priority document are not convincing. Since the passage in the second paragraph of page 4 of the priority document **specifically** discloses mutant alpha-amylases as claimed, the priority claimed in the patent is considered valid and the relevant date for the purpose of assessing novelty of the claimed subject-matter is

the priority of the previous US application, ie 11 February 1993.

Article 54 EPC - Novelty

The relevant state of the art

27. The appellant has questioned the novelty of the subject-matter of claims 1 and 14 in view of the international application PCT/DK93/00230 (document (1)). This international application, for which the European Patent Office was a designated Office, was filed on 6 July 1993 and published on 3 February 1994. The priority of three previous applications filed on 23 July 1992 (P1), 16 December 1992 (P2) and 15 March 1993, was claimed. Since the conditions laid down in Article 158(2) EPC are fulfilled, document (1) could be considered to be comprised in the state of the art under Article 54(3) EPC (cf. Article 158(1), 2nd sentence EPC).

28. Document (1) describes mutant *Bacillus* alpha-amylases in which one or more of the methionine residues is exchanged with any amino acid residue, except for cysteine and methionine. In a preferred embodiment, the exchanged methionine residue is the methionine residue at position 197 in *B. licheniformis* alpha-amylase or the methionine residue in homologous positions in other alpha-amylases. Among the preferred amino acid residues for replacement of a methionine at position 197, alanine, threonine and cysteine are mentioned.

29. Taking into account the board's finding on the relevant date for the assessment of novelty (cf. point 26 above),

document (1) is considered to be comprised in the state of the art under Article 54(3) EPC in conjunction with Articles 87 and 89 EPC only to the extent that the priority of the previous applications (P1) and (P2) has been validly claimed for the international application, ie to the extent that the international application and the previous applications disclose the "same invention" or, as defined in decision G 2/98 (OJ EPO 2001, 413), the "subject-matter" of the claim can be derived directly and unambiguously, using common general knowledge, from the previous applications as a whole.

Claim 1

30. Documents (P1) and (P2), which are essentially identical in the relevant passages, describe a mutant alpha-amylase in which one or more of the methionine amino acid residues is exchanged with a leucine, isoleucine, asparagine, serine, glutamine, aspartic acid or glutamic acid residue (cf. page 1, lines 17 to 20 of document (P1); and page 1, lines 14 to 16 of document (P2)). The methionine residue at position 197 is mentioned as one of the possible methionine residues to be exchanged in the alpha-amylase of *B. licheniformis* or *B. amyloliquefaciens* (cf. page 2, lines 14 and 18 of (P1); and page 2, lines 10 and 13 of (P2)). However, alanine, threonine or cysteine are not mentioned as possible substitute amino acids for the methionine residue at position 197.

31. The appellant argued that the description of a **mutant** alpha-amylase in document (1) and in the previous applications (P1) and (P2) represents an implicit disclosure of the substitution of the methionine amino

acid residue in position 197 with **any** possible amino acid residue. Thus, in respect of this subject-matter document (1) allegedly enjoyed the claimed priority and, as a consequence, constituted state of the art according to Article 54(3) EPC in conjunction with Article 89 EPC.

32. The board does not share this view. Even though the previous applications (P1) and (P2) disclose, generally, mutant *Bacillus* alpha-amylases, these applications provide neither an explicit nor an implicit specific disclosure of mutant alpha-amylases in which the methionine amino acid residue at position 197 is substituted by **any** other amino acid residue and, in particular, by alanine, threonine and cysteine. The alleged implicit disclosure of a substitution by any amino acid residue would be in clear contradiction with the passage on page 1, lines 17 to 20 of application (P1), where it is stated that:

> "*The mutant alpha-amylase according to the invention is characterized by the fact that one or more of the methionine amino acid residues is exhanged* [sic] *with a Leu, Ile, Asn, Ser, Gln, Asp, or Glu amino acid residue.*"

33. The same wording is found on page 1, lines 14 to 16 of application (P2), and in claim 1 of either (P1) or (P2). In view of these statements, the disclosure of (P1) and (P2) as a whole is considered to be **explicitly** limited to mutant *Bacillus* alpha-amylases in which one or more methionine residues, and in particular the methionine residue at position 197, is replaced by leucine, isoleucine, asparagine, serine, glutamine, aspartic

acid or glutamine. Thus, insofar as mutant *Bacillus* alpha-amylases with **any** amino acid other than methionine at position 197 are concerned - irrespective of which they may be -, document (1) is not entitled to the priority of the previous applications (P1) and (P2) and, consequently, does not constitute state of the art relevant to the assessment of novelty under Article 54(3) EPC.

