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D E C I S I O N
of 9 June 2005

Case Number: T 0660/02 - 3.3.8

Application Number: 92901590.7

Publication Number: 0563169

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Language of the proceedings: EN

Title of invention:
Enzyme mutants having a low degree of variation of the molecular charge over a pH range

Patentee:
Novozymes A/S

Opponent:
Genencor International, Inc.

Headword:
Enzyme mutants/NOVOZYMES

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and auxiliary requests 1 to 5: inventive step (no)"
"Auxiliary request 6: added matter (no)"
"Sufficiency of disclosure (yes)"
"Inventive step (yes)"

Decisions cited:
T 0537/02

Catchword:
-

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Case Number: T 0660/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 9 June 2005

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 24 April 2002 concerning maintenance of the European patent No. 0563169 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
M. B. Günzel

Summary of Facts and Submissions

I. The patent proprietor (appellant I) and the opponent (appellant II) each lodged an appeal against the interlocutory decision of the opposition division dated 24 April 2002, whereby the European patent No. 0 563 169 was maintained on the basis of the third auxiliary request filed at the oral proceedings on 23 January 2002. The patent had been granted on European application No. 92 901 590.7 which originated from an international application published as WO 92/11357 (to be referred to in the present decision as the application as filed).

II. The grounds for opposition were that, as set forth in Article 100(a) EPC, the invention was not inventive (Article 56 EPC), and, that, as set forth in Article 100(b) EPC, the invention was not sufficiently disclosed (Article 83 EPC).

III. The main request and the first auxiliary request were refused by the opposition division for lack of sufficient disclosure (Article 83 EPC) and the second auxiliary request for the presence of added matter (Article 123(2) EPC).

IV. Each appellant filed a statement of grounds of appeal, appellant I relying on the main request (claims as granted) and on the four auxiliary requests which were on file before the opposition division.

V. On 21 August 2003 appellant I filed a reply to the statement of grounds of appellant II and submitted therewith an amended new auxiliary request 3 in replacement of that accepted by the opposition division.

VI. A communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was then sent to the parties. In this communication, reference was made to decision T 537/02 of 19 October 2004.

VII. In reply to the Board's communication, appellant I filed with its letter of 6 May 2005 additional auxiliary requests 5 and 6, and with its letter of 9 May 2005 two pH titration curves, for subtilisin 309 and the mutant subtilisin protease a+g'.

VIII. Oral proceedings took place on 9 June 2005, at which appellant I filed a main request, which exactly corresponded to the first auxiliary request considered in the decision under appeal, and six auxiliary requests (1 to 6) to replace all the requests on file.

IX. Claim 1 of the main request and of auxiliary requests 1 to 5 read as follows:

(a) main request:

"1. A mutant subtilisin protease, characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range

of about pH 7 to about pH 11, said protease comprising at least one of the following substitutions: H17Q, H39S, E54D, H120N, Y167E, Y167F, Y171V, Y192E, Y192F, Y209F, Y214F, Y226S, Y263F **wherein, if the protease has only the substitution E54D out of the said substitutions, then it additionally has the K94R substitution**." (emphasis added by the Board to show the difference to claim 1 as granted, namely the presence of the sentence in bold characters)

(b) Auxiliary request 1:

"1. A mutant subtilisin protease, characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising at least one of the following substitutions: H17Q, H39S, E54D, H120N, Y167E, Y167F, Y171V, Y192E, Y192F, Y209F, Y214F, Y226S, Y263F, **wherein the protease comprises the Y263F substitution; or it comprises more than one of the said substitutions; or it comprises at least one of the said substitutions and additionally at least one of the following substitutions: K27R, Y91F, K94R, H120D, Y214T, K235L, K235R, K251E and K215N.**" (emphasis added by the Board to show the difference to claim 1 of the main request)

(c) Auxiliary request 2:

"1. A mutant subtilisin protease, characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising at least one of the following **sets of** substitutions:

b - H17Q+K27R+H39S;

c - E54D+Y91F+K94R;

d - E54D+Y91F+K94R+H120D;

e - E54D+Y91F+K94R+H120N;

f - Y167F+Y171V+Y192F+Y209F+Y214T;

g - K235L+K237R+K251E+Y263F;

h - K235L+K237R+K251N+Y263F;

i - H226S+K235L+K237R+K251N+Y263F;

k - H226S+K235L+K237R+K251E+Y263F;

g'- K235R+K237R+K251E+Y263F;

h'- K235R+K237R+K251N+Y263F;

i'- H226S+K235R+K237R+K251N+Y263F;

j'- H226S+K235R+K237R+K251E+Y263F."

