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 30 November 2004

Case Number: T 1067/02 - 3.3.8

Application Number: 92900779.7

Publication Number: 0561907

IPC: G01N 33/53

Language of the proceedings: EN

Title of invention:
Proteins with changed epitopes and methods for the production thereof

Patentee:
Novozymes A/S

Opponents:
(01) Baxter Aktiengesellschaft
(02) Genentech, Inc.
(03) GENENCOR INTERNATIONAL INC.

Headword:
Changed epitopes/NOVOZYMES

Relevant legal provisions:
EPC Art. 123(2)(3), 83

Keyword:
"Main request - added subject-matter (yes)"
"First and second auxiliary requests - extension of protection (yes)"
"Third, fourth and fifth auxiliary requests - added subject-matter (yes)"
"Sixth auxiliary request - extension of protection (yes)"
"Seventh auxiliary request - added subject-matter (no), extension of protection (no), sufficiency of disclosure (yes)"

Decisions cited:
T 0409/91, T 0694/92, T 0190/99, T 0537/02

Catchword:

-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1067/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 30 November 2004

Appellant: (Proprietor of the patent)
Novozymes A/S
Krogshoejvej 36
DK-2880 Bagsvaerd (DK)

Representative:
Sheard, Andrew Gregory
Andrew Sheard, Patent Attorney
P. O. Box 521
Berkhamsted, Herts. HP4 1YP (GB)

Respondent I: (Opponent 02)
Genentech, Inc.
1 DNA Way
South San Francisco
CA 94080-4990 (US)

Representative:
Kiddle, Simon John
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

Respondent II: (Opponent 03)
GENENCOR INTERNATIONAL INC.,
925 Page Mill Rd.
Palo Alto, CA 94304-1013 (US)

Representative:
Kiddle, Simon John
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 20 August 2002 revoking European patent No. 0561907 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
M. B. Günzel

Summary of Facts and Submissions

I. European patent No. 0 561 907, with the title "Proteins with changed epitopes and methods for the production thereof" and based on the European application No. 92 900 779.7 (published as WO 92/10755), was granted with 11 claims.

II. Notices of opposition were filed by three opponents requesting the revocation of the patent under Articles 100(a),(b) and (c) EPC. The opponent 01 withdrew its opposition when the case was still pending before the opposition division. The patent was revoked by the opposition division on the grounds that the main request, first, second, third and fourth auxiliary requests then on file did not fulfil the requirements of Article 83 EPC.

III. An appeal was lodged by the patentee (appellant), who maintained all the requests put forward before the opposition division.

IV. The opponents 02 and 03 (respondents I and II, respectively) filed jointly written comments on the grounds of appeal.

V. The parties were summoned to oral proceedings and, in a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal, they were informed of the board's preliminary, non-binding opinion.

VI. In reply to the board's communication, the appellant filed on 29 October 2004 further observations and a clean copy of the first, second, third and fourth

auxiliary requests corresponding to the ones originally put forward before the opposition division.

VII. Oral proceedings took place on 30 November 2004. During the oral proceedings, the appellant filed a new first and second auxiliary requests, whereas the previous first, second and third auxiliary requests were maintained as the third, fourth and fifth auxiliary requests, respectively. The previous fourth auxiliary request was amended and filed as a sixth auxiliary request. A seventh auxiliary request, comprising only subject-matter based on product claims, was also filed during the oral proceedings.

VIII. Claim 1 of the **main request** (claims as granted) read as follows:

*"1. A method of producing a protein variant evoking a lowered immunogenic response in animals including man in comparison to the response evoked by its parent protein, whereby said **complete** protein is epitope mapped using immunological and proteochemical methods, epitopes are determined, and at least one of said epitopes is changed through mutation of a DNA molecule coding for the expression of said **complete** parent protein or synthesis of a DNA molecule coding for the expression of said variant protein, said mutated or constructed DNA molecule subsequently being inserted into a vector for transformation or transfection into a suitable host, wherein said vector is functional or whereby said mutated or constructed DNA molecule is integrated functionally into the genome of said host, said protein variant is expressed in the host, and recovered.*" (emphasis added by the board).

IX. Claim 1 of the **first auxiliary request** read as follows:

"*1. A method of producing a variant of a protein of interest, the variant evoking a lowered immunogenic response in animals including man in comparison to the response evoked by its parent protein, whereby said protein of interest is epitope mapped using immunological and proteochemical methods, epitopes are determined, and at least one of said epitopes is changed through mutation of a DNA molecule coding for the expression of said parent protein of interest or synthesis of a DNA molecule coding for the expression of said variant protein, said mutated or constructed DNA molecule subsequently being inserted into a vector for transformation or transfection into a suitable host, wherein said vector is functional or whereby said mutated or constructed DNA molecule is integrated functionally into the genome of said host, said protein variant is expressed in the host, and recovered.*"

X. Claim 1 of the **second auxiliary request** read as follows:

"*1. A method of producing a variant of a protein of interest which is an industrial enzyme or medicinal product, the variant evoking a lowered immunogenic ...* (as claim 1 of the first auxiliary request)."

XI. Claims 1 of the **third and fourth auxiliary requests** read as claim 1 of the main request with the sentences :

"*...in which the parent protein and variants thereof are used for the production of antibodies,...*" (3rd AR)

"*...in which the epitope mapping uses polyclonal antibodies and is divided into two phases: (i) measuring the reactivity of the antibody preparations toward all proteins of interest; and (ii) measuring the reactivity left over to react with one antigen after reaction with another,...*" (4th AR)

added after the reference to the immunological and proteochemical methods.

XII. Claim 1 of the **fifth auxiliary request** read as claim 1 of the main request with the sentence:

"*...by combining this information with a 3-dimensional (3D) view,...*"

added after the reference to epitopes are determined.

XIII. Claim 1 of the **sixth auxiliary request** read as follows:

"*1. A method of producing a subtilisin 309 protease variant evoking a lowered immunogenic response in animals including man in comparison to the response evoked by subtilisin 309, whereby said subtilisin 309 is epitope mapped using immunological and proteochemical methods in which subtilisin 309 and variants thereof are used for the production of antibodies, epitopes are determined, and at least one of said epitopes is changed through mutation of a DNA molecule coding for the expression of said subtilisin 309 or synthesis of a DNA molecule coding for the expression of said variant protein, said mutated or constructed DNA molecule subsequently being inserted into a vector for transformation or transfection into a*

suitable host, wherein said vector is functional or whereby said mutated or constructed DNA molecule is integrated functionally into the genome of said host, said protein variant is expressed in the host, and recovered."

XIV. Claims 1 and 2 of the **seventh auxiliary request** (claims 8 and 9 as granted) read as follows:

"*1. A subtilisin protease variant, wherein the immunological potential has been changed in comparison to the parent protease, in that, in said protease changes have been performed among the amino acid residues at any one or more of positions 151, 174, 176, 193, and 196, by deletion, substitution, or insertion (single or multiple) adjacent to the indicated positions, whereby said subtilisin protease has an immunological potential lower than that of said parent protease, and in that it possesses at least one mutation affecting an amino acid residue occupying a position chosen from the group of positions 151, 174, 176, 193, and 196.*"

"*2. The protease as claimed in claim 1, further characterised in that it contains at least one or more sets of mutations affecting amino acid residues occupying a position chosen from the group of sets of positions:*
36+209, 89+120, 136+170, 36+89, 89+235, 136+195, 181+222, 209+222, 235+251."

XV. The following documents are cited in the present decision:

D1: B.J. Walsh and M.E.H. Howden, J. Immunol. Meth., 1989, Vol. 121, pages 275 to 280;

D13: H.M. Geysen et al., Science, 1987, Vol. 235, pages 1184 to 1190;

D14: H.M. Geysen et al., J. Mol. Recognition, 1988, Vol. 1, pages 32 to 41.

XVI. The appellant's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarised as follows:

Main request and third, fourth and fifth auxiliary requests
Article 123(2) EPC

The term "*protein*" was consistently used in the application as filed in the sense of "*complete protein*" and clearly distinct from peptides or polypeptides derived from said "*protein*". The immunological and proteochemical methods referred to in the application as filed always used "*the complete protein*" and thus, mapped the epitopes of "*the protein*" in the sense of "*the complete protein*". In particular, animals were immunised with "*the complete protein*" – not a peptide or a polypeptide - and sera from those immunised animals were incubated with "*the complete protein*" in ELISA assays too. The coating of the solid phase and the colorimetric assay used in these ELISA assays as well as the chemical synthesis of protein variants were

all proteochemical methods that used "*the complete protein*". None of the experimental work shown in the application as filed was performed using peptides or polypeptides. This was in contrast to the methods referred to in the prior art which used only peptides. There was a clear distinction between the peptide-based epitope mapping techniques of the prior art and the complete protein-based mapping techniques of the application as filed. It was only "*the complete protein*" that allowed the detection of conformational epitopes, which were the ones laying at the very heart of the invention.

In agreement with the established case law, the application had to be construed by a mind willing to understand. In the context of the claim itself and of the application as a whole, the interpretation of the term "*complete*" as requiring to map all the epitopes of the protein was unreasonable. The term "*complete*" was an adjective qualifying the noun "*protein*" and not an adverb that required the protein to be completely mapped. The term "*complete*" only clarified, in an explicit manner, the implicit meaning of the term "*protein*" as consistently used in the application as filed and it did not imply any change in the teaching of the disclosure as filed.

First and second auxiliary requests
Articles 123(3) and 84 EPC

The term "*complete*" was introduced during the examination proceedings as a mere clarification only and it did not add any technical feature. The deletion

of this term therefore did not amount to a violation of Article 123(3) EPC.

Claim 1 as granted embraced two possible embodiments. In a first embodiment, the protein was "*completely*" epitope mapped by immunological and proteochemical methods (all the epitopes of the protein were mapped). There were no conditions or limitations associated with those methods, which could be performed using peptides, polypeptides and/or "*the complete protein*" as well. In a second embodiment, "*the complete protein*" was mapped by immunological and proteochemical methods in the sense that the epitopes of the protein – not necessarily all epitopes - were mapped by methods that used - only and exclusively - the "*complete protein*" as opposed to peptides and polypeptides thereof. The first embodiment, however, arose only from an alleged lack of clarity and it went far beyond a reasonable interpretation of the patent when read as a whole. The deletion of the term "*complete*" removed only this lack of clarity and it did not extend the protection to peptide-based epitope mapping methods since in the patent in suit the term "*protein*" was consistently used in the sense of "*the complete protein*". The limitation to protein-based epitope methods was still implicitly present in claim 1 of the first and second auxiliary requests. Thus, claim 1 of these requests complied with Articles 123(3) and 84 EPC.

Sixth auxiliary request
Article 123(3) EPC

This request was restricted to subject-matter that related only to the specific protein "*subtilisin 309*".

The term "*complete*" in relationship to a particular protein specifically named in the claim was redundant, since the protein itself was always understood as being "*complete*" (the whole protein), as opposed to fragments (peptides or polypeptides) thereof.

Seventh auxiliary request
Article 83 EPC

There was no evidence on file showing that the immunological potential of a protein (or a variant thereof) could not be experimentally tested. It made no difference whether cell-mediated immunity or the production of antibodies were considered, since methods were available in the prior art for measuring both types of immunological response. On a reasonable interpretation of claim 1, it was apparent that the immunological potential had to be compared in the same species for both the parental and the variant protein – so as to compare like with like.

With regard to the cited case law, decisions T 694/92 (OJ EPO 1997, 408) and T 409/91 (OJ EPO 1994, 653) related both to broad claims functionally defined only, whereas in the patent in suit the desired effect was achieved by structurally well-defined subtilisin protease variants that could be easily constructed without encountering any particular technical problem. They were available to the skilled person without undue burden or inventive talent. The patent in suit further disclosed the presence of heteroclitic effects and of possible effects when combining several mutations. Whether or not these variants solved the technical problem underlying the patent in suit was a question

concerning the properties of these variants and merely related to Article 56 EPC. However, the requirements of Article 56 EPC were not assessed in the first instance, and certainly not for the specific variants of this request.

XVII. The respondents' arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarised as follows:

Main request and third, fourth and fifth auxiliary requests
Article 123(2) EPC

The term "*complete*" introduced ambiguity into claim 1 since it could be interpreted as requiring the use of "*the complete protein*" in epitope mapping or else that the protein had to be "*completely*" mapped - in the sense that all epitopes had to be characterized. None of these interpretations was directly derivable from the application as filed.

In the application as filed, the term "*complete*" was only found with reference to the deficiencies of the prior art, i.e. in relation to the problem addressed by the application, but not in relation to their solution. These deficiencies could be overcome with immunological and proteochemical methods that did not necessarily require the use of "*the complete protein*" as long as the epitopes folded in the same way as in "*the complete protein*" (use of globular domains, fusion in a display scaffold, etc). The immunological and proteochemical methods known to the skilled person were the ones that used protein fragments and these methods were not

excluded in the application as filed. Claim 1 used the term "*complete*" in a different context and with a technical meaning different from the one of the application as filed and thus, it contained added subject-matter which contravened Article 123(3) EPC.

First and second auxiliary requests
Articles 123(3) and 84 EPC

The term "*complete*" was a technical feature introduced into claim 1 during the examination proceedings in order to distinguish the claimed subject-matter from the prior art. Thus, the deletion of this term from the claim removed an essential technical feature and extended the scope of protection.

The immunological and proteochemical methods referred to in claim 1 of these auxiliary requests could be performed using protein fragments (peptides) too. If these methods were to be understood according to the appellant's interpretation of granted claim 1, i.e. as methods using – only and exclusively - the complete protein but not fragments thereof, then claim 1 of these requests was ambiguous and unclear.

Sixth auxiliary request
Article 123(3) EPC

The meaning of "*subtilisin 309 protease*" was not the same as that of "*complete subtilisin 309 protease*". The former was more generic and embraced variants of the "*complete subtilisin 309 protease*", such as short forms and small deletions thereof. Claim 1 of this auxiliary request did not exclude the use of fragments of the

"*subtilisin 309 protease*" in the immunological and proteochemical methods referred to in the claim. Thus, the deletion of the term "*complete*" extended the scope of protection in comparison to the granted claims.

Seventh auxiliary request
Article 83 EPC

The claimed subtilisin protease variants were required to have an immunological potential lower than that of the parent protein. However, the immunological response of a protein (or protein variant) depended on several mechanisms and factors, in particular the response of the B-lymphocyte cells (production of antibodies) and/or T-lymphocyte cells (stimulation of B-cells and cell-mediated immunity) and the immunological variability among different species and individuals of the same species. The patent in suit, however, failed to disclose any method for measuring this immunological potential. The skilled person was left in the dark as to the kind of assay to be used for determining this immunological potential. In the absence of this information, to test and to decide whether a certain subtilisin variant fulfilled the conditions required in the claim, placed an undue burden on the skilled person.

Claim 1 of this auxiliary request referred to changes among the amino acid residues at any one or more of several positions. These positions were cited in the description together with other positions, all of them chosen on the basis of a combination of experimental results and a 3-dimensional (3D) view. However, none of these positions was actually used in an immunological assay. The patent in suit did not provide any

experimental evidence supporting that changes in these residues resulted in the expected lower immunological potential. This was even worse for claim 2, which required not only changes at any one of the positions indicated in claim 1 but also the presence of sets of mutations at other positions. In that case, the experimental results disclosed in the patent in suit showed that for some of these sets of mutations the expected effect was not attained. In fact, a greater immunological potential was actually shown for some of them. Thus, the combination of claim 1 (positions with an ambiguous result) and claim 2 (positions that did not attain the desired effect) placed an undue burden on the skilled person. Reference was made to the established case law, in particular to decisions T 694/92 and T 409/91 (*supra*), which, for sufficiency of disclosure, stated that, after reading the description, the skilled person had to be in a position to perform the invention without undue burden over the whole area claimed. That was not the case for the patent in suit.

XVIII. The appellant (patentee) requested that the decision under appeal be set aside and that the case be remitted to the first instance for consideration of the remaining grounds of opposition on the basis of the claims as granted or, in the alternative, on the basis of the first to second auxiliary requests filed during the oral proceedings, or on the basis of first to third auxiliary requests filed on 29 October 2004, taken as third to fifth auxiliary requests, or on the basis of the sixth to seventh auxiliary requests filed during the oral proceedings.

XIX. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

Main request
Article 123(2) EPC

1. Claim 1 of this request (cf. Section VIII *supra*) is identical to claim 1 as originally filed except for the presence of the term "***complete***" which has been added before the expression "*protein is epitope mapped using immunological and proteochemical methods*" and between "*said*" and "*protein*".

2. The term "*complete*" is to be found nowhere in the application as filed except for the reference on page 4, line 6 of the application (as published). However, the term is found here in the context of a specific discussion of the problems encountered in the prior art when investigating the relative importance of the amino acid residues in the epitopes. There is stated that "*these investigations do not prove any effects to the epitopes in their native environment as parts of the complete protein, where phenomena only found in the tertiary structure of the protein, such as folding or the establishment of salt bridges etc., are in function.*" There is no direct link with the invention disclosed in the application and there is no indication in the application as filed that allows to derive from the reference to the prior art – in a clear and unambiguous manner - an extension of its meaning to the whole content of the application. Indeed, in the rest

of the application as filed, which is directly concerned with the invention ("*Summary of the Invention*", "*Detailed description of the invention*"), only the more general term "*protein*" is exclusively used.

3. The presence of the term "*complete*" in the specific context of claim 1 of the main request allows two different interpretations. The sentence "*said **complete** protein is epitope mapped using immunological and proteochemical methods*" might be interpreted, as the appellant does, as meaning that only the **complete** protein – in contrast to peptides or polypeptides thereof - is to be used for mapping the epitopes (protein-based epitope mapping methods), or else, as the respondents do, as meaning that all (**complete**) – conformational and linear - epitopes are to be mapped using any immunological and proteochemical method available in the prior art (protein-based and/or peptide-based epitope mapping methods). Both interpretations are regarded as being technically meaningful and plausible for a skilled person when reading, with a mind willing to understand (cf. T 190/99 of 6 March 2001), claim 1 of the main request. However, none of these interpretations is explicitly referred to as such in the application as filed. Moreover, they are not derivable directly and unambiguously therefrom.

4. As regards the former interpretation, the "*immunological and proteochemical methods*" mentioned in claim 1 are referred to in the application as filed only in general terms without any particular limitation to specific methods from which the reader would

necessarily derive the use of a "*complete*" protein (cf. page 4, lines 24 to 26 and page 6, lines 12 to 17). In particular, ELISA techniques are applied (cf. page 11, lines 16 to 19) where use is made of polyspecific polyclonal antibodies, i.e. antibodies with many specificities each reacting with each own epitope in the antigen (protein) or showing different reactivities to different related epitopes (cf. page 7, lines 9 to 14). However, in these techniques there is no limitation to the use of these antibodies nor to the use of a "*complete*" protein. Indeed, reference is explicitly made to the use of other antibodies, such as monospecific polyclonal antibodies or epitope specific monoclonal antibodies (cf. page 7, lines 1 to 30) and thus, the protein might be also a variant or a peptide of the "*complete*" protein.

5. The appellant has referred to the coating of the ELISA solid phases, the ELISA colorimetric assays and the chemical synthesis of protein variants as proteochemical methods which make use of the "*complete*" protein (cf. Section XVI *supra*). This is, however, only a possible, not a necessary, occurrence. In the application as filed, there is no limitation - either explicit or implicit - to (only and exclusively) these proteochemical methods wherein only the "*complete*" protein has to be used. Standard proteochemical methods known in the prior art are generally referred to in the application as filed and these involve: the proteolytic cleavage of a protein (or variants thereof) for producing peptides to be used either in the production of antibodies or directly in the detection of antibodies present in antisera raised against the protein; the chemical synthesis of peptides derived

from a protein (or variants thereof) to serve a similar purpose, etc. These methods do not by necessity require the use of a "*complete*" protein.

6. It has been argued by the appellant that the second interpretation given to claim 1, namely that all the epitopes of the protein are to be mapped (cf. point 3 *supra*), is unreasonable. However, in the light of the description of the application as filed and the references to the prior art cited therein (cf. D1, D13 and D14 on page 3, lines 19 to 29 of the application as published), such interpretation does not appear to be technically meaningless, inappropriate or beyond possible consideration by the skilled person. In particular, this prior art refers *inter alia* to an epitope mapping kit with a set of test peptides covering or overlapping the whole protein (cf. page 276, right-hand column, first full paragraph of document D1), a method for identifying linear and (partial) conformational epitopes (cf. page 1185, left-hand column, second and third full paragraphs of document D13) and the determination of the total (complete) number of (continuous) epitopes of a protein (cf. paragraph bridging pages 38 and 39 of document D14).

7. In conclusion, in the board's judgement, the unclear nature of the amendment introduced upon grant in claim 1 as filed, i.e. the introduction of the term "*complete*", allows two different interpretations and, although they are both technically sensible, neither of them is directly and unambiguously derivable from the general disclosure of the application as filed. Consequently, claim 1 of the main request extends beyond the overall teaching of this originally filed

application and thus, it contravenes the requirements of Article 123(2) EPC.

First and second auxiliary requests
Article 123(3) EPC

8. It has been argued by the appellant that the deletion of the term "*complete*" only excludes an (unreasonable) embodiment, namely the one concerning the mapping of all the epitopes of the protein, and it only limits – in an implicit manner - the claimed subject-matter to the second embodiment, namely the one concerning the use of protein-based mapping techniques. Thus, in its view, the subject-matter of claim 1 of the first and second auxiliary requests, which no longer comprises the term "*complete*", does not represent an extension of the protection conferred in comparison to the subject-matter of claim 1 as granted (cf. Section XVI *supra*).

9. The term "*complete*" has a technical connotation and its introduction, upon grant of the patent, in the context of claim 1 has had as a consequence that the claim can be given, from the technical point of view, two interpretations (cf. point 3 *supra*) with the result that the claim, by virtue of the lack of clarity, has been found to offend against Article 123(2) EPC (cf. point 7 *supra*). However, as the term has a limiting character under both interpretations (either the "*complete*" protein is mapped or "*complete*" mapping is carried out), its removal results in an offence against Article 123(3) EPC in consequence of the broadening of the scope of protection.

10. In fact, as regards the first interpretation, the term "*complete*" limited the immunological and proteochemical methods to those methods wherein only and exclusively the "*complete*" protein (protein-based epitope mapping techniques) was used. The deletion of the term "*complete*" removes this limitation and extends the scope of the claim so as to include methods that use peptides or polypeptides (peptide-based epitope mapping techniques). As regards the second interpretation, the term "*complete*" required the claimed method to map all the epitopes of the protein (or variant thereof). The deletion of the term "*complete*" removes this specific requirement and extends the scope of the claim so as to include methods that do not require to map all the epitopes of the protein but only some of them (at least one).

11. Consequently, claim 1 of the first and second auxiliary requests, which does not comprise the term "*complete*", contravenes Article 123(3) EPC.

Third, fourth and fifth auxiliary request
Article 123(2) EPC

12. Claim 1 of all these auxiliary requests comprises the term "*complete*" in a context identical to claim 1 as granted (cf. Sections XI and XII *supra*). Therefore, this term raises the issue of the two interpretations as for claim 1 as granted (cf. point 3 *supra*) the further amendments introduced in the claim having no influence on the issue itself. Thus, for the same reasons given above, these auxiliary requests offend against Article 123(2) EPC. Under these circumstances,

there is no need to examine the allowability of the other amendments.

Sixth auxiliary request
Article 123(3) EPC

13. Claim 1 of this request relates to the same method as granted claim 1 but limited to the production of the specific "*subtilisin 309 protease*" and "*variants thereof*" instead of generic proteins (cf. Section XIII *supra*), since the term "*complete*" is omitted from the claim. The "*subtilisin 309 protease*" is cited, among other subtilisin proteases, in claim 5 as granted, which is indirectly dependent on granted claim 1. The selection of "*subtilisin 309 protease*" actually restricts the choice of these proteins to a specific one.

14. However, claim 5 as granted - by its dependence on granted claim 1 – requires that the "***complete** subtilisin 309 protease is epitope mapped using immunological and proteochemical methods*", whereas claim 1 of this sixth auxiliary request only requires that the "*subtilisin 309 protease is epitope mapped using immunological and proteochemical methods*", with the absence of the term "*complete*". It has been argued by the appellant that the presence of this term in combination with a particular well-known protein, specifically named in the claim, is redundant and thus, the deletion of the term "*complete*" does not extend the scope of protection conferred (cf. Section XVI *supra*).

15. The board, however, cannot follow this argumentation since the presence of the term "*complete*" in

combination with a specific protein is considered to introduce the very same interpretations as for its combination with a generic protein. The presence of the term "*complete*" is not redundant but, in the context of the claim, technically meaningful and open to interpretation. In a first interpretation, the presence of the term "*complete*" emphasizes and requires that all the (complete) epitopes of the "*subtilisin 309 protease*" are to be mapped, whereas in a second interpretation the term "*complete*" restricts the immunological and proteochemical methods to the ones using – only and exclusively – the "*complete subtilisin 309 protease*". These requirements are removed by the deletion of the term "*complete*" and thus, for the reasons set out in points 9 and 10 *supra*, the scope of the protection conferred is extended by this deletion.

16. The board also notes that claim 1 of this sixth auxiliary request further states in an explicit manner that "*subtilisin 309 is epitope mapped using immunological and proteochemical methods in which subtilisin 309 and variants thereof are used for the production of antibodies*" (cf. Section XIII *supra*). These variants of subtilisin 309 are, however, generically defined and not characterized. Therefore, the use of small or short (deletion) variants of "*subtilisin 309*" or fragments thereof is not excluded, i.e. the claim embraces peptide-based epitope mapping methods.

17. Therefore, the sixth auxiliary request does not satisfy the conditions of Article 123(3) EPC.

Seventh auxiliary request
Articles 123(2)(3) and 84 EPC

18. The subject-matter of this request has been restricted to the subtilisin protease variants (and compositions thereof) of claims 8 to 11 as granted (cf. Section XIV *supra*). No formal objections were raised by the respondents against this request nor does the board have any objections.

Article 83 EPC

19. There is no doubt that the production of subtilisin variants with changes performed among the amino acid residues at one or more of the positions indicated in the claims of this auxiliary request does not require any undue burden or inventive talent from the person skilled in the art. The key question as regards sufficiency of disclosure in the present case is, therefore, whether the skilled person is in a position to assess the immunological potential of these subtilisin variants and to select the ones having the required lower immunological potential without undue burden or inventive skill.

20. Claim 1 requires the claimed subtilisin protein variants to have "*an immunological potential lower than that of said parent protease*" providing thus, in an explicit manner, a clear product as reference for the comparison and specifying in an implicit manner that for said comparison the same methods, systems and conditions, are to be used. It is further noted that the claimed subtilisin protease variants are not required to have a lower immunological potential in all

methods, systems and conditions, nor to have a particular degree of (lower) immunogenicity. In the light of the prior art on file, methods for determining the immunological potential of proteins (variants thereof) are available to the skilled person and the comparison of those immunological potentials neither requires a particular inventive skill nor represents an undue burden (cf. *inter alia* documents D1, D13 and D14).

21. The fact that, as alleged by the respondents (cf. Section XVII *supra*), for changes performed at some of the positions indicated in the claims, the required effect (lower immunological potential) is not attained, might be of relevance for the assessment of inventive step (Article 56 EPC) but it is of no relevance here in respect of the issue of sufficiency of disclosure. Indeed, in examining inventive step, it might have to be assessed whether the technical solution proposed by the patent in suit actually solves the technical problem underlying the patent, i.e. whether there is a cause-effect relationship between the proposed mutations and the lowered immunological potential (cf. recent decision T 537/02 of 19 October 2004).

22. The board thus comes to the conclusion that the claimed subject-matter of this seven auxiliary request fulfils the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution on the basis of the seventh auxiliary request filed during the oral proceedings.

The Registrar: The Chairman:

A. Wolinski L. Galligani