34. The board thus concludes that, since no other prior art document on file anticipates the subject-matter of claim 1, novelty must be acknowledged in this respect.

Claim 14

35. Document (1) explicitly discloses a detergent composition containing a mutant alpha-amylase and a protease (cf. last paragraph on page 3). Thus, it has to be examined whether or not in respect of this subject-matter document (1) validly claims the priority of either (P1) or (P2).

36. The appellant admitted that the detergent compositions containing a mutant alpha-amylase and a protease were not explicitly disclosed in the previous applications (P1) and (P2). He contended, nevertheless, that the skilled person, when reading the previous applications with the background of the common general knowledge, would have understood that the detergent compositions described in these applications had to contain - in addition to a mutant alpha-amylase - a protease. As support for his contention, the appellant pointed to, *inter alia*, documents (3), (8), (9), (10) and (22).

37. Document (3), however, does not give any indication to the effect that a detergent composition containing an alpha-amylase must necessarily contain also a protease. As for document (8), the specific composition pointed to by the appellant (cf. page 121) corresponds to a laundry liquid with fabric softener and enzymes, for which it is indicated that "*Protease and/**or** amylase enzymes can be used.*" (emphasis added by the board). In document (9) (cf. page 184, paragraph bridging left and right column), it is stated that "*In household and industrial laundering detergents, alpha-amylases are **usually** incorporated in combination with one or more proteases,...*" (emphasis added by the board).

38. Furthermore, even though in document (10) (cf. page 363, right column, second paragraph from the bottom) serine-active, alkali-stable proteolytic enzymes are said to constitute >95% of the enzymes used worldwide for detergent purposes, there is also no indication supporting an obligatory combination of proteases and alpha-amylases in detergent compositions. Finally, document (22), which was published two years after the priority date of the patent, only indicates that suitable amylases should be compatible with, *inter alia*, proteases present in a detergent (cf. page 175, second paragraph from the bottom).

39. Summarizing the above: the evidence presented by the appellant appears to indicate that the majority of the enzyme-containing detergent compositions known at the relevant date contained proteases, but it fails to show plausibly that each and every detergent composition containing an alpha-amylase would also contain a protease. Consequently, the board cannot accept

appellant's argument that a skilled person reading either (P1) or (P2) would have assumed that the detergent compositions containing an alpha-amylase described therein **must** necessarily contain a protease as well.

40. It follows from the above that the previous applications (P1) and (P2) fail to disclose detergent compositions containing an alpha-amylase **and** a protease, and that, in this respect, the priority claimed in document (1) is not valid. Consequently, document (1) is not considered to be comprised in the state of the art relevant to the assessment of novelty of the subject-matter claimed in claim 14. The novelty objection based on this document is, therefore, not justified.

Article 56 EPC - Inventive step

Closest prior art

41. In the framework of assessing inventive step following the problem-solution approach, the Boards of Appeal of the EPO have repeatedly defined the closest prior art as a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, ie requiring a minimum of structural modifications (cf. Case Law of the Boards of Appeal of the European Patent Office, 5th Edition, 2006, Chapter I.D.3.1, with further reference to decisions).

42. In the present case, the board considers that, as closest prior art, a document concerning the modification of alpha-amylases must be chosen, since it shares with the present invention not only the objective, but also the relevant structural features. Having this in mind, document (5) seems to be the most suitable starting point among the prior art documents on file.

43. Document (5) teaches the modification of a thermostable alpha-amylase from *B. stearothermophilus* by exchanging various amino acid residues located near the catalytic site, with the aim of assessing the role of the exchanged residues in catalysis under specific conditions. It is stated in document (5) that:

> "*... the enzyme activity, temperature/activity profile and pH/activity profile can be modified by site-directed mutagenesis of functionally non-essential amino acid residues adjacent to or near the catalytic residues... This type of strategy presents a new approach to engineering enzymes with improved functions under specific conditions, e.g. an enzyme that works efficiently at low temperatures, or one that has an altered pH optimum or substrate specificity.*" (cf. paragraph bridging pages 901 and 902)

Technical problem

44. Starting from document (5), the technical problem to be solved can be defined as producing further mutant alpha-amylases with improved properties, in particular with regard to oxidation and temperature stability, as

well as improved detergent compositions containing such mutant alpha-amylases and methods employing mutant alpha-amylases with improved temperature stability.

