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D E C I S I O N
of 20 November 2001

Case Number: T 0342/98 - 3.3.4

Application Number: 87103806.3

Publication Number: 0238023

IPC: C12N 15/80

Language of the proceedings: EN

Title of invention:
Process for the production of protein products in Aspergillus oryzae and a promoter for use in Aspergillus

Patentee:
Novozymes A/S

Opponents:
Röhm GmbH
GENENCOR INTERNATIONAL INC.

Headword:
A. orizae/NOVOZYME

Relevant legal provisions:
EPC Art. 54(2)(3), 123(2)(3), 56, 87, 89, 114, 107

Keyword:
"Priority right - (yes)"
"Appeal admissible - (yes)"
"Novelty - (yes)"
"Inventive step - Main request - (no) - Auxiliary request - (yes)"

Decisions cited:
G 0002/98, G 0009/91, G 0010/91, T 0081/87, T 0296/93, T 0506/92, T 0694/92, T 0114/95, T 0896/90, T 0274/95,

T 0430/96, T 0291/89, T 0386/94

Catchword:
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Case Number: T 0342/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 20 November 2001

Appellant: (Opponent 02)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 2 January 1998 rejecting the opposition filed against European patent No. 0 238 023 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: A. L. L. Marie
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division of 2 January 1998 to dismiss the oppositions according to Article 102(2) EPC and to maintain the European Patent EP 0 238 023 as granted (claiming priority from DK 1226/86 of 17 March 1986 and filed on 16 March 1987). This decision was based on a set of 17 claims, claims 1 and 12 of which read:

"1. A process for expression of a protein product in Aspergillus orizae comprising the steps of:
(a) providing a recombinant DNA cloning vector system capable of integration into the genome of an Aspergillus orizae host in one or more copies and comprising: DNA-sequences encoding functions facilitating gene expression; a suitable marker for selection of transformants; and a DNA-sequence encoding the desired protein product;
(b) transforming the Aspergillus orizae host which does not harbour a functional gene for the chosen selection marker with the recombinant DNA cloning vector system from step a; and
(c) culturing the transformed Aspergillus orizae host in a suitable culture medium."

"12. A process according to claim 1, wherein the vector system further comprises a preregion providing for secretion of the expressed product in the culture medium."

II. The Board issued a communication pursuant to Article 11(2) of the rules of the procedure of the boards of appeal giving the Board's preliminary, non-binding opinion.

III. Opponent 1 had indicated in his letter of 1 April 1997 his intention to no longer actively participate to the opposition procedure, but requested that his arguments be taken into consideration and the patent in suit revoked. Opponent 1 is thus a party as of right according to Article 107 EPC.

IV. Oral proceedings were held on 20 November 2001.

V. On 24 October 2001 auxiliary requests I to VII were submitted. Auxiliary request I consisted in a set of 16 claims, claim 1 of which was a combination of claims 1 and 12 as granted and read:

"1. A process for expression of a protein product in *Aspergillus orizae* comprising the steps of:
(a) providing a recombinant DNA cloning vector system capable of integration into the genome of an *Aspergillus orizae* host in one or more copies and comprising: DNA-sequences encoding functions facilitating gene expression; a suitable marker for selection of transformants; a preregion for secretion of the expressed product into the culture medium; and a DNA-sequence encoding the desired protein product;
(b) transforming the *Aspergillus orizae* host which does not harbour a functional gene for the chosen selection marker with the recombinant DNA cloning vector system from step a;
(c) culturing the transformed *Aspergillus orizae* host in a suitable culture medium; and
(d) isolating the expressed product from the culture medium."

VI. The following documents are cited in this decision:

(1) EP 0 215 594 (filing date: 27 August 1986)

(2) EP 0 126 206

(6) J.W. Bennett, Molecular Genetics of Filamentous Fungi, 1985, page 345-366

(7) J. Tilburn et al., Gene, 1983, Vol. 26, pages 205-211

(8) F.P. Buxton et al., Gene, 1985, Vol. 37, pages 207-214

(9) J.M. Kelly and M.J. Hynes, The EMBO Journal, 1985, Vol. 4, pages 475-479

(10) D. Cullen et al., Heredity (Scotland), June 1986, Vol. 57, No. 1, Abstract No. 20 of an oral disclosure given at a meeting of the Genetical Society, University College, London 15-16th November 1985

(11) Danish Patent Application No. 1226/86 (priority application of the patent in suit)

(12) D.J. Ballance et al., Biochemical and Biophysical Research Communications, 1983, Vol. 112, No. 1, pages 284-289

