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D E C I S I O N
of 3 November 2000

Case Number: T 1208/97 - 3.3.4

Application Number: 88904041.6

Publication Number: 0309565

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Language of the proceedings: EN

Title of invention:
SUBTILISIN ANALOGS

Patentee:
Amgen Inc.

Opponent:
(01) Novo Nordisk A/S
(02) Unilever N.V.

Headword:
Analogs/AMGEN

Relevant legal provisions:
EPC Art. 108, 54, 56
EPC R. 65(1)

Keyword:
"Appeal of Opponent 01 - inadmissible"
"Main request - novelty (no)"
"Auxiliary request - novelty (yes) - disclaimer"
"Inventive step (yes)"

Decisions cited:
T 0161/82, T 0165/84, G 0002/88, T 0626/91, T 0312/94, T 0337/95

Catchword:

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Case Number: T 1208/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 3 November 2000

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 15 October 1997 concerning maintenance of European patent No. 0 309 565 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani

R. T. Menapace

Summary of Facts and Submissions

I. The patentee and the two opponents lodged an appeal against the interlocutory decision of the opposition division issued on 15 October 1997 whereby the European patent, which had been opposed on grounds of Article 100(a), (b) EPC, was maintained in amended form on the basis of the claims 1 to 22 filed on 13 August 1997 and claim 23 as granted.

Claim 1 of the patent as granted read as follows:

" A subtilisin analog characterized as having an amino acid sequence of a naturally occurring Bacillus subtilisin that has been modified by:

(a) having one or more of the amino acids present in a calcium binding site represented by Asp^{41}, Leu^{75}, Asn^{76}, Asn^{77}, Ser^{78}, Ile^{79}, Gly^{80}, Val^{81}, Thr^{208}, and Tyr^{214} of the naturally occurring Bacillus subtilisin replaced by a negatively charged amino acid; and

(b) having one or both of the amino acids comprising any Asn-Gly sequence of the naturally occurring Bacillus subtilisin deleted or replaced by a different amino acid, the analog having improved calcium binding capacity with respect to the naturally occurring Bacillus subtilisin."

Claims 2 to 20 concerned particular embodiments of the analog according to claim 1. Claim 21 was directed to a DNA sequence encoding said analog. Claim 22 concerned a method for improving thermal and pH stability of a Bacillus subtilisin, while claim 23 was directed to a composition comprising a subtilisin analog according to

claim 1.

II. The claims accepted by the opposition division differed from the claims as granted in that in claims 1 and 21 the qualifier "non-naturally occurring" was added before the term "analog" at the beginning of the claim, and an obvious error was rectified in claim 11 (Asp changed to Asn in position 109).

The opposition division decided that the qualifier "non-naturally occurring" amounted to a clear disclaimer suitable for overcoming a novelty objection against granted claim 1 as it was possible "that also natural occurring subtilisins are within the scope of claim 1". In the view of the opposition division, the skilled person would have been able to make the amino acid replacements (or deletions) which were required in order to perform the claimed invention. The latter involved also an inventive step having regard in particular to the following documents:

(14) Bryan P.N. et al., Proteins: Structure, Function and Genetics, 1986, Vol. 1, pages 326 to 334,

(15) Bode W. et al., EMBO Journal, 1986, Vol. 5, No. 4, pages 813 to 818.

This was because the skilled person would not have tried to improve the calcium binding properties of subtilisin by making the proposed substitutions.

III. A statement of grounds of appeal was filed by the patentee (appellant I) and by opponent 02 (appellant II).

IV. Opponent 01 did not file a statement of grounds of appeal. On 11 May 1998, by a communication pursuant to Article 108 and Rule 65(1) EPC, the board informed the opponent that it had to be expected that the appeal would be rejected as inadmissible. Attention was also drawn to Article 122 EPC (re-establishment of rights). Neither a reply to this communication, nor a request for re-establishment of rights were received.

V. On 10 July 2000, the board issued a communication with a provisional view on the issues to be discussed.

VI. In reply thereto, appellant I made further submissions on 4 October 2000.

VII. Oral proceedings took place on 3 November 2000. Appellant I submitted claims 1 to 22 as auxiliary request A. Claim 1 therein read as claim 1 as granted with the addition at the end of the claim of the expression "the subtilisin analog not being subtilisin Carlsberg or subtilisin DY". Claims 2 to 20 were as granted, except for the correction of two obvious clerical errors in claims 2 (Cacillus changed to Bacillus) and 11 (Asp changed to Asn in position 109). Claims 21 and 22 were identical to claims 22 and 23 as granted, except for the renumbering necessary in consequence of the deletion of claim 21 as granted.

VIII. In addition to the documents referred to in Section II above, the following documents are quoted in the present decision:

(2) Jacobs M. et al., Nucl. Acid Res., 1985, Vol. 13, No. 24, pages 8913 to 8926;

(7) Nedkov P. et al., Biol. Chem. Hoppe-Seyler, April 1985, Vol. 366, pages 421 to 430.

IX. Appellant I submitted in support of the main request (claims as granted) essentially that the naturally occurring subtilisins DY and Carlsberg (cf eg documents (2) and (7)) did not anticipate claim 1 because i) the patent specification stated the intention not to cover known subtilisins; ii) the claim used the expression "a naturally occurring Bacillus subtilisin that **has been modified**" which necessarily implied a difference vis-à-vis the natural products; and iii) the claim referred to a subtilisin "analog", a term which distinguished the claimed product from natural products. Thus, having regard to Article 69 EPC and to the protocol of interpretation of that provision (cf also T 312/94 of 4 September 1997), it was evident from the patent specification as a whole that known subtilisins did not fall under the scope of the claim. Known subtlisins did not infringe claim 1, and thus the novelty of the latter could not be prejudiced by them. Moreover, when Article 64(2) EPC was taken into consideration, claim 1, being a "product-by-process" claim where the positive feature "has been modified" was used, necessarily related to a patentable product if the process was patentable.

Appellant I further submitted that the claimed subtilisin analogs involved an inventive step because the skilled person would not have combined the teachings of document (14) with the teachings of document (15) and replaced amino acid residues in the calcium binding region with negatively charged amino acid residues in order to increase calcium binding. As for the experiments which had been submitted by

opponent 01 during the opposition phase, they were meaningless as they were not carried out under the conditions of the patent.

X. Appellant II argued that claim 1 of the main request, which was directed to a composition of matter, lacked novelty vis-à-vis the known subtilisin DY and Carlsberg that fulfilled the features of the claim. In respect of the auxiliary request, it submitted that, as the problem of stabilising subtilisin initially set by the patent in suit (cf page 4, lines 20 to 22) had already been solved in document (14) by the substitution of Ser for Asn at position 208 (cf Table on page 331), the underlying technical problem was finding further stable subtilisins in alternative to that described in the said document. As the latter made reference on page 329 to the stabilising effect of calcium ions, the skilled person would have readily taken into consideration modifications at the calcium binding site which had been studied in document (15). One of the obvious replacements was that of Asp^{76} with a negatively charged amino acid. This would have been considered by the skilled person to be a safe replacement as it was already present in the natural subtilisins Carlsberg und DY.

Appellant II additionally referred to the experiments submitted by opponent 01 during the opposition phase which showed that certain variants according to claim 1 were either destabilised or had reduced thermostability, which implied that the patent did not provide a technical effect over the whole area claimed.

XI. Appellant I requested that the opponents' appeals be dismissed, that the decision under appeal be set aside

and that the patent be maintained:

- as granted (main request) or

- on the basis of claims 1 to 22 and amended pages 3, 4, 5 and 21 as filed in the oral proceedings, remaining pages 6 to 20 of the description and the drawings as granted (auxiliary request A).

Appellant II and opponent 01 requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Admissibility of the appeal by opponent 01

1. Opponent 01 filed in due time a notice of appeal and paid the appeal fee. However, it did not file a statement of grounds of appeal and did not reply to the board's communication pursuant to Article 108 and Rule 65(1) EPC. Nor did the opponent request the re-establishment of its rights. The appeal is thus rejected as inadmissible because it does not fulfill all conditions laid down in Article 108 EPC.

The main request: claims as granted

2. Claim 1 as granted is a product claim directed to a subtilisin analog which has an amino acid sequence of a naturally occurring Bacillus subtilisin that has been modified as indicated under items (a) and (b) of the claim (cf Section I above). The claim does not refer to

any specific amino acid sequence of a naturally occurring Bacillus subtilisin as a starting point for the modifications. If the known subtilisin BPN', which is normally used as a standard for numbering (cf page 3, lines 17 to 19 of the patent specification), is taken as a starting point, it is to be noted that both the known subtilisin Carlsberg and subtilisin DY (cf documents (2) and (7)) are encompassed by the terms of the claim. In fact, both contain the negatively charged amino acid Asp in replacement of Asn^{76} and the amino acid Ser in replacement of Asn^{109} of the Asn-Gly sequence in positions 109-110.

3. Appellant I, while not contesting this, argues that a novelty objection cannot apply because the patent specification states the clear intention not to cover known subtilisins. Moreover, claim 1 uses the expression "a naturally occurring Bacillus subtilisin that **has been modified**" which necessarily implies a structural change away from the natural products. Furthermore, the claim refers to a subtilisin "analog", a term which distinguishes the claimed product from natural products. Thus, having regard to Article 69 EPC and to the protocol of interpretation of that provision, and also in accordance with decision T 312/94 (supra), if the patent specification is read as a whole, it is evident that known subtilisins do not fall under the scope of claim 1. Appellant I further submits that, when judging novelty, considerations of infringement should be taken into account. Accordingly, as known subtlisins do not infringe claim 1 at issue, its novelty cannot be prejudiced by them. Appellant I also argues that, in view of Article 64(2) EPC, a "product-by-process" claim like claim 1 at issue, where the positive feature "has been modified" is used,

necessarily relates to a patentable product if the process is patentable.

4. The board does not agree with the position of appellant I based on the following considerations:

(a) The purpose of the claims under the EPC is to enable the protection conferred by the patent to be determined (Article 69(1) EPC). For this reason, they must be clearly and unambiguously formulated in terms of the technical features of the invention (cf G 2/88 OJ EPO 1990, 93). These should allow the reader to learn from the claims the exact distinctions which delimit the scope of protection (cf eg decisions T 337/95 OJ EPO 1996, 628 and T 165/84 of 29 January 1987).

(b) The object of the Protocol on the Interpretation of Article 69 of the Convention is balancing between fair protection for the patentee and a reasonable degree of legal certainty for third parties. However, as explicitly stated in the Protocol, this does not mean that the claims serve only as a guideline and that the actual protection is to be determined from a consideration of what the patentee has contemplated in the description. The role of the claims is thus crucial in fixing the boundaries of the protection. Article 69 EPC does not offer any basis for reading into a claim features which can be found in the description when judging novelty. As this article and the Protocol concern the extent of protection, they are primarily for use by the judicial instances which deal with infringement issues. In this respect, it should also be noted that infringement

considerations are not of relevance when judging novelty. Article 64(3) EPC leaves explicitly questions of infringement to be dealt with by national law.

(c) Although Article 84 EPC is not a ground for opposition under the terms of Article 100 EPC, questions of clarity or support may affect the decision on issues under Article 100 EPC such as eg novelty (Article 54 EPC) if the wording of a claim does not allow a clear distinction of its subject-matter vis-à-vis known subject-matter (cf eg T 626/91 of 5 April 1995).

(d) If follows from the considerations made under (a) to (c), that in the present case it has to be established whether or not the wording of claim 1, independently from any alleged intention derivable from the description, allows a clear distinction between the claimed subtilisin analogs and the known subtilisins Carlsberg and DY.

(e) Claim 1 is a product claim, which, although making reference to a process feature ("has been modified"), confers absolute protection for a composition of matter, however made, which displays features (a) and (b). Thus, a known product that has the same features affects the novelty of the claim. It is established case law that claims for products defined in terms of processes for their preparation have to fulfil the requirements of patentability and that this is independent from the patentability of the processes. Thus, a product is not rendered novel and/or inventive merely by the fact that it is

produced by a new and inventive process. Notwithstanding Article 64(2) EPC, a distinction is to be made between claims to a new and inventive product defined by its method of manufacture and claims to a new and inventive process (cf Case Law of the Boards of Appeal of the EPO, 3rd edition 1998, Section II-B-6).

(f) The term "analog" per se is not sufficient to distinguish between a product falling under the scope of the claim and a natural product because it merely indicates that the subtilisin of the claim is analogous, ie similar in some way, to known subtilisins. Analogy exists also among natural subtilisins.

5. In conclusion, as the known subtilisin Carlsberg and subtilisin DY fall under the terms of claim 1, the claim lacks novelty and the request of which it is part cannot be allowed under Article 54 EPC.

The auxiliary request A

Novelty

6. Claim 1 disclaims "subtilisin Carlsberg and subtilisin DY" which were within the wording of claim 1 of the main request. The disclaimer is formally acceptable as it serves the purpose to exclude from protection known subtilisins which anticipated the claim by chance (T 161/82 OJ EPO 1984, 551) because the specification refers to said subtilisins as a starting point for the proposed structural modifications, **not** as a point of arrival.

7. Since there is no evidence that other known subtilisins either of natural or synthetic origin fall within the wording of the claim, novelty is acknowledged.

Inventive step

8. The closest prior art is represented by document (14), which describes a thermostable variant of subtilisin BPN' characterised by a single substitution of Ser for Asn at position 218. This variant is found to undergo thermal inactivation at one fourth the rate of the wild-type enzyme when incubated at elevated temperatures (cf Table II on page 331). On page 333 the document reports that the enhanced stability is kept under a variety of conditions, eg in the presence of the chelating agent EDTA, "which has been previously shown to eliminate the well-known stabilizing effect of calcium ions".

9. In the light of document (14), the problem to be solved can be defined as being the provision of further thermostable subtilisin variants.

10. As a solution, the claims propose subtilisin variants characterised by the combination of two kinds of modifications, one at the level of the calcium binding site (cf feature (a) in claim 1), the other at the level of the Asn-Gly sequences (cf feature (b) in claim 1), and methods for making them, as well as compositions containing them.

11. The patent in suit provides examples of some variants according to the claims and data in respect of the effects of the structural changes on their thermostability. Apart from experiments submitted by

opponent 01 during the opposition phase, which do not adhere completely to the teaching of the patent in suit (eg thermostability is measured at pH 7.0, not at pH 11.0), there is no evidence on file that for any significant area of the claims the rationale provided by the patent specification produced deterioration of thermostability. In view of the broad range of the proposed modifications proposed, it can, of course, not be excluded that some potential variant(s) covered by the claims will be unsuitable or not particularly suitable. However, this possibility, which is recognised by the skilled reader, is per se not sufficient to undermine the rationale on which the claims are based because, firstly, occasional failure is part of any scientific work, and, secondly, no evidence is available showing that the claimed technical effect can definitely not be achieved within the whole range of application or that it can be achieved only with undue burden.

For these reasons, the board is satisfied that the claims at issue provide indeed a solution to the underlying technical problem.

12. The essential question is whether the skilled person, looking for further thermostable subtilisin variants, would have readily taken into consideration further modifying the subtilisin variant described in document (14), which already contained a substitution at the level of the Asn-Gly sequence at position 218-219 (corresponding to feature (b) of claim 1), by introducing a substitution at the level of the calcium binding site (corresponding to feature (a) of claim 1).

13. In respect of this question, appellant II argues in

essence that the skilled person, being aware of the stabilising effect of calcium ions on subtilisins (cf page 329 of document (14)), would have readily come to the idea of replacing, for example, Asp^{76} with a negatively charged amino acid, especially in view of document (15) which indicated the amino acid residues responsible for calcium binding.

14. As repeatedly emphasized in the case law of the boards of appeal, in the assessment of inventive step it is important to avoid any ex-post-facto analysis.

15. In the board's judgement, there is no hint in document (14) to modify the calcium binding site in a subtilisin. On page 333 the document confirms only that the enhanced stability obtained in consequence of the single replacement at position 218 was retained also when calcium ions, which are known to stabilise the molecule, were made unavailable by chelation. This observation can hardly be seen as a suggestion to carry out amino acid replacements at the calcium binding site.

Document (15), which is mainly preoccupied with the study of the crystal structure of the complex formed between subtilisin Carlsberg and the inhibitor eglin c, points on page 817 to the folding of loop segment Leu^{75} - Thr^{79} around a calcium ion and observes that "this calcium is octahedrally liganded by the oxygen atoms of three carbonyls (Leu75, Thr79 and Val 81), of two carboxamides (Gln2 and Asn77) and of the carboxylate of Asp41.". The board does not see in these observations any suggestion to carry out replacements at the level of these amino acids in combination with modifications at the level of an Asn-Gly sequence.

As a matter of fact, the skilled person had no reasons to combine the teachings of documents (14) and (15) as no logical "real life" links exist between the two documents.

16. For these reasons, the board judges that the subject-matter of the claims at issue involves an inventive step.

The adaptation of the description

17. Appellant II had no objections to the proposed amendments to the description. Nor does the board have any objection to them as they consist essentially in a clarification of the background of the invention by reference to the prior art.

Order

For these reasons it is decided that:

1. The appeal of opponent 01 is rejected as inadmissible.

2. The decision under appeal is set aside.

3. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 22 and amended pages 3, 4, 5 and 21 as filed in the oral proceedings, pages 6 to 20 of the description and the drawings as granted.

The Registrar: The Chairperson:

U. Bultmann U. Kinkeldey