45. In view of the statements in document (5) quoted above, the sole formulation of this technical problem does not require inventive skills.

Solution to the technical problem

46. The solution to this technical problem proposed in the patent is a mutant alpha-amylase as defined in claim 1.

47. The board is convinced that the technical problem formulated above is in fact solved by mutant *Bacillus* alpha-amylases being derived from a precursor *Bacillus* alpha-amylase either by deletion of a methionine which corresponds in position in the primary structure to M+197 in *B. licheniformis* alpha-amylase, or by substitution of this methionine by alanine, threonine or cysteine.

48. The patent provides experimental evidence for the improved properties of such alpha-amylases. In particular, a mutant alpha-amylase derived from *B. licheniformis* alpha-amylase by substitution of the methionine at position 197 by alanine is shown to be more stable under oxidative conditions (cf. Figures 13 and 14). The substitution of methionine by threonine or cysteine results in mutant alpha-amylases which are more stable at high temperatures (cf. Figure 10).

49. The appellant did not dispute the purported improvement of the properties of mutants in which the methionine at

position 197 has been deleted. The appellant, however, argued that, whereas claim 1 encompasses mutant alpha-amylases derived from **any** *Bacillus*, the experimental evidence provided in the patent concerns solely mutant *B. licheniformis* alpha-amylases. Whereas this is true, it is noted that no evidence has been provided by the appellant casting any doubts in respect of the improved properties of other mutant *Bacillus* alpha-amylases. In view of the similarity in the primary structure between *Bacillus* alpha-amylases having a methionine at a position corresponding to M+197 in *B. licheniformis* alpha-amylase (cf. Figure 3B in the patent and document (A2)), the board has also no serious doubts that the results provided in the patent for mutant *B. licheniformis* alpha-amylases as claimed can be extrapolated to mutant alpha-amylases derived from other *Bacillus* species. Thus, the board accepts that the technical problem is solved over the whole scope of claim 1.

50. It was also not questioned by the appellant that the subject-matter of claims 10, 14 and 17 solves the technical problem formulated above. In fact, the improved properties of mutant alpha-amylases having alanine, threonine or leucine at position 197 as claimed in claims 10 and 14 (see in this respect Figures 13 and 14 of the patent, in which an improved oxidation stability of this mutant is shown) make plausible an improvement of the properties of detergent compositions containing any of these enzymes. Finally, the use of thermally more stable mutant alpha-amylases having a threonine or cysteine residue at a position corresponding to M+197 is expected to lead to an

improved method of liquefying a granular starch slurry (cf. claim 17).

Not obvious to try

51. The board disagrees with the appellant in that the deletion or substitution of a methionine which corresponds in position in the primary structure to M+197 in *B. licheniformis* alpha-amylase was obvious to a person skilled in the art, in view of document (9) or document (12).

52. Document (9) may provide an incentive for the improvement of alpha-amylases used in detergents, but does not provide any hint with respect to the deletion or substitution of the specific methionine residue at position 197. Nor does document (12), which is rather concerned with three-dimensional modelling of the alpha-amylase protein, or any other prior art document presently on file.

53. In the absence of any hint towards the proposed solution in the prior art, the board must conclude that the solution proposed in the claims on file was not obvious to try and, therefore, the subject-matter of claims 1 to 17 involves an inventive step.

54. It follows from the above that, taking into consideration the amendments made during the appeal proceedings, the respondent's sole request and the invention to which it relates meet the requirements of the EPC (cf. Article 102(3) EPC). Thus, the decision must be set aside and the patent maintained in amended form on the basis of this request.

Remittal to the opposition division (Article 111(1) EPC)

55. The case is remitted to the opposition division for adaptation of the description and the figures of the patent to claims 1 to 17 on file and for grant of a patent on this basis. In adapting the description, attention must be paid to the definition of the methionine residue to be deleted or exchanged, so that the amendments introduced to the patent do not offend against Article 123(2),(3) EPC.

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 in amended form on the basis of claims 1 to 17 filed during oral proceedings and the description and figures 1 to 15 to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski F. Davison-Brunel