(13) M.M. Yelton et al., Proc. Natl. Acad. Sci. USA, 1984, Vol. 81, pages 1470-1474

(14) M.A. John and J.F. Peberdy, Enzyme Microb. Technol., 1984, Vol. 6, pages 386-389

(18) Introductory Mycology, 1962, second edition, John Wiley & Sons, Inc., pages 271-278

(19) US patent application No. 6/771,374 (filing date 29 August 1985)

(22) Declaration of Dr T. Christensen (dated 15 November 1995)

(23) Declaration of Dr T. Christensen (dated 30 November 1995)

(25) M.E. Case et al., Proc. Natl. Acad. Sci. USA, 1979, Vol. 76, pages 5259-5263

(27) U. Stahl et al., Proc. Natl. Acad. Sci. USA, 1982, Vol. 79, pages 3641-3645

(28) P. Tudzynsky et al., Current Genetics, 1980, Vol. 2, pages 181-184

(29) R.C. Ullrich et al., Molecular Genetics of Filamentous Fungi, 1985, pages 39-57

(32) Dedclaration of Dr T. Christensen dated 13 June 1997

(33) Y. Iimura et al., Agric. Biol. Chem., 1987, Vol. 51, No. 2, pages 323-328.

(34) Y. Iimura et al, submitted with third party observations on 17 April 2001

(35) EP 0 184 438 (priority date: 5 December 1984, filing date: 4 December 1985, publication date:

11 June 1986)

(36) EP 0 054 440 (page 2)

(37) EP 0 249 350

(38) K.B. Raper and D.I. Fenell, The Genus Apergillus, 1965, Williams & Wilkins editors, pages 70 and 71

(39) Declaration of M. H.P. Heldt-Hansen (dated 19 October 2001)

(40) Declaration of Dr T. Christensen (dated 19 October)

(41) Declaration of Dr. T. Christensen (dated 22 October 2001)

(42) US 3,666,487

(43) US 4,478,854

(44) Declaration of Dr C.M. Hjort (dated 17 October 2001)

(45) Declaration of Dr C.M. Hjort (dated 19 October 2001)

(46) B. Berse et al., Gene, 1983, Vol. 25, pages 109-117

VII. The arguments of the appellant may be summarized as follows:

Article 114 EPC: documents (36) to (46) were submitted

less than one month before the oral proceedings. Document (39) was not in relation with the subject-matter of the patent in suit, document (41) was not signed and the declarations (ie documents (39), (40), (41), (44) and (45)) were not related to the claims, which no longer referred to a "high level of expression" of the desired protein product.

Articles 87 to 89 EPC: the patent in suit was not entitled to the priority of document (11), because it did no longer mention in the claims the "high level of expression"-feature, so that the *A. niger* acid amylase and *A. oryzae* triose phosphate isomerase promoters of documents (22) and (23), which resulted in a lower expression than the TAKA promoter, were within the scope of the patent in suit, although they were excluded from that of document (11). Furthermore, document (11), mainly concerned *A. niger* and *A. nidulans,* contained a single example (Example 10) disclosing the transformation of *A. orizae*, which was only predictive, as shown by the fact that, contrary to the other examples, it was written in the present tense, and non-enabling, since it did not involve a gene of interest, but only a marker gene. Furthermore, it made use of a single vector. In this context, the enabling character of document (11) over the whole area claimed was questioned in view of decision T 694/92 (EPO OJ 1997, 408). Similarly, as far as the auxiliary request was concerned, it was again concluded in view of the predictive character of Example 10 that there was no demonstration that the invention had been performed.

Article 123(3) EPC: claim 1 of the auxiliary request extended the scope of the protection beyond that of

claim 1 as granted to the expression and secretion of a mature protein.

Article 54(3) EPC: document (1), seen as a whole, was considered as disclosing the transformation of *A. niger*, *A. nidulans* and *A. orizae*.

Article 56 EPC: document (6), seen as reflecting the common general knowledge on industrially important fungi, only identified, among the numerous fungi cited, *A. niger* and *A. orizae* as obvious targets for intensive research because of their recognition as "GRAS" organisms (ie "generally regarded as safe") by the Food and Drug Administration. An analysis of the chronology of the transformation of fungi demonstrated that, at the priority date of the patent in suit, homologous as well as heterologous transformation of *A. nidulans* and *A. niger* were known from documents (25), (12), (7), (13), (14), (8) and (9). In particular, document (9) stated in the last two sentences of the introduction part that the demonstration of the transformation of *A. niger* and the obtention of a high level of expression opened up possibilities of DNA-mediated manipulations of non-mutant commercially useful fungi, the development of expression vectors for use with filamentous fungi and the study of heterologous gene regulation. Further, document (9) demonstrated that an unrelated plasmid was co-transformed, hence suggesting the use of 2 plasmids, and finally concluded that the introduction of desired genes into industrially important fungal species should be relatively simple. Document (13) stated that expression had been achieved in *A. nidulans* and *A. orizae*. Document (10) further described the secretion of rennin from *A. nidulans*.

