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D E C I S I O N
of 11 January 1996

Case Number: T 0386/94 - 3.3.4

Application Number: 82201272.0

Publication Number: 0077109

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
DNA molecules comprising the genes for preprochymosin and its maturation forms, and microorganisms transformed thereby

Patentee:
UNILEVER N.V., et al

Opponent:
Celltech Limited
Chr. Hansens Laboratorium A/S

Headword:
Chymosin/UNILEVER

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 83, 54(3)(4), 56, 87, 88

Keyword:
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
T 0269/87, T 0081/87, T 0690/91, T 0292/85, T 0019/90, T 0158/91, T 0412/93, T 0223/92, T 0923/92, T 0128/92, T 0816/90

Headnote:
Inventive step may be acknowledged in the field of gene technology if there is no reasonable expectation of success that the cloning and expression of a given gene can be carried out. However, in a case where, at the priority date, a skilled person can expect to perform the cloning and expression of a gene in a fairly straightforward manner, and the cloning and expression, although requiring much work, does not pose such problems as to prove that the expectation of success was ill-founded, inventive step cannot be acknowledged.

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0386/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 11 January 1996

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office dated 21 February 1994 concerning maintenance of European patent No. 0 077 109 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
J. Saisset
L. Galligani
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 077 109 (application No. 82 201 272.0) relating to "DNA molecules comprising the genes for preprochymosin and its maturation forms and micro-organisms transformed thereby" was granted for ten Contracting States with eighteen claims. The priority of the earlier application GB 8131004 (14 October 1981) was claimed.

II. Claims 1, 14 and 18 of the patent as granted for all designated states except Austria read:

"1. A recombinant plasmid comprising the following elements in the order given:
(1) a ds-rDNA coding for preprochymosin, prochymosin, pseudochymosin or chymosin,
(2) a translational stop codon bound to the 3'-end of the plus strand of the ds-rDNA of (1),
(3) both an **E.coli** replication site and a selective marker,
(4) an **E.coli** expression regulon upstream of the plus strand of the ds-rDNA of (1) and
(5) when the ds-rDNA codes for prochymosin, pseudochymosin or chymosin, a translational initiation ATG-triplet bound to the 5'-end of the plus strand of the ds-rDNA of (1)."

"14. Micro-organisms, which are transformed by incorporation of
(a) a ds-rDNA coding for preprochymosin, prochymosin, pseudochymosin or chymosin,
(b) a translational stop codon bound to the 3'-end of the plus strand of the ds-rDNA of (a),
(c) a selective marker and preferably a replication site adapted to said micro-organisms,

(d) an expression regulon suitable for said micro-organisms upstream of the plus strand of the ds-rDNA of (a), and
(e) when the ds-rDNA codes for prochymosin, pseudochymosin or chymosin, a translational initiation ATG-triplet bound to the 5'-end of the plus strand of the ds-rDNA of (a), whereby the elements a,b,d and optionally e are present in the order d-(e)-a-b."

"18. A process for producing preprochymosin or any of its maturation forms prochymosin, pseudochymosin or chymosin, which comprises culturing a micro-organism according to any one of claims 14-17, optionally under selection pressure, and collecting the preprochymosin or a maturation form thereof."

Claims 2 to 11 are directly or indirectly dependent on claim 1 and relate to particular embodiments of the plasmid. Claim 12 relates to a bacterial culture containing a plasmid according to claims 1 to 11 and claim 13 relates to a process to produce the protein using the bacterial culture of claim 12. Claims 15 to 17 concern specific embodiments of the micro-organisms of claim 14. The claims for Austria are in the process form and correspond to the claims for the other Contracting States.

III. Notices of opposition were filed against the European patent by two parties (Opponents 01 and 02). Opponent 02 then withdrew the opposition. A notice of intervention under Article 105 EPC was also filed.

Revocation of the patent was requested on the grounds of Articles 100(a) to 100(c) EPC.

During the procedure before the Opposition Division, eighty-seven documents were relied upon by the parties. Of these documents, the following are referred to in the present decision (the numbering used by the Opposition Division is adhered to).

(1) : EP-A-0 068 691 (Celltech)

(2) : EP-A-0 057 350 (Coll.Res.)

(3) : EP-A-0 073 029 (Beppu)

(15) : "Principles of Gene Manipulations" by R. W. Old and S. B. Primrose, Blackwell Scientific Publications, 1980, pages 59 to 88.

(17) : "Molecular Cloning, A laboratory Manual" by T. Maniatis et al., Cold Spring Harbor Laboratory, 1982, pages. iii, v, 211 to 246, 309 to 361 and 403 to 433.

(63) : Blobel et al., Symp.Soc.Exp.Res., 1979, vol. 33, pages 9 to 36.

(68) : Williams J. G., The preparation and screening of a cDNA clone bank, in "Genetic Engineering", ed. by R. Williamson, Academic Press, 1981, pages 2 to 49.

(87) : Nishimori et al., J. Biochem., 1981, vol. 90(3), pages 901 to 904.

IV. On 21 February 1994, the Opposition Division issued an interlocutory decision within the meaning of Article 106(3) EPC whereby the admissibility of the intervention was acknowledged (Opponent 03) and the patent was maintained in an amended form on the basis of auxiliary request E with seventeen claims. In claims 1 and 14, the ds-rDNA of (1) or (a) was restricted to that coding for preprochymosin and pseudochymosin. Claims 2 to 13, 15 to 17 remained alike to the claims 2 to 13, 15, 16 and 18 as granted, claim 17 as granted being deleted. The claims for Austria were similarly amended.

V. The Opposition Division considered said claims to be allowable under Articles 123(2)(3) and 84 EPC.

It was determined that the specification disclosed the invention in an enabling manner so that the requirements of Article 83 EPC were seen as fulfilled.

The British priority application being essentially identical to the European patent application, the Opposition Division also held that the latter was entitled to priority rights.

Novelty was acknowledged under Article 54(2) EPC. The three documents which were discussed under Article 54(3)(4) EPC were documents (1), (2) and (3). Following the decisions of the Board of Appeal T 0269/87 of 24 January 1989 (not published in OJ EPO) and T 0081/87 (OJ EPO 90, 250) which denied documents (1) and (2) priority rights earlier than from 11 June 1982 and 1 December 1981 respectively, the Opposition Division found that neither document (1) nor document (2) were detrimental to novelty. The same conclusion was reached with document (3) as the priority document filed on 24 August 1981 disclosed subject-matter different from that claimed in the patent in suit.

The closest prior art document was identified as document (87). All claims disclosing prepro- and pseudochymosin whether it be in a generic or specific way were acknowledged inventive. All claims where the DNAs were characterized by their specific sequence or said to be attached to specific sequences were also considered allowable under Article 56 EPC in view of the very specificity of the sequences.

VI. Appeals were lodged against the decision of the Opposition Division by the Patentee and Opponents 01 and 03 (respectively named Appellants I, II and III for the purpose of this decision). Appellant I filed one main and three auxiliary requests together with the grounds of appeal.

VII. Appellants III and I filed answers to their respective submissions.

VIII. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the Boards of appeal, setting out the Board's preliminary position.

IX. Appellant II indicated that he would not be present at the oral proceedings.

X. Oral proceedings were held on 11 January 1996. At these proceedings, new first and second auxiliary requests were introduced in replacement of all auxiliary requests filed so far.

The main request contains three claims. Claim 1 reads as follows:

"1. A process for producing **preprochymosin** or any of its maturation forms **prochymosin, pseudochymosin or chymosin**, which comprises culturing a transformed micro-organism, optionally under a selection pressure, and collecting the **preprochymosin** or a maturation form thereof,
whereby said micro-organism is transformed by the incorporation of
(a) a ds-rDNA coding for **preprochymosin, prochymosin, pseudochymosin or chymosin**,
(b) a translational stop codon bound to the 3'-end of the plus strand of the ds-rDNA of (a),

(c) a selective marker and preferably a replication site adapted to said micro-organisms,
(d) an expression regulon suitable for said micro-organism upstream of the plus strand of the ds-rDNA of (a),
and
(e) when the ds-rDNA codes for **prochymosin, pseudochymosin or chymosin**, a translational initiation ATG-triplet bound to the 5'-end of the plus strand of the ds-rDNA of (a),
whereby the elements a,b,d and optionally e are present in the order d-(e)-a-b.

Claim 2 concerns a process according to Claim 1, wherein the ds-rDNA codes for preprochymosin. Claim 3 concerns the process of claim 1, where the ds-rDNA encodes preprochymosin and is defined by a number of specific sequences.

Auxiliary request I differs from the main request in that the expression "naturally occurring" is inserted in the first line of claim 1 before the word "**preprochymosin**".

Auxiliary request II containing two claims differs from the main request in that in claim 1, the ds-rDNA of (a) is limited to preprochymosin. Claim 2 corresponds to parts (i)(a)-(d) of claim 3 of the main request.

XI. Appellant I argued that the claims were clear in light of the description, and the description enabling with regard to producing preprochymosin and its maturation forms in micro-organisms when account was taken of the existing knowledge.

The claims contained novel subject-matter over documents (1) and (2) as it had already been decided by the Boards of Appeal in T 0269/87 (**supra**) and T 0081/87 (**supra**) that these documents did not enjoy any priority rights from their earliest priority applications. It was also novel over document (3) since the earliest priority application of document (3) did not disclose any recombinant DNA encoding full size chymosin.

The main argument presented in favour of inventive step was that the skilled person would not have tried with a reasonable expectation of success the combination of steps described in the patent specification. This was proven by the fact that three other groups failed to succeed, and that it took them two further years before reducing the invention to practice. The patent was, thus, the first teaching to provide the hitherto unknown and unexpected complete preprochymosin sequence. The patent filled a gap in the knowledge of the chymosin gene.

The case law in relation to inventive step concerning patent applications of the same time period was also discussed as well as the general perception of the state of the art in cloning, in 1982.

XII. In his written submission, Appellant II addressed the argument that a mistake had been made by the Examining Division in refusing European patent application 82 303 035.8 (document (1); Celltech) for lack of novelty over the present patent in suit, after the Board of Appeal in T 0269/87 (**supra**) had denied document (1) any priority rights for lack of enablement of the priority documents. Decision T 0269/87 (**supra**) should be disregarded and document (1) be acknowledged an earlier priority than that of the patent in suit when assessing novelty.

XIII. Appellant III objected that the patent specification did not provide enough information to reproduce the invention as described in claim 1 and that claim 1 lacked novelty over document (2) insofar as it disclosed a process for expressing chymosin from a DNA encoding mature chymosin.

With regard to inventive step, it was argued that in view of document (87), it was obvious to complete the task of cloning the DNA encoding chymosin or its precursors. Expression of foreign genes in **E.coli** did not pose a problem. The fact that four groups had started the project at the same time was clearly indicative of a reasonable expectation of success. All had achieved the task within a few months of each other. These few months were not even meaningful in terms of inventive step but rather reflected the patenting strategies of the different groups.

Furthermore, it was argued that, although preprochymosin had not yet been discovered at the priority date, its existence would have been expected since secreted mammalian proteins (such as chymosin) were known to be initially synthesized with a leader sequence. Since the cloning of prochymosin DNA was straightforward, the discovery and elucidation of the presequence should be regarded as an obvious, almost inevitable consequence of the cloning work and, therefore, lacked inventive step.

XIV. Appellant I requested that the appeal be dismissed and the patent be maintained on the basis of the main request filed on 1 July 1994 or on the basis of auxiliary requests I or II as filed during oral proceedings.

Appellant II requested that the decision under appeal be set aside insofar as it related to priority entitlement of the Celltech application.

Appellant III requested that the decision under appeal be set aside, that the patent be revoked in its entirety and that the appeal fee be refunded.

XV. At the beginning of the oral proceedings, the Chairwoman of the Board announced that in the case T 0690/91 (Celltech, not to be published in OJ EPO), the decision was taken on 10 January 1996 to dismiss the appeal.

Reasons for the Decision

1. The appeals are admissible.

The main request

Formal admissibility under Article 123(2) and 123(3) EPC

2. The claims find formal support in the application as filed so that no objection under Article 123(2) EPC arises.

3. Claims 1 to 3 correspond to granted claim 18 when dependent upon granted claims 14, 16 and 15 respectively, the subject-matter of these latter claims being incorporated in full into claim 18. Moreover, the DNA sequences originally referred to in claim 15 by reference to granted claims 2 to 5 are cited **expressis verbis** in claim 3. None of these amendments amounts to an extension of the protection conferred. The requirements of Article 123(3) are, thus, fulfilled.

Clarity and support (Article 84 EPC)

4. Although identical in substance to granted claims, the claims of the main request on appeal are different in their wording (see point 3, **supra**). It must, thus, be assessed whether they fulfil the requirements of Article 84 EPC.

5. While Appellant I argues that the claims are clear when read in the light of the specification which provides the sequences of the claimed proteins either by way of references (pro-, pseudo-chymosin and chymosin) or, for the hitherto unknown protein, preprochymosin, in Figure 1, Appellant III is of the opinion that, in the absence of any technical characterization of the preprochymosin molecule, a claim to its production can only be read as the statement of an obvious wish.

6. The Board considers that introducing the sequence of preprochymosin in claims 1 and 2 would make them more lengthy and confusing. It is accepted that the subject-matter of these claims is clear when read in the light of the specification which also provides the necessary technical teaching to support the claims over their entire width (see points 8 to 16, **infra**)

7. The requirements of Article 84 EPC are, thus, fulfilled.

Sufficiency of disclosure (Article 83 EPC)

8. The patent specification provides a technically detailed example for the expression of preprochymosin and its maturation forms in **E.coli**. The parties agree that sufficient information is thereby given to reproduce the invention in this organism. The problem, however,

remains whether sufficiency of disclosure is achieved in relation with a process for expression in any micro-organisms.

9. Appellant's I position is that expression in micro-organisms was definitely intended as early as the filing date of the priority application. The references to expression contained therein and in the European patent specification (page 3, lines 33 to 36) sufficed to establish enablement, as the state of the art provided examples of foreign gene expression in eucaryots (such as yeasts) and procaryots. Chymosin being a eucaryotic gene should be more likely to express in eucaryots than in **E.coli**.

Moreover, it was established EPO case law that an invention is sufficiently disclosed if at least one way is clearly indicated enabling the skilled person to carry out the invention (T 0292/85, OJ EPO 1989, 275).

10. Contrary to this, Appellant's III position is that, before the filing date of the application, foreign genes had only been expressed in eucaryotic hosts in a fortuitous manner, not likely to provide useful information on directed gene expression. **E.coli** was the most explored organism; if inventive step was to be acknowledged for the reason that successful expression was still unexpected in this organism, then sufficiency of disclosure could not be acknowledged for expression in other micro-organisms, without specific instructions on how to perform the relevant manipulations. Decision T 0292/95 (**supra**) could not support Appellant's I position on enablement. Firstly, it was not concerned with the expression of a specific gene but rather with a general methodology for expression in bacteria so that criteria for enablement could not be the same. Secondly, the process claimed in the case dealt with in T 0292/85

(**supra**) was clearly of a much narrower scope than the present process, since it only covered expression in bacteria and not in micro-organisms in the largest sense.

11. The Board considers that the patent specification discloses the cloning of the cDNA encoding an almost full length preprochymosin gene with the help of standard protocols. No specific experimentation is described, but adequate reference is given to all pertinent techniques. Detailed information on how to construct the vectors necessary to produce chymosin or its precursors in **E.coli**, starting from the originally cloned cDNA is also provided, alleviating the need for a deposition of the recombinant clones. The protocol for recovery of the recombinant proteins is described.

12. The written specification, thus, teaches that the genes encoding preprochymosin and its maturation forms may successfully be expressed in a biological environment which is phylogenically extremely far apart from the one, they were isolated from (**E.coli** versus calf). Moreover, it suggests the possibility of expressing said proteins in micro-organisms, in general.

13. The state of the art, on the other hand, contains no evidence that foreign genes cannot be expressed in other organisms than **E.coli**. To the contrary, both Appellants I and III seem to accept that expression in alternate hosts had already been tried.

14. The Board, thus, believes that one way to carry out the invention is clearly indicated and that there exist no serious doubts that the invention could eventually be carried out with other micro-organisms than **E.coli** (T 0019/90, OJ EPO 90, 476, point 3.3 of the decision).

15. The Board does not agree with Appellant III that the findings of T 0292/85 (**supra**) on enablement cannot apply in this case because the invention dealt with in T 0292/85 (**supra**) is of farther reaching consequences for the field of biotechnology than the present invention. Although it is true that the nature of both inventions is different, the technical character of both is similar in such a way that, nonetheless, the conclusions reached by the Board in T 0292/95 (**supra**) apply to the present case as well. Thus, the sufficiency of disclosure is recognized.

16. The above reasoning leads the Board to decide that the requirements of Article 83 EPC are fulfilled.

Entitlement to priority (Articles 87 and 88 EPC).

17. The application GB 8131004 filed on 14 October 1981, which constitutes the priority document, is essentially identical to the European patent application. They differ in that the latter specifies on page 10, lines 13 to 15 which micro-organisms might be of use in carrying out the claimed process and provides the information required under Rule 28(1)a) EPC for the deposition of micro-organisms. However, these specifically mentioned micro-organisms are not claimed in the patent in suit and the deposited clones are not essential to reproduce the invention (cf. point 11, **supra**). Furthermore and contrary to the Appellant's III submission that it is not made mention in the priority document of making preprochymosin and its maturation forms in micro-organisms, the Board is satisfied that such an indication could be found in the priority application (page 1, lines 8 to 12). From all this it follows that, irrespective of the above mentioned differences, the patent in suit claims the same invention as the priority

document discloses within the meaning of Article 87(1) EPC. Therefore, in the Board's judgment, the claim to priority derived from the priority document is valid.

Novelty (Article 54(3) EPC).

18. Two European patent applications are cited as novelty destroying within the meaning of Article 54(3) EPC: document (1) claiming a priority right from 17 June 1981 and document (2) claiming a priority right of 16 January 1981.

19. In his written submission, Appellant II argued that the decision T 0269/87 (**supra**) which denies priority rights to document (1) on the count that its priority filing does not disclose the invention in an enabling manner was not to be followed as the Board had been mistaken in its assessment of enablement. Thus, according to Appellant II, document (1) destroyed the novelty of the present claims in view of its earlier priority date.

20. In addition, Appellant III raised the point that the priority document of document (2) disclosed a recombinant phage said to carry the chymosin encoding DNA. Taking into account that it was a matter of routine to fit an ATG at the relevant position to achieve expression, document (2) should be seen as disclosing the subject-matter of claim 1 ((a), chymosin, b-e).

21. The present Board's findings with regard to the priority rights of document (1) constitute the subject-matter of decision T 0690/91 (unpublished, see section XV **supra**). In this earlier decision, the Board reached the conclusion that the findings of T 0269/87 (**supra**) with regard to priority were **res judicata** and, thus, were not amenable to being re-investigated.

22. Thus, priority may not be acknowledged to document (1) from the 17 June 1981 and document (1) may not be taken into account when assessing novelty under Article 54(3)(4) EPC.

23. As regards the argument presented by Appellant III, the Board observes that the priority document pertaining to document (2) filed on 16 January 1981 discloses the isolation of one recombinant clone containing a chymosin DNA sequence which was later on shown to be partially deleted. The disclosure of this incomplete clone cannot destroy the novelty of the subject-matter of claim 1.

24. In the Board's judgment, there are no other documents which could destroy the novelty of the claims of the present request whether it be under Article 54(2) or 54(3)(4) EPC. Accordingly, novelty is acknowledged.

Inventive step (Article 56 EPC)

25. All of the parties and the Board are of the same opinion that document (87) represents the closest prior art for the claims at issue. It discloses that chymosin is a milk clotting protein essential for cheese making which is excreted from the fourth stomach of the newborn calf as a precursor, prochymosin, with a size of 365 amino acids. The NH_2 terminal peptide of 42 amino acids is removed from prochymosin autocatalytically under the acidic conditions in the stomach to form active chymosin of a size of 323 amino acids. Document (87) also describes the isolation in **E.coli** of a recombinant clone containing sufficient cDNA to code for 80% of the prochymosin molecule.

26. In light of document (87), the technical problem to be solved can be seen as devising such recombinant DNA processes as are necessary to produce chymosin or its precursors.

27. The solution provided by claim 1 includes a series of independent undertakings, each comprising the cloning and expression of a DNA sequence encoding chymosin or one of its precursors and collecting the protein thus synthesized.

28. The first question to be asked when assessing inventive step is whether, at the date of filing, starting from the disclosure of document (87), the person skilled in the art would attempt anyone of these undertakings with a reasonable expectation of success. There should also carefully be taken into account whether unforeseeable difficulties occurred while reducing the invention to practice, which required inventive effort to be solved (T 0816/90 dated 7 September 1993, not published in the OJ EPO).

29. Appellant's I position is that the patent in suit represented a much higher achievement than the document (87), which did not provide more than a fragment of the DNA necessary to encode prochymosin. It filled up a gap in the knowledge about the gene and demonstrated the feasibility of expression in an alternate host. The work required careful experimentation and could not have been achieved by any other methods (i.e. chemical DNA synthesis) than the one chosen.

30. It was also pointed out that at the priority date of the patent in suit, there certainly existed a hope to succeed in producing chymosin by recombinant DNA techniques, as evidenced by the fact that three groups

Celltech (document (1)), Collaborative Res. (document (2)) and Beppu (document (3)) started the work at about the same time as Appellant I. However, only Appellant I came to the solution of the problem in a rather straightforward manner when the others failed in their initial attempts. The priority applications of documents (1) and (2) filed on 17 June 1981 and 16 January 1981 were found non-enabling by the Boards of Appeal in decisions T 0269/87 (**supra**) and T 0081/87 (**supra**), respectively. The clone disclosed in the priority application of document (3), (24 August 1981), was too small to encode the whole of prochymosin. The only conclusion which could be drawn was, thus, that Appellant I must have exercised an inventive activity to succeed at the time he did when it took a period of about two years before all other groups had achieved the task.

31. Appellant I further argued that none of the instances of the EPO which had to assess patent applications disclosing chymosin production by recombinant DNA techniques came to a conclusion of lack of inventive step. Decisions dealing with other genetic engineering cases filed in the same period supported the view that cloning and expression were inventive in 1981 (e.g. T 0158/91 dated 30 July 1991, not published in the OJ EPO; decision of the Opposition Division in case EP-B 0 148 605). Finally, it was stressed that such a reliable text book as Maniatis (document (17), published in 1982), clearly stated that molecular cloning was difficult to put into practice although it seemed straightforward on paper.

32. In contrast, Appellant's III position is that none of the groups which achieved the expression of chymosin or its precursors experienced any difficulties. Starting from document (87), it would have been an obvious step

to complete the cloning work which would only require the use of variations of techniques which had become standard. Expression of foreign proteins whether it be in a fused or unfused state was well documented.

33. Furthermore, it was argued that if, at a given point in time, two groups started on the same project, it might be that both were driven by the hope to succeed. If, however, as many as four groups simultaneously started on the same project, it must be that, in view of the existing knowledge, there was a reasonable expectation of success. In the present case, moreover, one of the groups was a team of researchers from a university, who must have thought possible to achieve the project with the kind of means at the disposal of such institutions. Success, therefore, could not have been considered as unattainable, all to the contrary.

34. Appellant III also stressed that even if the priority documents of documents (1) and (2) filed on 17 June 1981 and 16 January 1981 did not disclose the cloning of the full length preprochymosin DNA molecule, it would be totally unjustified to describe them as failures. These early filings were simply the reflection of the patenting strategies of the firms involved, who filed applications on their way to success. And success was, in fact, reached on 11 June 1981 and 8 January 1982, that is a few months after Appellant I and not a few years as Appellant I has alleged.

35. Finally, it was remarked that in order to produce chymosin, the full length preprochymosin DNA was not required.

36. The Board considers that in 1981, each step in the synthesis and cloning of cDNA could still be fraught with difficulties (document (68)). Obtaining large

amounts of mRNA was quite difficult when the mRNA was naturally produced in low abundancy. The polymerising capacities of reverse transcriptase were not so optimized that mRNAs with big sizes were easily transcribed in full. The feasibility of devising efficient methods for the screening of the positive clones very much depended on the cDNA to be screened.

37. Thus, before embarking on the cloning and expression of the chymosin encoding DNA, the skilled person would carefully consider if any of these problems can be expected to occur.

38. The closest prior art, i.e. document (87) provides the relevant answers. It discloses that the prochymosin mRNA is isolatable from the newborn calf stomach in 90% pure form and in high amounts (30 micrograms are available for the cloning). The size of the prochymosin encoding mRNA is determined (1500bp) and found commensurate with the size of mRNAs which can be fully transcribed into cDNAs. The successful screening of positive clones by differential colony hybridization to two mRNA populations respectively containing and lacking prochymosin mRNA is also described. A DNA molecule encoding 80% of prochymosin is, moreover, isolated which indicates that the cloning of the full DNA sequences encoding prochymosin, pseudochymosin and chymosin should be feasible, especially that of both the latter molecules which are of a smaller size than the prochymosin DNA.

39. Thus, the teachings of document (87) lead to the conclusion that none of the difficulties expected from the prevailing knowledge on cDNA cloning would be encountered. Accordingly, the person skilled in the art would be fairly confident at the onset of the project that the combination of these teachings and such

standard knowledge on biotechnological protocols as gathered in documents (15) or (17) would lead to the successful cloning of the genes encoding preprochymosin and its maturation forms.

40. Moreover, document (15) also describes an alternative, potentially simpler means for the screening of the positive clones when, as in the present case, the sequence of the protein is known (document (7)), as well as methods for the expression of recombinant DNA sequences.

41. To the question by the Board of whether reducing the invention to practice had brought unexpected difficulties, Appellant I replied that the invention had been performed in a fairly straightforward manner.

42. It would, thus, appear that, at the date of priority, the cloning and expression of the chymosin DNA would have been perceived as an endeavour likely to succeed and that achieving this cloning did not pose such problems as to prove that this assumption was wrong. Therefore the Board must already conclude on this basis that the main request lacks inventive step.

43. In the Board's view, the two further considerations submitted by Appellant I (see points 30 and 31, **supra**) have no bearings on this conclusion. The Board does not find the argument of point 30 relevant because of the time scale involved (one and a half month for Collaborative Res.). It would rather seem that all groups performed the invention in parallel and that the narrow time differences observed in filing the invention are more representative of a filing strategy than of a level of inventive step. As to the argument of point 31,

the Board believes that each of these cases has been assessed on its own merits which obviously cannot be decisive for any other cases.

44. For the above reasons, the Board decides to reject the main request as not fulfilling the requirements of Article 56 EPC.

45. This decision is not in contradiction with other appeal decisions in some cases of the same time period, which acknowledged the cloning of other specific cDNA molecules as involving an inventive step (T 0923/92, (tissue plasminogen activator), OJ EPO to be published, T 0412/93, (erythropoietin) dated 21 November 1994, T 0223/92, (IFN-gamma) dated 20 July 1993 and T 0128/92 dated 30 November 1994, (interleukin-II), all not published in OJ EPO).

46. In all of these earlier cases, however, it was concluded by the competent Boards of Appeal that the isolation of the cDNAs would only be successful if one or more of the difficulties enumerated in point 36 **supra** could be solved. In each case, the mRNA was present in low abundancy and the sequence of the protein to be expressed was either unknown or ambiguous. In the case of tissue plasminogen activator, the mRNA was, moreover, of a very large size. As for erythropoeitin, no reliable source of mRNA was available.

47. Thus, the present decision is an illustration of the general principle expressed in particular in decision T 0158/91 (**supra**) that each case must be assessed on its own merits.

Auxiliary request I

48. Auxiliary request I differs from the main request in that the expression "naturally occurring" has been added in front of the word **preprochymosin** in the first sentence of claim 1: "1. A process for producing naturally occurring **preprochymosin** or any of its maturation forms...".

49. The Board remains in doubt whether the requirements of Article 123(2) are fulfilled by such a claim as there is no evidence that the protein made by the micro-organisms would necessarily be the same as naturally occurring preprochymosin, especially since it is difficult to grasp the precise meaning of "naturally occurring". However, in view of the findings on inventive step (see point 50, **infra**), the Board does not need to decide on this issue.

50. No evidence has been provided by Appellant I that a process for recombinantly producing **naturally occurring** preprochymosin would be in any way different from the process disclosed in the main request. In fact, during oral proceedings, Appellant I agreed that the arguments presented in favour of the inventive step of the latter process equally applied to the earlier. These arguments, however have not been found convincing by the Board (see points 36 to 44, **supra**). Thus, the addition of the expression "naturally occurring" to the first claim does not alter the claimed subject-matter in a way which would justify a different finding on inventive step than given for the main request. Accordingly, auxiliary request I must be rejected.

Auxiliary request II

51. Auxiliary request II differs from the main request in that, in claim 1, the ds-rDNA is restricted to the one encoding preprochymosin, claim 2 corresponds to part (i) (a) of claim 3 of the main request. The same reasons given for the allowability of the main request with regard to Articles 123(2)(3), 83, 84 and 54 EPC apply here and, thus, the subject-matter covered by auxiliary request II fulfils the requirements of these articles. There remains to evaluate inventive step.

52. The closest prior art is still document (87). It conveys the information that chymosin is naturally synthesized as a precursor, prochymosin, which is excreted from the cells which produces it. It describes the cloning of a DNA of a sufficient size to encode 80% of the prochymosin molecule.

53. In the light of document (87), the problem to be solved can be seen as devising a recombinant DNA process for producing chymosin or any of its precursors.

54. The solution consists in cloning the DNA encoding the hitherto unknown protein, preprochymosin, adding such regulatory elements as necessary for recombinant expression, expressing and performing the post-translational modifications necessary to obtain chymosin or its precursors.

55. The question to be asked with regard to inventive step is whether, at the onset of the project, the person skilled in the art might have expected the DNA directing the synthesis of prochymosin to be bigger than that necessary to encode prochymosin and, if so, whether a reasonable expectation of success might have existed for the cloning and expression of such a bigger molecule.

56. Appellant's I position is that none of the very many research workers who studied the chymosin molecule ever hypothesized the existence of preprochymosin. That preprochymosin was ever isolated should, thus, be considered unexpected. Furthermore, all of the arguments raised earlier on in favour of inventive step in the case of pro-, pseudo-chymosin and chymosin also applied.

57. In contrast, Appellant's III position is that the existence of preprochymosin could not have been unexpected as essentially all secreted mammalian proteins studied up until 1981 had been shown to be synthesized as pre-secretory proteins. There was no prejudice in the art against the fact that prochymosin might also be synthesized in the same manner. Cloning the cDNA encoding preprochymosin was obvious for the same reasons as presented in the case of chymosin and its other precursors. The Appellant was bound to find out the existence of the "pre" portion of the prochymosin encoding DNA because the cDNA synthesis would not have stopped at the codon encoding the first amino-acid of prochymosin.

58. The Board considers that document (87) unambiguously discloses that prochymosin is an excreted protein. What was known at the priority date of the patent in suit about excreted mammalian proteins is summarized in document (63). This document teaches that secreted proteins carry an NH_2-terminal extension of about 15 to 29 amino acid residues which serves to direct translocation. Of 26 excreted mammalian proteins cited in document (63), 25 are synthesized as larger pre-secretory proteins. The twenty-sixth, chicken ovalbumin is not cleaved off a higher molecular weight precursor. Yet, it still carries what is recognizable as an uncleaved signal sequence at the NH_2 terminal end.

59. In the Board's opinion, the person skilled in the art simultaneously considering the teachings of documents (87) and (63) would have expected that prochymosin was synthesized as a pre-secretory protein, most probably larger than prochymosin by 15 to 29 amino acids. Otherwise stated, it would have been expected that the DNA encoding the excreted prochymosin would be some 45 to 87 base pairs longer than the prochymosin DNA. In the Board's view, this expected difference of no more than one hundred base pairs would not have deterred the person skilled in the art from believing that the cloning and expression were possible with a reasonable expectation of success.

60. During oral proceedings, Appellant I stated that the cloning and expression of preprochymosin DNA proceeded without any hurdles.

61. The Board considers that the situation is identical to that encountered when assessing inventive step in relation with the cloning of pro-, pseudo- chymosin or chymosin. Thus, the detailed reasoning given for lack of inventive step (points 36 to 44 **supra**) with regard to the main request also applies to the recombinant DNA preparation of preprochymosin as claimed in claim 1 of auxiliary request II.

62. Auxiliary request II is, thus, rejected for lack of inventive step.

Substantial procedural violation

63. Appellant III argues that a substantial procedural violation occurred during opposition proceedings in that the Opposition Division based its findings in favour of inventive step on an assumption as to fact which has no basis in the evidence, namely that natural allelic or

other DNA variation in the chymosin genome in the bovine population is so widespread and varied that it is inherently impossible that the specific DNA sequence disclosed in the patent would be obtained again. For this reason, Appellant III requests a refund of the appeal fee.

64. In the Board's opinion, all assumptions as to facts in the reasons for a decision by the Opposition Division should always be backed up by the teachings of some documents. Nonetheless, the reasoning used in the assessment of patentability is of a substantive rather than a procedural nature. Thus, no procedural violation within the meaning of Rule 67 EPC has occurred and the request for reimbursement of the appeal fee is rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

3. The request for reimbursement of the appeal fee is rejected.

The Registrar: The Chairwoman:

A. Townend U. M. Kinkeldey