(emphasis added by the Board to show the difference to claim 1 of the main request)

(d) Auxiliary request 3:

"1. A mutant subtilisin protease, characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH

range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising one of the following **sets of** substitutions:
E54D+Y91F+K94R
K235R+K237R+K251E+Y263F, and
K235R+K237R+K251E+Y263F+K27R."
(emphasis added by the Board to show the difference to claim 1 of the main request)

(e) Auxiliary request 4:

"1. A mutant subtilisin protease, **which is a mutant of a parent enzyme selected from subtilisin BPN', subtilisin amylosacchariticus, subtilisin 168, subtilisin mesentericopeptidase, subtilisin Carlsberg, subtilisin DY, subtilisin 309, subtilisin 147, subtilisin thermitase, protease TW7, protease TW3, and proteinase and aqualysin,** characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising at least one of the following substitutions: H17Q, H39S, E54D, H120N, Y167E, Y167F, Y171V, Y192E, Y192F, Y209F, Y214F, Y226S, Y263F."
(emphasis added by the Board to show the difference to claim 1 of the main request)

(f) Auxiliary request 5:

"1. A mutant subtilisin **309** protease, characterised in that it carries at least one mutation of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising at least one of the following substitutions: H17Q, H39S, E54D, H120N, Y167E, Y167F, Y171V, Y192E, Y192F, Y209F, Y214F, Y226S, Y263F."
(emphasis added by the Board to show the difference to claim 1 of the main request)

X. Auxiliary request 6 consisted of six claims.

(a) Claim 1 read as follows:

"1. A mutant subtilisin **309** protease, characterised in that it carries **mutations** of its amino acid sequence resulting in a lower degree of variation, compared with the parent protease, of the molecular charge of the protease over a pH range of at least 0.5 pH unit within the pH range of about pH 7 to about pH 11, said protease comprising at least one of the following **sets of** substitutions:
(i) K235R+K237R+K251E+Y263F
(ii) K235R+K237R+K251E+Y263F+K27R
(iii) E54D+Y91F+K94R."
(emphasis added by the Board to show the difference to claim 1 of the main request)

(b) Claims 2 to 6 were dependent on claim 1 and directed to particular amendments thereof.

XI. The following documents are referred to in the present decision:

(D5) WO-A-89/06279 (published on 13 July 1989)

(D7) WO-A-91/00345 (published on 10 January 1991)

XII. The submissions made by appellant I (patent proprietor), insofar as they are relevant to the present decision, may be summarised as follows:

Inventive step (auxiliary requests 1 to 5)

The problem that the invention solved was to provide enzymes that performed better than those in the prior art. As was demonstrated in the patent, these enzymes had an improved wash performance as a result of having less variation of electrical charge over at least some of the pH range 7 to 11.

The evidence provided in the patent in suit was sufficient, even if a limited number of mutant subtilisin proteases had been tested as to their wash performance as reported in Example B, to establish that an association existed between the presence of a mutation chosen out of thirteen specific substitutions which resulted in the flattening of the titration curve over at least some of the pH range 7 to 11 and the improvement of the wash performance. In the absence of evidence (which should have been provided by

appellant II who had not discharged its burden of proof in this respect) that the mutation Y263F and the mutation E54D (in association with the mutation K94R) were not responsible for the wash performance improvement exhibited by the three mutant proteases tested (B, C and a+g'), the contrary had to be accepted and an extrapolation could be made with respect to mutants containing any of the eleven other specific substitutions referred to in claim 1 of each of the requests.

No parallel with the reasoning made in decision T 537/02 (supra) could be drawn as the claimed subject-matter was not the same and the facts were different in view of the filing by appellant I of additional titration curves.

Auxiliary request 6

- Added matter and clarity

Claim 14 in the application as filed provided a support for the subject-matter of claim 1 of this request. Clarity of claim 1 was not open to discussion, as the appellant II's objection had not been raised against an amendment occasioned by the grounds of opposition.

- Sufficiency of disclosure

It was the burden of appellant II to provide evidence showing that mutant proteases encompassed by claim 1 of auxiliary request 6 could not have been derived from mutant proteases B, C and a+g' by the introduction therein of further substitutions.

- Inventive step

Insofar as the mutant proteases B, C and a+g' were acknowledged to represent inventive embodiments of claim 1, it had to be considered that claim 1 of auxiliary request 6 as a whole involved an inventive step as any other mutant protease encompassed by the claim had included the technical features of any of said three mutant proteases tested. In any case, appellant I had to be given the benefit of doubt.

XIII. The submissions made by appellant II (opponent), insofar as they are relevant to the present decision, may be summarised as follows:

Inventive step (auxiliary requests 1 to 5)

There was no clear causal relationship between the concept of curve flattening between pH 7 and pH 11 and improvements in wash performance.

The concept of reducing variation charge over an alkaline pH range (curve flattening) had no link to any technical benefit and provided no contribution to the art.

The improvements shown in Example B could only be provided by the specific mutations present in the exemplified mutant proteases B, C and a+g'.

The only contribution to the art made by the patent was the provision of three specific combinations of mutations in the form of mutant proteases B, C and

a+g', each of which provided some technical benefit, but there were no concept fit for generalisation which could be derived from these mutants.

The reasoning made in decision T 537/02 (supra) which was based on the analysis of the same wash performance experiments, ie with the same mutant proteases, also applied to the claims of these requests.

Auxiliary request 6

- Added matter and clarity

There was no support in the application as filed for embodiments of claim 1 which contained in addition to the set of substitutions (ii) additional unspecified substitutions. Indeed, the set of substitutions (ii) was only referred to once in the application as filed, in Example B, in relation with the particular mutant protease a+g' which differed from the parent enzyme, subtilisin 309, only by the presence of the five substitutions of the set (ii). Therefore, claim 1 represented a non-permissible generalisation of a particular example and contained added matter.

It was not clear whether the mutations first mentioned in the claim and the specific substitutions referred to later in the claim were one and the same.

- Inventive step

The provision of three specific combinations of mutations in the form of mutant proteases B, C and a+g', each of which providing some technical benefit,

represented a contribution to the art. But there was no indication that additional mutations in said muteins did not abrogate the said beneficial effects. Therefore, claim 1 of auxiliary request 6 lacked inventive step in its breadth as it could not rely on any positive data from the examples.

- Sufficiency of disclosure

There was no indication in the patent in suit that also mutant proteases other than the three exemplified and encompassed by claim 1 would exhibit a reduced variation charge over an alkaline pH range (curve flattening). This amounted to an insufficiency of disclosure.

XIV. As main request, appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed during the oral proceedings. As auxiliary requests 1 to 5, appellant I requested that the patent be maintained on the basis of any of auxiliary requests 1 to 5 filed during the oral proceedings. As auxiliary request 6, appellant I requested that the patent be maintained with the following documents: claims and description pages 4, 5, 6, 8, 10, 13, 14, 19 as filed during the oral proceedings, remaining description pages and Figures 1 to 4 as granted.

XV. Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request

Article 56 EPC (claim 1)

1. **Subtilisins**, ie within the meaning of the patent in suit (see from line 50 on page 5 to line 5 on page 6 in the patent specification) subtilisin BPN' and serine proteases having homology therewith, such as subtilisin amylosacchariticus, subtilisin 168, subtilisin Carlsberg, subtilisin DY, subtilisin 309, subtilisin 147, thermitase, Bacillus PB92 protease (all produced by Gram-positive bacteria), or such as aqualysin (produced by a Gram-negative bacterium), or such as proteinase (produced by a fungus) **and muteins thereof** exhibiting physical properties advantageous to industrial application, in particular in the detergent industry, were known in the art. Document D5 is regarded in this respect as the closest state of the art. It is reported therein that subtilisin genes were cloned from the 147 and 309 variants of the bacterium Bacillus lentus, and that the cloned genes were sequenced. By comparing the deduced amino acid sequences of subtilisins 147 and 309 with each other and then, respectively, with sequences of other known subtilisins, sites were identified which, upon mutation, might alter the physical properties of the parent enzyme. Site-directed mutagenesis was used to generate mutations at several of these sites in the subtilisin 309 gene. The resultant mutant enzymes were then expressed in a Bacillus strain and tested in respect of various physical and chemical parameters. Several of

the mutants were shown to exhibit properties desirable in enzymes used in detergent compositions.

2. In view of this state of the art, the technical problem to be solved by the invention may be regarded as the provision of further muteins of subtilisin, in particular subtilisin 309, showing improved properties in relation to their wash performance compared with a wild-type subtilisin.

3. As a solution, claim 1 proposes a mutant subtilisin protease that contains at least one of thirteen specific mutations, each of said mutations (the mutation E54D in association with the mutation K94R) resulting in a lower degree of variation, compared with the parent protease, of its molecular charge over the alkaline pH range of 7 to 11. Further sets of additional mutations are indicated in claim 7 which refers back to claim 1.

4. As the simple proposal of further mutations *per se* is considered to be an exercise which involves no inventive talent, the proper question, within the framework of the evaluation of the inventive step, to be addressed is whether the proposed solution solves indeed the underlying technical problem, ie whether there is a plausible cause-effect relationship between the proposed mutation and the improved wash performance.

5. To answer this question, one has to take into consideration the wash tests which are reported in the patent in suit.

6. Wash tests have been performed using subtilisin 309 and three muteins thereof encompassed by claim 1, namely proteases B, C and a+g', each of them containing a set of mutations including either the mutation **Y263F** (see proteases B and a+g'), or the mutation **E54D** (in association with the mutation K94R; see protease C) which are two of the thirteen mutations listed in claim 1 (see Example B on pages 14 to 16 in the patent specification). In addition to the mutations E54D and K94R, protease C contains the mutation Y91F and in addition to the mutation Y263F, protease B contains the three mutations K235R, K237R and K251E while protease a+g' contains the four mutations K235R, K237R, K251E and K27R.

7. Titration curves with respect to proteases B and C have been provided in the patent (see Figure 1) while titration curves with respect to protease a+g' have been enclosed with the appellant I's letter of 9 May 2005.

8. As a measure of the wash performance, differential reflectance has been used and an improvement factor has been calculated from a dose-response curve which relates to the amount of enzyme needed for each of the mutant proteases tested for obtaining a given differential reflectance in comparison with subtilisin 309. From the table bridging pages 15 and 16 in the patent specification, it can be seen that an improvement of the wash performance was observed for each of the three muteins B, C and a+g'. These results show that **co-introduction** of any of the three sets of mutations K235R+K237R+K251E+**Y263F**, **E54D**+Y91F+K94R and K27R+K235R+K237R+K251E+**Y263F** in subtilisin 309 has

resulted in a mutant protease, namely protease B, protease C and protease a+g', performing better than the parent wild-type subtilisin 309 during wash processing at a pH within the pH range of 7 to 11 at which the titration curves of the proteases are flattening compared to that of subtilisin 309. However, the experiment does not allow to evaluate the individual impact of each of the three, four or five mutations of each of the sets of mutations on the wash performance. Nor does it permit to ascribe the improvement in wash performance to the specific mutation Y263F or E54D (the latter in association with the mutation K94R) out of the three, four or five mutations of each set. Thus, since it is not possible to establish a causal link between the specific mutation and the improvement in wash performance, it is impossible to plausibly state that the proposed structural change constitutes indeed a solution to the underlying technical problem.

9. The proof lacks in the file that any of the mutant proteases tested represents a solution to the technical problem. In the absence of a general concept associating a mutant protease, which differs from the parent subtilisin by the presence of just one of the thirteen specific mutations and by the resulting flattening of the titration curve at a given pH within the pH range of 7 to 11, with a wash performance improvement at that pH, it should have been proved **for each of the compounds encompassed by the claim** that it exhibited such an improvement. Appellant I has not discharged its burden of proof in this respect.

10. Under these circumstances, inventive step cannot be acknowledged, as simply proposing a series of possible mutations without showing an effect is not considered to involve any inventive contribution over the prior art wherein a number of other mutations has already been proposed. This finding is identical to the one of decision T 537/02 (supra, see in particular points 14 to 22 of the Reasons). In the said decision, the reasoning was also based on an analysis of exactly the same wash performance experiment and this applies in a similar way to the present case in spite of the fact that titration curves for the mutant protease a+g' have here been filed (cf Section VII).

11. Thus, the requirements of Article 56 EPC are not met by the main request which, consequently, has to be refused.

Auxiliary requests 4 and 5

Article 56 EPC (claim 1)

12. Claim 1 of auxiliary request 4 essentially differs from claim 1 of the main request in that the parent enzyme is selected from a limited list of enzymes (see granted claim 9) while claim 1 of auxiliary request 5 essentially differs from claim 1 of the main request in that the parent enzyme is subtilisin 309. However, these modifications cannot change the reasoning made in respect of claim 1 of the main request which applies identically to these two auxiliary requests. Thus, the requirements of Article 56 EPC are not met by auxiliary requests 4 and 5 which, consequently, have to be refused.

Auxiliary request 1

Article 56 EPC (claim 1)

13. Claim 1 of auxiliary request 1 is *inter alia* directed to those particular embodiments of claim 1 of the main request, wherein the claimed mutant subtilisin protease comprises the **Y263F** substitution together with at least one of the twelve other specific mutations referred to therein.

14. Document D5 remains the closest state of the art and the underlying technical problem is the same as mentioned in point 2 above, the solution being *inter alia*, a mutant subtilisin protease that contains the **Y263F** substitution together with at least one of the twelve other specific mutations, the said mutations resulting in a lower degree of variation, compared with the parent protease, of its molecular charge over the alkaline pH range of 7 to 11.

15. As said above (see point 8) the wash performance experiment reported in the patent does not permit to ascribe the improvement in wash performance to the specific mutation **Y263F**. Moreover, as no mutant protease comprising the **Y263F** substitution together with at least one of the twelve other specific mutations has been tested, there is no indication or suggestion in the patent in suit that such a mutant protease would induce a wash performance improvement at a pH comprised between 7 and 11 for which a flattening of the titration curve is expected and, thereby, would represent a solution to the technical problem.

16. Therefore, the requirements of Article 56 EPC are not met by auxiliary request 1 which, consequently, has to be refused.

Auxiliary requests 2 and 3

Article 56 EPC (claim 1)

17. Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that it is directed to a mutant subtilisin protease comprising one of the sets of substitutions [E54D, Y91F and K94R], [K235R, K237R, K251E and Y263F] and [K235R, K237R, K251E, Y263F and K27R], the parent subtilisin being any subtilisin within the meaning of the patent in suit. Further specific sets of substitutions to be added to those of claim 1 are indicated in claim 7.

18. Document D5 is again taken as the closest state of the art. The technical problem to be solved by the invention is the same as mentioned at point 2 above. The solution thereto as proposed in claim 1 is a mutant subtilisin protease that contains at least one set of substitutions as indicated resulting in a lower degree of variation, compared with the parent protease, of its molecular charge over the alkaline pH range of 7 to 11. Claim 7 proposes further specific sets of substitutions in addition to those of claim 1.

19. The question to be addressed is whether the proposed solution solves indeed the underlying technical problem, ie whether there is a cause-effect relationship between the three particular sets of substitutions and the improved wash performance over the whole range claimed,

ie, not only for subtilisin 309 but also for any other subtilisin as meant in the patent in suit, and whether this holds true also when further specific sets of substitutions according to claim 7 are introduced.

20. The wash performance experiment reported in the patent indicates that mutant proteases B, C and a+g' exhibit a wash performance improvement in comparison with subtilisin 309, their parent subtilisin, which means that these muteins of subtilisin 309 solve indeed the underlying technical problem.

21. Nevertheless, the said wash performance experiment provides no indication that mutant proteases derived from any subtilisin other than subtilisin 309 by the introduction of anyone of the sets of mutations [E54D, Y91F and K94R], [K235R, K237R, K251E and Y263F] and [K235R, K237R, K251E, Y263F and K27R] would also exhibit a wash performance improvement. Nor is it shown that the addition of at least one of the sets of substitutions listed in claim 7 does not alter the effect.

22. Subtilisins within the meaning of the patent in suit represent a group of proteases sharing some structural homology (with reference to subtilisin BPN') - which may be regarded as an indication of the probable existence of a common ancestor. Nevertheless they differ substantially in the nature and place of a number of their amino acid residues (see, for example, as expert evidence, Table I on pages 14 to 20 of document D7 which shows that subtilisin 309 and subtilisin 147 share only 65% of their amino acid residues). Therefore, it is not possible to extrapolate

the conclusions drawn on the basis of the reported experiment carried out with subtilisin 309 and proteases B, C and a+g' to any other subtilisin and mutant proteases derived therefrom. Consequently, it cannot be considered that the proposed solution solves indeed the underlying technical problem in the case where the parent subtilisin is a subtilisin other than subtilisin 309.

23. Under these circumstances, inventive step cannot be acknowledged for the whole breadth of the claim. Thus, the requirements of Article 56 EPC are not met by auxiliary request 3 which, consequently, has to be refused.

24. According to an aspect, claim 1 of auxiliary request 2 is directed *inter alia* to the same mutant proteases as those covered by claim 1 of auxiliary request 3 (see the embodiments thereof according to which the mutant protease contains either of the sets of substitutions c and g'). Moreover, the claim is directed to a number of other specific muteins for which no effect is shown. Therefore, for the same reasons as for claim 1 of auxiliary request 3, the requirements of Article 56 EPC are not considered to be met by auxiliary request 2 which, consequently, has to be refused.

Auxiliary request 6

Formal requirements

25. Appellant II had no objections under Article 123(3) EPC. Nor does the Board have any. Therefore, the requirements of that article are met.

26. A support for the claimed subject-matter can be found in claim 14 in the application as filed (see the published international application WO 92/11357) in view of the wording "it carries at least one of the following mutations or sets of mutations" when considering the mutation "a" (K27R) and the two sets of mutations "c" (E54D+Y91F+K94R) and "g'" (K235R+K237R+K251E+Y263F). Therefore, the requirements of Article 123(2) EPC are also met.

27. Appellant II contends that claim 1 lacks clarity in that it is not clear whether the mutations first mentioned in the claim and the substitutions referred later on are one and the same. As the wording objected to, ie "mutations" in line 1 of the claim and "substitutions" in line 1 of the claim, is the same as in claim 1 as granted, the only difference being the list of substitutions proposed, the appellant's II objection under Article 84 EPC is not against an amendment newly introduced and is thus not open to discussion before the Board.

Article 56 EPC

28. This set of claims concerns in essence the three exemplified mutant proteases B, C, and a+g' derived from subtilisin 309 for which an improved wash performance has been shown in the specification (cf point 20 supra). For these muteins an inventive step can thus be acknowledged. This is not denied by appellant II which however maintains that claim 1 as formulated (cf "at least" language) covers also the possibility of combining in different ways the

substitutions (i), (ii) and (iii) and, furthermore, the possibility to introduce further unspecified mutations (cf "carries mutations" language). In its view, the effect of such further changes is unpredictable and thus, according to the rationale which led the board to deny inventive step to the preceding requests, inventive step should be denied to the whole of the claim. The Board cannot follow such line of reasoning. This is because, it having been shown that **each of the sets** of mutations B, C, and a+g' results in a positive effect on the wash performance, and it being a permanent requirement of the claim that the mutations introduced in subtilisin 309 result in a lower degree of variation of the molecular charge, there is no *a priori* reason to believe that any of the few possible combinations (cf "at least" language) would not equally solve the underlying technical problem. No proof to the contrary has been put forward by appellant II. As for the possibility to introduce further **unspecified** mutations in the advantageous muteins of the claim, this is a matter of pure speculation as no further specific mutations are indicated in claim 1 or in the subclaims. For these reasons, the Board concludes that the whole of claim 1 together with its dependent claims 2 to 6 involves an inventive step.

Article 83 EPC

29. Proteases B, C and a+g' are sufficiently disclosed in the sense that the skilled person would be in a position to prepare each of them and to test their properties. In this respect, the same conclusions reached in the parallel case of decision T 537/02 (supra, see in particular points 2 to 8) apply to the

present case. Therefore, auxiliary request 6 is considered to meet the requirements of Article 83 EPC.

Conclusion

30. For the above reasons it is the Board's judgment that auxiliary request 6 can form a basis for the maintenance of the patent in an amended form.

Adaptation of the description

31. Appellant I has proposed amendments to the description pages 4 to 6, 8, 10, 13, 14 and 19 which have not been objected to by appellant II. The Board considers that those amendments result in an appropriate adaptation of the description to the claims of auxiliary request 6 and are in compliance with the requirements of Article 123(2) 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 with the following documents:

   Claims 1 to 6 of auxiliary request 6 filed during oral proceedings;

   Description pages 4 to 6, 8, 10, 13, 14 and 19 as filed during the oral proceedings, description pages 2, 3, 7, 9, 11, 12 and 15 to 18 as granted;

   Figures 1 to 4 (pages 23 to 40) as granted.

The Registrar: The Chairman:

A. Wolinski L. Galligani