In view of this prior art the technical problem was seen in the extension of the transformation system of *A. nidulans* and *A. niger* to *A. orizae*. The solution was to be found in document (8), describing the transformation of *A. niger* with the *arg*B gene from *A. nidulans* or in document (9) disclosing the transformation of *A. niger* with the *amdS* gene of *A. nidulans*. Since document (11) did not contain more technical information than the prior art, the reasonable expectation of success must have come from the technical knowledge available to the skilled person at the priority date of the patent in suit. The "high level of expression"-feature was no longer mentioned in the claims of the main request and documents (22) and (23) also demonstrated a "low level of expression" in *A. orizae* with promoters other than the TAKA one. Finally, if *A. orizae* was better than expected, this was a "bonus effect" which did not render *A. orizae* non-obvious to be used. The conclusions drawn by document (29) were to be seen with caution, because this document was primarily concerned with *Basidomycetes* and its author was obviously not aware of the technology transfer from *A. nidulans* to *A. niger* concerning the transformation, since it only made reference to documents concerned with *A. nidulans*.

As far as the auxiliary request was concerned, document (10) described the secretion of rennin in *A. nidulans*, so that its obvious combination with document (8) deprived the subject-matter of the claims of this request of any inventive step.

Article 107 EPC: the appellant considered himself as entitled to appeal against auxiliary request I,

corresponding to the introduction of the subject-matter of claim 12 as granted into claim 1 as granted, although he had not argued against said claim 12 as granted in his grounds of opposition, since he requested in his notice of opposition the revocation of the patent in suit *in toto*. Furthermore, claim 12 as granted had been objected to by opponent 1 and was hence within the legal framework of the appeal proceedings.

VIII. Observations by third parties under Article 115 EPC have also been made and were directed to the following points in addition to the submissions by the appellant:

Article 54(3) EPC: according to decision T 274/95 (EPO OJ 1997, 099), novelty was not a "fresh ground" subjected to the consent of the patentee, since it had already been introduced by opponent 1 into the opposition proceedings, so that appellant was allowed to use this ground at the appeal stage, even if he did not do so during the opposition. Document (1) was novelty-destroying, since it disclosed the expression of a desired protein in filamentous fungi and cited *A. orizae* in this context.

***Article 54*(2) EPC**: document (34), published before the priority date of the patent in suit, disclosed the expression of a desired protein in *A. orizae* conferring methionine prototrophy to this organism.

Document (33), already mentioned in the search report, was published on 2 February 1987 and thus prior art within the meaning of Article 54(2) EPC, if the patent in suit did not enjoy the priority of document (11). It disclosed, as document (34), the transformation of

A. orizae to methionine prototrophy as a result of the expression of a desired protein.

Article 56 EPC: if the patent in suit did not enjoy the priority right from document (11), then document (35), published on 11 June 1986, disclosing the transformation of *A. niger*, was prior art in the meaning of Article 54(2) EPC and the closest prior art. The problem to be solved was the provision of a process to express a desired protein in *A. orizae* and the solution was the obvious combination of documents (35) and (33).

If the patent was found to enjoy the priority right from document (11), which did not specifically disclose the expression in *A. orizae,* but only in *A. nidulans* and *A. niger*, then this implied that no difference was to be made between *A. nidulans*, *A. niger* and *A. orizae*. In this context, documents (8) or (9), which disclosed the transformation of *A. niger* would render the subject-matter of the patent in suit obvious.

IX. The respondent argued in the following way:

Article 114 EPC: the filing of the documents (36) to (46) on 22 October 2001 was in agreement with the dead-line defined by the Board (ie one month before the oral proceedings), since said dead-line fell within a week-end. Document (41) could be signed, since its author was attending the oral proceedings before the Board. Document (39) mentioned plasmid p960 also used in document (32) and was hence related to the present case.

On the contrary, documents (33) and (34) should not be

admitted in the proceedings. Document (33), cited in the search report, but not used during the opposition procedure, was, according to decision T 291/89 (14 May 1991), not necessarily part of the appeal procedure. The enabling character of both documents (33) and (34) was objectionable in view, for instance, of the strains M-28 and M-28W mentioned therein. Furthermore, neither a publication date and nor the name of a scientific journal were to be found in document (34).

Articles 87 to 89 EPC: document (11) did not exclusively concern high level expression of a desired protein, as shown by its title or the description on page 2, lines 10 to 15, where the term "expression" was not related to "high level".

The prior art before document (11) disclosed the transformation of some filamentous fungi without expression, whereas the expression was the achievement of document (11) and the "high level" was not an essential feature of said expression, but only an advantage. The concept of "high level expression" was further to be seen by reference to the non-transformed host cell, which did not synthesize at all the desired protein, so that even the weaker promoters of documents (22) and (23) were within the scope of both the patent in suit and document (11). The only difference between document (11) and the patent in suit was that document (11) concerned the filamentous fungi in general, whereas the patent in suit was restricted to *A. orizae*. The concept of "high level expression" as used in the expression "a process for high level expression" only defined the process as being "**suitable for** high level expression" and was not construed as a limitation.

The allegedly predictive character of Example 10 of document (11) was without importance for the question of priority, since Example 10 was nevertheless enabling. Further, Example 10, although not disclosing the use of two separate vectors or of a gene of interest, was to be read in the context of the whole disclosure of document (11), which indicated the use of two separate vectors on page 5 (lines 6 to 8) and that of a gene of interest throughout the whole disclosure. Therefore, the decision T 694/92 (cf. supra) did not apply to the present situation, since document (11) fully enabled the skilled person to perform the invention over the whole claimed area without undue burden. Furthermore, as required by the decisions G 2/98 (EPO OJ 2001, 413) and T 81/87 (EPO OJ, 1990, 250) the features of the invention claimed in the patent in suit were directly and unambiguously derivable from document (11) and thus related to the same invention.

Article 123(3) EPC: the scope of protection of the auxiliary request I had not been extended, since the additional step (d) introduced in claim 1 as granted amounted to a restriction of its scope.

Article 54(3) EPC: as far as introduced by the appellant this objection based on document (1) was a "fresh ground", since it had been introduced into the opposition proceedings by opponent 1. Furthermore, the appellant, asked during the oral proceedings before the opposition division whether he has novelty objections, answered negatively. As a consequence, no consent as required in decision G 9/91 (EPO OJ 1993, 408) was given. Moreover, document (19), the priority document of document (1), was silent about *A. orizae*.

Article 54(2) EPC: even if allowed into the appeal procedure under Article 114(1) EPC, documents (33) and (34) were not novelty-destroying because they were not enabling in view, for instance, of the non-precisely identified M-28 and M-28W strains.

Article 56 EPC: three reasons were in favour of the acknowledgement of an inventive step. First, there was no reasonable expectation of success; second, *A. orizae* was not an obvious choice and, third, *A. orizae* was an unexpectedly good host organism.

As far as the first statement was concerned, the knowledge of the skilled person at the priority date of the patent in suit was not such as to justify more than a "hope to succeed" (cf. Decision T 296/93 (EPO OJ 1995, 627)). Document (29) talked about "prodigious effort", "magical method", variations from species to species and defined thus a **prejudice** against the obviousness of a technology transfer from *A. nidulans* and/or *A. niger to A. orizae*. Document (6) mentioned on page 360 a "hope" and, if it suggested the use of *A. orizae*, this was for "intensive research", so that the conclusions of decision T 386/94 (EPO OJ 1996, 658) (ie acknowledgement of inventive step, if a scientific research rather than a routine work had to be done) applied to the patent in suit. Documents (8) and (9) did not suggest the extension of the teachings to *A. orizae.* Furthermore, the present case was different from that of decision T 430/96 (11 November 1999), in which document (3)(referred to as document (12) in the present procedure) clearly pointed at *A. niger* as a suitable host for transformation and expression of heterologous proteins on the basis of the work done

with *A. nidulans*.

As far as the second line of argumentation was concerned, document (6) showed that other *Aspergilli* were also considered as industrially important and probably recognized as "GRAS". Furthermore, documents (8) and (9) were only concerned with the transformation of *A. nidulans* and *A. niger*, so that the next step, and hence the technical problem to be solved, was not the extension of their teaching to *A. orizae*, but the achievement of the expression in *A. niger* and *A. nidulans*. Document (19) was also silent about *A. orizae*, whereas documents (37), (42) and (43) indicated other *Aspergilli* or even other genera, such as *Neurospora* or *Penicillium*. There was therefore no "one way street"-situation pointing at *A. orizae* as a suitable host for transformation and expression of heterologous proteins.

Finally, *A. orizae* proved to be an unexpectedly good host organism as demonstrated by document (32) or the comparative tests submitted during the oral proceedings before the opposition division. The concept of "bonus effect", as defined in decision T 506/92 (3 August 1995) was restricted to "one way street"- situations and thus did not apply to the patent in suit.

Article 107 EPC: basically, the opponent defined the legal and factual framework of the appeal by its notice and grounds of opposition. Auxiliary request I resulted from the introduction into claim 1 as granted of the features of claim 12 as granted. However, the appellant had never argued against claim 12 as granted and was therefore not adversely affected by the decision of the

first instance in the meaning of Article 107 EPC, as far as the subject-matter of said claim 12 was concerned. As a consequence, the appellant was not allowed in the appeal procedure to plead against claim 1 of auxiliary request I.

X. The appellant requested that the decision under appeal be set aside and the patent No. 0 238 023 be revoked.

XI. The respondent requested as main request that the appeal be dismissed and the patent be maintained as granted and as auxiliary request that the decision be set aside and the patent be maintained on the basis of claims 1 to 16 filed as auxiliary request I on 24 October 2001.

Reasons for the Decision

Article 114 EPC

1. The date of filing of the respondent’s last submissions (ie 22 October 2001) is in agreement with the period of one month indicated by the Board in its communication under Article 11(2) of the rules of procedure of the boards of appeal, since the 20 and 21 October 2001 fell within a week-end.

2. Documents (39), (40), (41), (44) and (45), which are declarations concerning comparative experiments, are not admitted into the procedure under Article 114(2) EPC. In the Board’s view, not only the relevance and the date of submission are important factors for the admissibility of late-filed documents into the procedure, but also their nature in connection with the

principle of fair and equal treatment of the parties involved. Comparative data, contrary to scientific publications, are specifically directed to a particular technical aspect having a particular importance in the context of the procedure concerning a specific patent. Their teaching may accordingly be of a particular value. As a consequence, the reaction to such comparative data is for the other party (parties) particularly cumbersome, time-consuming and extends beyond the normal analysis of a scientific publication. The Board considers that to place a party in such a situation at a time so close to the oral proceedings is not in agreement with the principle of fair and equal treatment of the parties.

3. Document (34) submitted with third party observations under Article 115 EPC cannot be identified as a scientific publication, since it mentions neither the name of a scientific journal nor a publication date. Therefore, document (34) is not admitted into the appeal procedure according to Article 114(2) EPC.

4. Document (33) has been cited as a "P"-document in the search report, but has not been used during the opposition procedure. It could only be possibly relevant, if the claims of the patent in suit were not entitled to the priority of document (11). In view of the conclusions reached (cf infra, points 6 to 10 and 31 to 32), document (33) is not taken into consideration.

5. Documents (36) to (39), (42), (43) and (46) are admitted into the proceedings, since they relate to the subject-matter of the appeal, have been introduced in answer to arguments submitted by the appellant or

remarks made by the Board in its communication under Article 11(2) of the rules of the procedure of the boards of appeal and are *prima facie* relevant.

Main request

Articles 87 to 89 EPC

6. The right of priority is governed by Articles 87 to 89 EPC which require that the European patent application and the application, the priority of which is claimed relate to the same invention, ie to the same subject-matter. Decision G 2/98 (cf supra) has decided that a narrow interpretation should be given to the concepts of "the same invention" and "the same subject-matter". The main criterion in this respect is whether the claimed invention is disclosed in the priority document, seen as a whole, with all its essential features. According to decision T 81/87 (cf supra) the disclosure of these essential features "must be either express, or be directly and unambiguously implied in the text". Identical wording is nevertheless not required and the common general knowledge of the skilled person may also be used.

7. Document (11) discloses in Example 10 the transformation of *A. orizae* with the *amds* and *argB* genes of *A. nidulans*. Since the transformed organisms are able to grow on acetamide or become prototroph toward arginine, a protein or a group of proteins must have been expressed. Thus, document (11), besides the transformation, also discloses the expression in *A. orizae*. Document (11) further discloses on page 4 the use of a two vector system. From the fact that Example 10 has been written in the present tense the

Board cannot conclude with certainty that it has not been reduced to practice. Furthermore, there is no evidence on file that could lead the Board to the conclusion that Example 10 is not enabling.

8. As far as the question of "high level expression" is concerned, no prior art document on file describes the expression of a foreign gene in *A. orizae*. Therefore, the only *A. orizae*, which could be considered as a comparison reference, is the non-transformed *A. orizae* itself. Of course, in this context, even the slightest expression, such as that obtained with the weaker promoters used in documents (22) and (23), is already a "high level expression" as mentioned in the claims of document (11).

9. Furthermore, the Board is of the opinion that the concept of "high level expression" should be understood as defining a **range** rather than a single point. Indeed, if an expression system allows under certain circumstances a certain level of expression, the physico-chemical conditions of this system (culture medium composition, temperature, pH, etc...) may be so modified using the common general knowledge of the skilled person as to allow a lower level of expression, which could for instance be desired to avoid too high a viscosity of the culture medium due to a high concentration of secreted protein or the formation of insoluble refractile bodies within the cells in the case of non-secreted proteins. In view of this interpretation, document (11) could well confer the priority right to claims directed to both high and low levels of expression. It seems in this context that all the subject-matter covered by the claims of document (11) is enabled, so that decision T 694/92 (cf. supra)

does not apply.

10. As a consequence, the patent in suit enjoys the priority right from document (11).

Article 54(3) EPC

11. Document (1) (filing date: 27 August 1986, publication date: 25 March 1987) would only be novelty-destroying as far as it related to the subject-matter disclosed in its priority document (19) (filing date: 29 August 1985). Document (19), contrary to document (1), is silent about *A. orizae*. Therefore, document (1) cannot enjoy the priority of document (19) as far as *A. orizae* is concerned and cannot destroy the novelty of the subject-matter of the claims of the main request.

Article 54(2) EPC

12. Since the claims of the main request enjoy the priority right from document (11), document (33), published after the priority date, is no longer prior art in the meaning of Article 54(2) EPC. There is therefore no need to answer the question of its admissibility into the procedure (cf supra, point 4).

Article 56 EPC

13. Since the claims of the main request enjoy the priority right of document (11), document (35) published on 11 June 1986 is under Article 56 EPC (second sentence) no prior art.

14. The closest prior art is represented in the Board’s view by either document (8) or document (9), which are

very similar in their disclosures and equivalent in their teaching, since they both describe the transformation of *A. niger* by foreign genes using the transformation method already designed for *A. nidulans*.

Document (8) describes the transformation of *A. niger* cells defective in ornithine transcarbamylase function with the *A. nidulans argB* gene, which results in an arginine prototrophy of the transformed *A. niger* cells. Further, document (8) indicates that the foreign gene has been integrated into the genome of the host (page 211) and concludes (page 212) that the transformation system described allows foreign genes to be introduced and maintained stably in *A. niger*.

Document (9) describes the transformation of *A. niger* with the *amd*S gene encoding the acetamidase of *A. nidulans*, which results in the ability of the transformed *A. niger* cells to grow on acetamide. The transformed gene is stably integrated in the recipient genome. Co-transformation is said to allow manipulation without complex plasmid constructions because selected and unselected genes need not to be on the same plasmid (pages 477 and 478). It is concluded that the introduction of desired genes into industrially important fungal species should be relatively simple and the development of high level expression vectors for filamentous fungi possible (page 478).

15. Since a new function (arginine prototrophy or growth on acetamide) appeared in the transformed *A. niger* cells of documents (8) and (9), the expression of the foreign gene (*amds* or *arg*B) must have occurred. Therefore, contrary to the respondent’s interpretation (cf supra, paragraph IX), the technical problem to be solved in

view of documents (8) or (9) is no longer the expression of a foreign gene in *A. niger*, but the provision of an alternative expression system to the already existing *A. niger* system.

16. The solution of this problem as proposed in the claims of the main request is the use of *A. orizae* as a host organism and the examples disclosed in said patent show that the problem mentioned above has been solved.

17. The question to be answered in view of the assessment of inventive step under Article 56 EPC is whether *A. orizae* was an obvious choice for the skilled person at the priority date of the patent in suit in view of the cited prior art and/or whether its use was related to a reasonable expectation of success.

18. The Board is of the opinion that this question has to be positively answered in view of the disclosure of document (6), which only recognizes *A. niger* and *A. orizae* as "GRAS" organisms among all the fungi cited, so that the skilled person, even if documents (6), (25), (27), (28), (42) or (43) mention other *Aspergilli* or other fungi, was caught into a "one-way-street" situation and led to give the preference to *A. orizae*.

19. Furthermore, the Board is of the opinion that it was part of the common general knowledge of the skilled person at the priority date of the patent in suit that *A. niger* and *A. orizae* are phylogenically more closely related to each other than any of them to *A. nidulans*. This can be seen, for instance, from the fact that neither *A. niger* nor *A. orizae*, contrary to *A. nidulans*, exhibit parasexual phenomena. Confirmation

of this common general knowledge can be found in document (18), a textbook published for the first time in 1932 and present on file in its edition of 1962 (ie almost 25 years before the priority date of the patent in suit). Therefore, the skilled person, aware from documents (8) and (9) of the fact that the technology transfer took place between *A. nidulans* and *A. niger*, would have been confident in the successful transfer of technology between *A. niger* and *A. orizae*.

20. In this context, the Board considers document (29), containing some sceptical comments, as irrelevant, since it concerns *Basidomycetes*, which are not closely related to the *Ascomycetes*, to which the *Aspergillus* genus belongs. Furthermore, the author of document (29) was obviously not aware of (or not interested in) the technology transfer, which had occurred between *A. nidulans* and *A. niger*, since document (29) only makes reference to scientific publications related to *A. nidulans* and is silent about said technology transfer.

21. The Board thus considers that the choice of *A. orizae* for the technology transfer from *A. niger* was obvious for the skilled person and related to a reasonable expectation of success in view of the combined teaching of either document (8) or document (9) with that of document (6). Therefore, decision T 386/94 (cf supra), which suggests the acknowledgment of inventive step in cases where success could not reasonably be expected, does not apply to the present case.

As a consequence, the claims of the main request do not fulfil the requirements of Article 56 EPC.

Auxiliary request I

Article 107 EPC

22. Claim 1 of auxiliary request I is a combination of claims 1 and 12 of the main request. The claims of the main request are the claims **as granted,** which have been maintained by the opposition division. In his notice of opposition, the appellant had not explicitly argued against claim 12, although he indicated on the EPO Form 2300 that the opposition was directed to the **whole** patent.

23. The question is whether an argumentation of the appellant at the appeal stage against claim 1 of auxiliary request I would constitute a "fresh ground" of opposition in the sense of decisions G 9/91 (EPO OJ 1993, 408) and G 10/91 (EPO OJ 1993, 420) and would extend beyond the factual and legal framework defined in the appellant's notice of opposition.

24. Decision T 114/95 (8 April 1997), in a case concerned with the same legal question, came to the conclusion that the appeal is admissible, since it suffices for an opponent to substantiate an attack under Article 100 EPC on only one claim of the patent, and that there is no obligation under the EPC to object to any of the claims at the stage of filing the notice of opposition (cf points 1.1 to 1.5).

Decision T 896/90 (22 April 1994) in a case concerning the extent of opposition under Rule 55(c) EPC, also came to a similar conclusion (points 4 to 5) and decided that it cannot be concluded from an argumentation only directed against claim 1 that this

sole claim be attacked. Reference was made to Decision G 9/91 (cf supra) stating that subject-matters of claims depending on an independent claim, which falls in opposition or appeal proceedings, may be examined as their patentability even if they have not been explicitly opposed, if their validity is *prima facie* in doubt on the basis of already available information.

25. In this context it should be kept in mind that opponent 1 had indicated during the opposition procedure (letter of 1 April 1997) that, although he did not intend to attend the oral proceedings before the opposition division, he still requested the patent in suit to be revoked and his arguments under Articles 54(3) and 56 EPC to be taken into consideration. Opponent 1 had indicated on EPO Form 2300 that the opposition was directed to the **whole** patent and that, more particularly, the objection of lack of novelty was directed to claims 1 to 6, 12, 16 and 17. Claim 12 was directly objected on page 5 of the notice of opposition under Article 54(3) EPC and on page 16 under Article 56 EPC. Therefore, the legal framework defined by opponent 1 included and still includes Articles 54(3) and 56 EPC objections directly raised against claims 1 and 12 as granted.

26. Decision T 114/95 (cf supra) also dealt with such a situation and concluded that there is no limitation set by the EPC to allowing an opponent whose opposition is considered admissible to support and use grounds, evidence and arguments for revocation of the patent that were submitted by other opponent(s) (point 1.5).

27. Therefore, the appeal of the appellant against auxiliary request I is admissible under Article 107

EPC.

Article 123(2)(3) EPC

28. Claim 1 of auxiliary request I differs from that of the main request by the introduction into claim 1 as granted of the feature "preregion allowing the secretion of the expressed product into the culture medium" and of an additional step (d) of recovery of said secreted product in the culture medium.

29. This amendment does not contravene the requirements of Article 123(2) EPC, since secretion and recovery from the culture medium are disclosed in the application as filed (claims 12 to 15, for instance).

30. This amendment also meets the requirements of Article 123(3) EPC, because *prima facie* the introduction of the technical feature of a dependent claim into an independent one results in the restriction of the scope of the latter. In the present case, the scope of claim 1 of auxiliary request I has been restricted to proteins excreted from the bacteria by the introduction of the feature "preregion" of claim 12.

Articles 87 to 89 EPC

31. Claim 1 of auxiliary request I now requests the presence of a preregion providing for secretion of the expressed product into the culture medium and the isolation of the expressed product from the culture medium.

32. Priority document (11), seen as a whole, mentions the

secretion on pages 2 (line 2) and 3 (lines 4 to 9 line 23), the preregions or signal/leader sequences on page 4 (lines 3 to 21) and indicates on page 4 (line 3) that secretion of the expressed product in the culture medium is a preferred embodiment. This teaching is not brought in relation with a particular *Aspergillus* species, but refers to all the cited *Aspergillus* species, ie *A. nidulans*, *A. niger* and *A. orizae*. This gives a basis for claim 1 of auxiliary request I, which is thus entitled to the priority right of document (11).

Article 54(2)(3) EPC

33. Since the right of priority from document (11) can be acknowledged for auxiliary request I, the conclusions reached in view of the main request (cf supra, points 10 and 12) equally apply to auxiliary request I.

Article 56 EPC

34. Therefore, as in the case of the main request (cf supra, point 13), document (35) is according to Article 56 EPC (second sentence) no prior art.

35. The closest prior art is document (10) which discloses the secretion of rennin in *A. nidulans* under the control of various secretion signals and heterologous promoters.

36. The technical problem to be solved is to find an alternative to the secretion system of document (10), specially in view of the fact that *A. nidulans* is a "laboratory strain" unsuitable for commercial purpose.

37. The solution given in the patent in suit is the use of *A. orizae* as a host organism for the secretion.

38. The question to be answered in view of inventive step is whether the extension of the teaching of document (10) to *A. orizae* would have been considered at the priority date of the patent in suit as obvious and promising by the skilled person.

39. In view of the finding under point 40 (cf infra) the question whether document (10) is an enabling disclosure appears to be of minor importance. It can nevertheless be noted that document (10) does not precisely identify any signal sequences and is silent about modifications which seem to be possibly necessary, since the sentence referring to the signal sequences begins with "*Further modifications involved...*". Furthermore, document (10) is a descriptive abstract, which merely states the results obtained, but does not provide the skilled person with any technical information on the possibility to reduce this teaching to practice.

40. The key problem in view of document (10) is, however, that it does not point at all to any other *Aspergillus* than *A. nidulans*. In that sense the situation is different from that encountered with the main request, for which *A. orizae* was the only alternative to the already used *A. niger*, since both *Aspergilli* were the only obvious choices in view of document (6) considering them as "GRAS" organisms. In the present case, even if document (6) is combined with document (10), the skilled man has still two possibilities for extending the teaching of document (10) to an *Aspergillus* other than *A. nidulans*, namely *A. niger* and

A. orizae. This means that the skilled person is not in a "one-way-street" situation as in the case of the main request, but has to make a deliberate choice. Therefore, *A. orizae* is, as far as the secretion is concerned, no longer an obvious choice, but one of the two possibilities offered to the skilled man by document (6).

41. Furthermore, nothing suggests in document (10) that the technology transfer between *A. nidulans* and *A. orizae* concerning the secretion may be possible. It can also not be extrapolated from the positive results obtained with the technology transfer concerning the expression from *A. nidulans* to *A. niger* that similar positive results could be obtained for the secretion, since expression and secretion are different phenomena involving different molecular mechanisms.

42. Moreover, contrary to the situation evoked in the case of the main request for the transformation and expression (points 17 to 21) , the technology transfer in the case of the secretion should no longer take place between *A. niger* and *A. orizae*, ie two closely related fungi (cf supra, point 19), but between *A. nidulans* and *A. orizae*, which are phylogenically much more remote from each other than are *A. niger* and *A. orizae*, so that a success could not have been reasonably expected.

43. Document (2) which describes the secretion of *A. awamori* glucoamylase in yeast under the control of its own signal sequence is of no help as far as secretion in *A. orizae* is concerned, since it concerns another *Aspergillus* strain and the secretion does not occur in a filamentous fungus, but in a yeast.

44. As a consequence, the Board is of the opinion that *A. orizae* was not an obvious choice as a host organism for a secretion system in filamentous fungus and that a success could not have been reasonably expected. Therefore, claim 1 of the auxiliary request I fulfils the requirements of Article 56 EPC. Since claims 2 to 16 directly or indirectly depend on claim 1 they as such meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside,

2. The case is remitted to the first instance with the order to maintain the present patent on the basis of claims 1 to 16 filed as auxiliary request I on 24 October 2001 and on the basis of pages 2, 3, 6 and 18 filed during the oral proceedings and pages 4, 5, 7 to 17 and the drawings as granted.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey