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Datasheet for the decision of 15 June 2018

Case Number: T 1754/12 - 3.3.08

Application Number: 03711261.2

Publication Number: 1530637

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Language of the proceedings: EN

Title of invention:
Subtilisin Carlsberg proteins with reduced immunogenicity

Patent Proprietor:
Genencor International, Inc.

Opponent:
Novozymes A/S

Headword:
Subtilisin variants with reduced immunogenicity/GENENCOR INTERNATIONAL

Relevant legal provisions:
EPC Art. 83, 113(1)

Keyword:
All requests - sufficiency of disclosure - (no
Substantial procedural violation - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1754/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 June 2018

Appellant I: (Patent Proprietor)	GENENCOR INTERNATIONAL, INC. 925 Page Mill Road Palo Alto, California 94304 (US)
Representative:	Kiddle, Simon John Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Appellant II: (Opponent)	NOVOZYMES A/S Krogshoejvej 36 2880 Bagsvaerd (DK)
Representative:	Wright, Andrew Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 June 2012 concerning maintenance of the European Patent No. 1530637 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. Montrone
	R. Winkelhofer

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietor (hereinafter appellant I) and the opponent (hereinafter appellant II) against the decision of an opposition division to maintain European patent No. 1 530 637, entitled "*Subtilisin Carlsberg proteins with reduced immunogenicity*" in amended form.

II. The patent had been opposed under Article 100(a) EPC on the grounds of lack of novelty and inventive step and under Article 100(b) EPC in the notice of opposition. Later in the opposition proceedings, also the compliance of the patent with Article 123(2) EPC was contested (Article 100(c) EPC).

III. The opposition division admitted Article 100(c) EPC as novel ground into the proceedings. Furthermore, it held in the decision under appeal that the main request met the requirements of Article 123(2) EPC, while the subject-matter of claim 9 lacked novelty. Furthermore, it took the view that auxiliary request 1 met the requirements of Article 54 EPC, while the subject-matter of claim 9 lacked an inventive step. Lastly, it held that auxiliary request 2 met the provisions of the EPC.

IV. Appellant I submitted with its notice of appeal a main request which corresponded to the main request dealt with in the decision under appeal. Furthermore, in reply to appellant II's statement of grounds of appeal, it filed eight auxiliary requests. Auxiliary requests 1 to 6 were new in the proceedings, while auxiliary requests 7 and 8 corresponded to auxiliary requests 1 and 2 dealt with in the decision under appeal.

Claims 1 of the main request and auxiliary requests 1, 4, 7 and 8 read:

"1. A method of reducing the immunogenicity of a subtilisin having at least 80% sequence identity to SEQ ID NO:1 by modifying at least one T-cell epitope of said subtilisin selected from the group consisting of SEQ ID NO:2, SEQ ID NO:90, SEQ ID NO:15 and SEQ ID NQ: 30."

Claims 1 of auxiliary requests 2, 3, 5 and 6 differ from claim 1 of the main request in that the term "*subtilisin*" is replaced by "*parent subtilisin*" and by adding the features "*to generate a modified subtilisin, wherein the immunogenic response produced by said modified subtilisin is less than the immunogenic response produced by said parent subtilisin*".

V. Appellant II submitted arguments why *inter alia* all claims of the main request did not comply with the requirements of Article 83 EPC.

VI. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's provisional opinion that *inter alia* the decision under appeal did not suffer from a substantial procedural violation and that claims 1 of the main request and auxiliary requests 1 to 8 did not meet the requirements of Article 83 EPC. The board indicated that it was thus minded to dismiss the appeal.

VII. In reply, both appellants withdrew their requests for oral proceedings.

VIII. Oral proceedings took place on 15 June 2018, in the absence of both appellants. At the end of the oral proceedings the board's decision was announced.

IX. Documents cited in this decision:

D7: WO 99/53038

D9: WO 02/077187

X. The submissions made by appellant I, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of the ground of opposition under Article 100(c) EPC - alleged substantial procedural violation

The opposition division held that the main request met the requirements of Article 123(2) EPC, although Article 100(c) EPC - due to a lack of substantiation in the notice of opposition - was not a valid ground of opposition. The admission of this new ground of opposition into the opposition proceedings suffered from a procedural error, since the issue of whether or not the objection of added matter was *prima facie* relevant was not considered by the opposition division. Although the opposition division eventually rejected the objection of added matter, the admission of this ground of opposition into the proceedings deprived appellant I of its right to prevent its introduction at the appeal stage by not giving its consent.

Sufficiency of disclosure (Article 83 EPC)

Main request - claim 1

The patent in suit provided, for example, in examples 4 and 5 ample guidance for the skilled person how to generate subtilisin Carlsberg variants with a reduced immunogenicity by the method according to claim 1. The methods applied in these two examples were likewise applied in documents D7 and D9 for the generation of subtilisin variants having a reduced immunogenicity, providing thus evidence that the skilled person had no difficulties with the practical implementation of the invention.

Although a certain amount of experimentation may be required to perform the invention, the implementation relied solely on routine practice for the skilled person in view of the extensive teaching and the knowledge of the specific T-cell epitopes to be modified, both as disclosed in the patent in suit. This was in line with the case law which allowed a reasonable amount of trial and error with regard to sufficiency of disclosure.

Furthermore, the fact that the patent in suit did not disclose a single example of the invention, i.e. a subtilisin Carlsberg variant having a reduced immunogenicity produced by the method according to claim 1, was immaterial since the invention did not go against a prevailing technical opinion and built on the work and techniques described in documents D7 and D9.

Lastly, the objections with regard to insufficient disclosure were based entirely on speculation and supposition and failed to meet the standards required,

in particular the raising of serious doubts substantiated by verifiable facts.

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

Admission of the ground of opposition under Article 100(c) EPC - alleged substantial procedural violation

The decision under appeal did not suffer from a substantial procedural violation, since all claim requests before the opposition division were amended and Article 101(3) EPC empowered the opposition division to decide on an amended patent in the light of the EPC as a whole, which included the examination of Article 123(2) EPC. Furthermore, the opposition division had a discretion to examine added matter as a new ground of opposition pursuant to Article 114(1) EPC, since the objection was *prima facie* relevant to prejudice the maintenance of the patent in suit.

Sufficiency of disclosure (Article 83 EPC)

Main request - claim 1

The subject-matter of all claims lacked sufficient disclosure in the patent in suit, since it did not provide an enabling disclosure of how to make subtilisin Carlsberg variants having a reduced immunogenicity.

Firstly, the patent in suit did not provide a single example of a subtilisin Carlsberg variant with the desired properties. The teaching of examples 4 and 5 was of no help for the skilled person, since it was

prophetic and rather represented a proposal for a research project.

Secondly, the patent in suit solely disclosed that a method of screening overlapping peptides of subtilisin Carlsberg in an *in vitro* T-cell based assay resulted in the identification of putative T-cell epitopes (see examples 2 and 3). Thus, the scientific basis of the patent in suit relied solely on the assumption that the proliferative response of T-cells observed in the *in vitro* assay of example 3 demonstrated that the regions of subtilisin Carlsberg recited in claim 1 were true T-cell epitopes.

Even assumed that the patent in suit indeed disclosed T-cell epitopes in subtilisin Carlsberg, the mere provision of these epitopes was not enough to ensure a reduced immunogenicity of the full-length protein. Appellant I itself submitted that "*Some modifications will decrease immunogenicity, others will be neutral, while still others will increase immunogenicity*" (see submission of 24 June 2011, page 2, second paragraph). Thus, the skilled person required additional information which modification within the T-cell epitope regions defined by the sequences encoded in SEQ ID Nos:2, 90, 15 and 30 reduced the immunogenicity of the protein.

Thus, contrary to the established case law, the patent in suit did not teach at least one way of obtaining subtilisin Carlsberg variants with a reduced immunogenicity.

In these circumstances, in order to nevertheless achieve this aim, the skilled person had to consider numerous parameters that all had a direct impact on the

induction of an immunogenic response. This included, for example, the type of T-cell epitope to be modified; the position(s) within the T-cell epitope to be modified; the type of modification, i.e. an addition, substitution or deletion of amino acids; in case of an addition: a selection from 20 naturally occurring amino acids; in case of a substitution: a selection from 19 alternative existing amino acids.

Thus in the present case, the skilled person could only establish by trial and error whether or not a particular choice of numerous parameters would have provided a satisfactory result which amounted to undue burden.

XII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request submitted with the notice of appeal, or any of auxiliary requests 1 to 8, all filed in reply to appellant II's statement of grounds of appeal.

XIII. Appellant II requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Admission of the ground of opposition under Article 100(c) EPC - alleged substantial procedural violation (Article 113(1) EPC)

1. Appellant I submitted that the admission of objections under Article 100(c) EPC into the opposition proceedings constituted a substantial procedural

violation, since the opposition division had not considered whether or not these objections were *prima facie* relevant.

2. In the decision under appeal, the opposition division found that the main request complied with the provisions of Article 123(2) EPC, but not with the provisions of Article 54 EPC. Furthermore, auxiliary request 1 was found to comply with the provisions of Article 54 EPC but not with the provisions of Article 56 EPC. Lastly, auxiliary request 2 was held to comply with the provisions of Articles 123, 54, 56 and 83 EPC.

3. A "substantial procedural violation" is an objective deficiency affecting the entire proceedings, which accordingly is to be determined on an objective basis. Such a deficiency can only be a substantial procedural violation, if it adversely affects a party's rights (see Case Law of the Boards of Appeal, 8th edition 2016 (hereinafter "CLBA"), IV.E.8.4.1, IV.E.8.4.1(b)).

4. The assessment of all claim requests dealt with in the decision under appeal with regard to Article 123(2) EPC was in appellant I's favour. Thus, had the opposition division not considered the compliance of the claim requests with Article 123(2) EPC, its decision would have remained the same; the patent would still have been maintained in amended form.

5. Thus, no substantial procedural violation occurred that could justify the setting aside of the decision under appeal.

6. Furthermore, it is derivable from the minutes summarising the content of the oral proceedings before the opposition division that the parties were heard on

the issue of admission of Article 100(c) EPC as a new ground of opposition and that both parties expressed their opinions with regard to the *prima facie* relevance of the late filed arguments (see minutes, page 1, paragraphs 4 to 6).

7. Thus, appellant I's right to be heard (Article 113(1) EPC) before admitting the new ground of opposition was not violated.

8. It may have been an error on the part of the opposition division exercising its discretion pursuant to Article 114(1) EPC, to decide immediately on the substantive merits of the main request with Article 123(2) EPC, without deciding first on the admission of this new ground of opposition to avoid "*a lengthy discussion about prima facie relevance of the arguments*" (see decision under appeal, page 3, first paragraph).

9. However, in view of the board's findings on sufficiency of disclosure below (see points 12 to 30), the issue of admission of objections on the ground of Article 100(c) EPC into the opposition proceedings needs no further consideration.

Introduction to the invention

10. The patent in suit concerns *inter alia* a method for reducing the immunogenicity of subtilisin Carlsberg identified by the amino acid sequence of SEQ ID NO:1, likewise known under its commercial name Alcalase®, and variants thereof sharing at least 80% sequence identity (see paragraph [0019] of the patent in suit).

11. Subtilisin Carlsberg is a bacterial serine protease derived from *Bacillus licheniformis* that is widely used in industry, for example as an ingredient in washing powders. It is known to be associated with allergic reactions in individuals due to a sensitisation during the industrial manufacturing process (see paragraphs [0002] and [0020] of the patent in suit).

Sufficiency of disclosure (Article 83 EPC)

Main request - claim 1

12. Article 83 EPC stipulates that the invention shall be disclosed in the patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. According to the established case law of the boards of appeal, this requires that the application as a whole taking common general knowledge into account must disclose at least one way of performing the invention such that the skilled person is in a position to perform the claimed invention readily and without undue burden substantially across the whole range claimed. In this context, although a reasonable amount of trial and error is permissible, the skilled person has to have at his or her disposal, adequate information leading necessarily and directly towards success through the evaluation of initial failures (see CLBA, II.C.4.2, II.C.5.6.1).

13. Claim 1 is directed to a method of reducing the immunogenicity of subtilisin having at least 80% sequence identity to SEQ ID NO:1 by modifying at least one T-cell epitope selected from the group consisting of SEQ ID NOs:2, 90, 15 and 30.

14. Thus, claim 1 is directed to a method of reducing the T-cell response against a subtilisin Carlsberg variant by modifying at least one T-cell epitope within four defined regions of the full-length protein consisting either of 15 amino acids (SEQ ID NOs:2, 15 and 30) or 18 amino acids (SEQ ID NO:90).

15. It is common ground between the parties that the patent in suit does not disclose a single example of a subtilisin Carlsberg variant obtained by the method according to claim 1 that exhibits a reduced immunogenicity.

16. Thus, the issue to be assessed in the context of sufficiency of disclosure in the present case is whether or not the patent in suit or the prior art provide information disclosing the suitability of the four T-cell epitope regions identified by SEQ ID NOs:2, 90, 15 and 30 in subtilisin Carlsberg for generating without undue burden a protein having a reduced immunogenicity.

17. The patent in suit discloses in examples 2 and 3 that the screening of 88 overlapping peptides comprising the entire sequence of subtilisin Carlsberg/Alcalase® (SEQ ID NO:1) (see point 10 above) in an *in vitro* assay based on T-cells and dendritic cells presenting the peptides allowed the identification of four 15-mer peptides and one 18-mer peptide, that evoke an immunogenic response in T-cells as indicated by their increased proliferation rate (see paragraph [0188] and figure 3). These peptides correspond to the sequences identified by SEQ ID NOs:2, 90, 15, 30 and 40, which indicates that they comprise (a) putative T-cell epitope(s). Thus, with the exception of SEQ ID NO: 40,

these epitopes correspond to the epitope regions referred to in claim 1.

18. Furthermore, example 4 of the patent in suit reports that peptides 7 and 29, corresponding to SEQ ID NOs:90 and 30, respectively, are selected to be modified, for example, by performing an alanine scan, to be tested for their potential to induce T-cell responses in the assay disclosed in example 3 (see paragraph [0190]). The example further mentions criteria for selecting modified peptides to determine their potential usefulness in the creation of modified hypo-allergenic subtilisin Carlsberg/Alcalase® variants, i.e. enzymes having a reduced immunogenicity (see paragraph [0191]).

19. However, example 4 does not disclose variants of peptides 7 and 29 (SEQ ID NOs:90 and 30), or results of a T-cell based assay disclosing a reduced immunogenicity of variants of these two peptides, let alone full-length subtilisin Carlsberg/Alcalase® variants exhibiting a reduced immunogenicity.

20. Example 5 reports in general that, if variant peptides exhibiting a reduced T-cell response could be identified in the tests reported in example 4, the HLA-type of the human T-cell donors could be determined, to ascribe a certain HLA-type to each of those peptide epitopes. This might further assist in the identification of T-cell epitopes in wild-type subtilisin Carlsberg/Alcalase® (see paragraphs [0192] to [0194]).

21. Thus, it is derivable from the experimental data disclosed in the examples of the patent in suit that isolated peptides derived from five different regions of subtilisin Carlsberg/Alcalase® consisting of 15 to

18 amino acids in length, induce a T-cell response *in vitro*.

22. In this context the board observes that experimental data on T-cell responses obtained with isolated peptides derived from subtilisin Carlsberg/Alcalase® are not directly transferable to a T-cell response against the full-length protein because linear peptide T-cell epitopes might - due to the three-dimensional structure of the subtilisin - not be accessible to T-cells, since they are buried within the enzyme. In other words, the mere provision of T-cell epitopes located in peptides is not sufficient to allow the skilled person to predict that the same epitopes induce a T-cell response in the full-length subtilisin.

23. In these circumstances, the skilled person requires additional information which modification(s) within the epitope regions identified might result in subtilisin variants having a reduced immunogenicity.

24. However, indications which of the 78 individual amino acids (4 x 15 and 1 x 18) encompassed by these five peptide sequences are responsible for the observed T-cell response are not derivable from the teaching of the patent in suit. The same applies to indications for suitable amino acid modifications in these peptides, e.g. replacement(s) of the wild-type amino acid by another amino acid or deletions, or addition(s) of amino acid(s), that might cause a lower T-cell response and hence a reduced immunogenicity.

25. Furthermore, the patent in suit is silent on whether or not at least one amino acid modification in at least one of the five T-cell epitopes disclosed in example 3 is suitable, let alone sufficient, for reducing the T-

cell immunogenicity of a full-length subtilisin Carlsberg/Alcalase® variant.

26. Furthermore appellant I has submitted during the opposition proceedings that not all modifications within these epitopes reduce the immunogenicity of subtilisin, since "*Some modifications will decrease immunogenicity, others will be neutral, while still others will increase immunogenicity*" (see appellant I's submission dated 24 June 2011, page 2, second paragraph).

27. In these circumstances, the skilled person has to consider numerous different modifications in the T-cell epitope regions defined in claim 1 which have an impact on the immunogenicity of the subtilisin Carlsberg/ Alcalase® without knowing whether or not he or she will succeed at all.

28. Thus, since neither the patent in suit nor the skilled person's general knowledge allow predictions which of the numerous possible modifications will result in subtilisin Carlsberg/Alcalase® variants having a reduced immunogenicity, - if at all - the skilled person has to test each and every of these modifications by trial and error. Since this amounts to a research program without having adequate information at hand that he or she will lastly succeed in this task, identifying subtilisin Carlsberg/Alcalase® variants having a reduced immunogenicity in the present case constitutes an undue burden to the skilled person.

29. Appellant I submitted that the technical information disclosed in examples 4 and 5 of the patent in suit provided ample guidance for the skilled person how to generate subtilisin Carlsberg/Alcalase® variants having

a reduced immunogenicity by the method according to claim 1 without undue burden, in particular, in view of the specific T-cell epitope regions to be modified disclosed in example 3. Evidence that the implementation of the invention solely required routine experimental work without encountering technical difficulties was derivable from documents D7 and D9, since both reported that subtilisin variants having a reduced immunogenicity were obtained, relying on the methods likewise mentioned in examples 4 and 5 of the patent in suit.

29.1 The board is not convinced by these arguments for the following reasons. As set out in points 17 to 19 above, examples 4 and 5 in the patent in suit disclose general methods suitable for testing peptide candidates for a potential T-cell immunogenicity. Both examples, however, do not disclose that by relying on these methods the skilled person will necessarily succeed in identifying peptides with a reduced immunogenicity, let alone a subtilisin Carlsberg/Alcalase® variant with the claimed properties.

29.2 Document D7 discloses alanine variants of BPN' subtilisin modified at positions 170 to 173 exhibiting a reduced immunogenicity (see page 5, lines 19 to 25 and page 23, lines 13 to 15).

29.3 Document D9 discloses that variants of "*subtilisins, including subtilisin BPN', have prominent epitope regions at amino acid positions 70-84, a first epitope region, and 109-123, a second epitope region, corresponding to BPN'*" (see lines 28 to 30), having either an aspartate replacement at position 76 and/or alanine replacements at positions 79 and/or 120, 122 exhibiting a reduced immunogenicity (see page 56, lines

23 to 27 and page 58, Table 1, page 59, line 14 to page 60, line 8).

29.4 BPN' is a subtilisin which is structurally related to subtilisin Carlsberg/Alcalase®. The epitope regions reported for BPN' or BPN'-like subtilisins in documents D7 and D9 are however not identical to the four regions defined in claim 1 in the subtilisin Carlsberg/ Alcalase®. This has also not been argued by appellant I. Solely document D9 discloses an epitope region in the BPN' subtilisin that is located at the position "*109-123*" (see page 59, lines 14 to 16), which partially overlaps by eight amino acids with the epitope region defined by SEQ ID NO:40 in the subtilisin Carlsberg/Alcalase® recited in claim 1. This is derivable from the location of the latter region at position "*115-129*" that corresponds to position "*116-130*" according to BPN' numbering (see appellant II's statement of grounds of appeal, page 12, table, last line).

29.5 Since neither the type of subtilisin nor the epitope regions referred to in claim 1 are identical to the subtilisin proteins including their epitope regions disclosed in documents D7 and D9, no evidence can be derived from these two documents that any of the claimed epitope regions are suitable for reducing the immunogenicity of the subtilisin Carlsberg/Alcalase®, let alone that the skilled person will succeed in generating variants thereof having a reduced immunogenicity.

30. Thus, the patent in suit does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Auxiliary requests 1 to 8 - claim 1

31. Claims 1 of auxiliary requests 1 to 8 are either identical to claim 1 of the main request (auxiliary requests 1, 4, 7 and 8) or differ in that the term "*subtilisin*" is replaced by "*parent subtilisin*" and by adding the features "*to generate a modified subtilisin, wherein the immunogenic response produced by said modified subtilisin is less than the immunogenic response produced by said parent subtilisin*" (auxiliary requests 2, 3, 5 and 6).

32. The method according to claims 1 of auxiliary requests 1 to 8 does not substantially differ from the method according to claim 1 of the main request. Thus, the objections with regard to sufficiency of disclosure set out above for claim 1 of the main request equally apply to claims 1 of auxiliary requests 1 to 8, which therefore do not comply with the provisions of Article 83 EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated