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# D E C I S I O N
## of 27 September 1996

**Case Number:** T 0078/95 - 3.3.4

**Application Number:** 87300916.1

**Publication Number:** 0235951

**IPC:** C12N 15/80

**Language of the proceedings:** EN

**Title of invention:**
Penicillium chrysogenum

**Patentee:**
Antibioticos, S.A.

**Opponent:**
Gist-brocades n.v.

**Headword:**
Penicillium chrysogenum/ANTIBIOTICOS

**Relevant legal provisions:**
EPC Art. 54, 56

**Keyword:**
"Novelty (yes) - prior art citation not enabling"
"Inventive step (yes) - no reasonable expectation of success"

**Decisions cited:**
T 0206/83, T 0296/93, T 0923/92, T 0694/92

**Catchword:**
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**Case Number:** T 0078/95 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 27 September 1996**

**Appellant:** (Proprietor of the patent)
Antibioticos, S.A.
Bravo Murillo 38
28015 Madrid (ES)

**Representative:**
MARKS & CLERK
57-60 Lincoln's Inn Fields
London WC2A 3LS (GB)

**Respondent:** (Opponent)
Gist-brocades n.v.
Wateringsweg 1
NL-2611 XT Delft (NL)

**Representative:**
Visser-Luirink, Gesina, Dr.
c/o GIST-BROCADES N.V.
Patents and Trademarks Dept.
Wateringseweg 1
PO Box 1
2600 MA Delft (NL)

**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office dated 1 December 1994 revoking European patent No. 0 235 951 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** L. Galligani
S. C. Perryman

## Summary of Facts and Submissions

I. European patent No. 0 235 951 was granted on 1 July 1992 with eleven claims for thirteen contracting states, based on European patent application No. 87 300 916.1.

Claims 1, 5 and 11 read as follows:

"1. A selectable transformation technique for Penicillium chrysogenum, wherein an auxotrophic strain of P. chrysogenum is first selected and is transformed with a plasmid containing DNA from a fully prototrophic strain of P. chrysogenum, which plasmid has been selected by prototrophic transformation of a suitable auxotrophic strain of a host microorganism.

5. A plasmid as defined in claim 1.

11. A prototrophic strain of P. chrysogenum when obtained by introduction of exogenous DNA in to an auxotrophic mutant of P. chrysogenum."

Claims 2 to 4 related to embodiments of the method of claim 1. Claims 6 to 7 concerned embodiments of the plasmid of claim 5. Claims 8 and 9 were directed to specific, deposited plasmids, while claim 10 related to a specific, deposited strain of Penicillium chrysogenum.

II. Opposition to the patent in suit was filed by one party requesting its revocation on the grounds of

lack of novelty and lack of inventive step (Article 100(a) EPC).

III. With decision dated 1 December 1994, the opposition division revoked the patent pursuant to Article 102(1) EPC. Basis of this decision were claims 1 to 11 as filed on 8 July 1994 (main request) and two auxiliary requests. Claim 1 of the main request was identical to claim 1 as granted, while Claims 5 and 11 now read as follows:

"5. A plasmid containing a wild type gene from a fully prototrophic strain of P. chrysogenum, which plasmid has been selected by prototrophic transformation of a suitable auxotrophic strain of a host microorganism, said plasmid being capable of restoring an auxotrophic strain of P. chrysogenum to prototrophy.

11. A prototrophic strain of P. chrysogenum when obtained by introduction into an auxotrophic strain of P. chrysogenum of a plasmid containing DNA complementary to said auxotrophy, said introduction resulting in the introduction into the genome of exogenous plasmid DNA in excess of the DNA restoring the strain to prototrophy."

The wording of all the remaining claims was identical to the wording of the corresponding granted claims.

During the proceedings before the opposition division, the parties relied upon a large number of

documents, including in particular the following (numbering as used by the opposition division):

(1) J. Cell. Biochem., Supplement 9c, 1985, 174, Abstract No. 1576;
(3) Process Biochemistry, October 1986, pages 153 to 159;
(4) Proc. Natl. Acad. Sci. USA, 1984, Vol. 81, 1470-1474;
(5) Current Genetics, 1985, Vol. 9, 361-368;
(8) J. Gen. Microbiol., 1954, Vol. 11, 94-104;
(12) Curr. Genet., 1987, Vol. 11, 639-641;
(13) Biochem. Biophys. Res. Comm., 1983, Vol. 112, 284-289;
(14) Gene, 1984, Vol. 32, 487-492;
(15) Gene, 1985, Vol. 37, 207-214;
(17) Molec. Cell. Biol., 1984, Vol. 4, No. 10, 2041-2051;
(18) Enzyme Microb. Technol., 1984, Vol. 6, 386-389;
(19) The EMBO J., 1985, Vol. 4, No. 2, 475-479;
(20) Gene, 1985, Vol. 39, 231-238;
(21) MICROBIOLOGY, American Society of Microbiology, D. Schlessinger ed., 1985, 468-472;
(22) Gene, 1983, Vol. 26, 205-221.

Ground for the revocation was lack of inventive step having regard to document (4), which was considered to represent the closest prior art, in combination with further general knowledge as represented inter alia by documents (5), (8), (13)-(15), (17)-(19), (20)-(22)).

IV. The appellants (patentees) lodged an appeal against the decision of the opposition division. With the statement of grounds they submitted inter alia the following document:

(24) the relevant correspondence from the prosecution of the European patent application EP 87 201 761.1.

V. With letter dated 26 June 1995, the respondents withdrew the opposition and informed the Board that they agreed with the grounds of appeal and with the request of the appellants.

VI. The appellants request that the decision under appeal be set aside and the patent be maintained on the basis of claims 1 to 11 as filed on 8 July 1994. Oral proceedings were requested in the event the Board did not contemplate setting aside the contested decision.

## Reasons for the Decision

1. The appeal is admissible.

2. According to Rule 60(2) EPC opposition proceedings may be continued by the European Patent Office of its own motion even if the only opposition is withdrawn, and the opposition division is still entitled to revoke the patent. A fortiori, withdrawal of the opposition by the sole opponent after the decision of the opposition division has been issued, as is the case here, is not per se a ground for allowing an

appeal by the patentee, though the fact that the opponent no longer supports the arguments for revoking the patent may be taken into account in considering the facts and evidence. The Board must therefore consider the appeal on its merits.

*Article 123(2) and (3) EPC*

3. Formal objections to claims 1 to 11 filed on 8 July 1994 were raised neither by the respondents nor by the opposition division. The Board notes that claims 1 to 4 and 7 to 10 have a wording identical to that of the granted claims. As for claims 5 and 11, the amendments introduced in comparison with claims 5 and 11 as granted do not lead to an extension of the protection conferred and can unambiguously be derived from the application as filed (see eg page 2). Thus, no objections under Article 123(2) and (3) EPC exist.

*Article 84 EPC*

4. No objections were raised under Article 84 EPC to the amended claims by the respondents or by the opposition division. The Board sees no reasons for objecting to the clarity of the claims on file.

*Novelty (Article 54 EPC)*

5. Throughout the opposition proceedings, the respondents attacked novelty of claims 1, 5 and 11 as granted on the basis of document (1) published in 1985 with the title "Transformation of Penicillium chrysogenum", and reading:

"By complementation of an auxotrophic mutation, we have been able to transform P. chrysogenum with low frequency. The transforming plasmid pGB83, which also contains a piece of P. chrysogenum ribosomal DNA, becomes integrated into the Penicillum genome, as indicated by Southern blot analysis. In several instances, we succeeded in recovering pGB83, or its derivatives, from P. chrysogenum transformants by restriction endonuclease digestion of chromosomal DNA, ligation, and transformation to E. coli."

This is an abstract corresponding to an intended presentation during a symposium before the priority date of the patent in suit. However the presentation did not take place, and the appellants contend that the published abstract is not, by itself an enabling disclosure. During the prosecution of the European patent application No. 87 201 761.1 (cf. document (24)), the respondents, in contrast with the submissions in the present case during the opposition stage, provided evidence and arguments in order to show that document (1) would **not** have enabled one skilled in the art to put into practice the transformation of Penicillium chrysogenum with a plasmid. In particular, they filed as evidence a copy of the letter by Dr. B. P. Koekman (one of the authors) dated 22 March 1985 informing the symposium organisers before the symposium started of the withdrawal of the intended poster presentation and requesting the cancellation of the publication of the abstract (notwithstanding this request the abstract was published). Thus, the appellants and the respondents now both agree that document (1) is not

an enabling disclosure. This conclusion has been reached also by the opposition division in its decision on the basis of the consideration that "since none of the documents available to the Opposition Division deals with P.chrysogenum transformation the missing teaching of D1 cannot be supplemented by the general knowledge of the skilled person" (see point 2.1). The Board sees no reason for coming to any different conclusion. Indeed document (1) is per se not enabling in the sense that, although it announces the successful complementation of an auxotrophic mutation by transformation in Penicillium chrysogenum, it does not provide enough information to allow others to reproduce the experiment. In fact, as the corresponding presentation did not take place, the skilled reader cannot derive from the abstract alone any information about the auxotrophic mutation which was complemented, the preparation of the ribosomal DNA referred to (incidentally, the expression ribosomal DNA is per se technically unclear), the preparation of the transforming plasmid pGB83 or its derivatives, which were not generally available through other sources, and/or the Penicillium chrysogenum strains used. Accordingly, in line with established case law whereby a prior art document causes lack of novelty only if it contains an enabling disclosure (see eg T 206/83, OJ EPO 1987, 5), document (1) is not regarded as prejudicial to the novelty of any of the claims at issue. None of the remaining documents affects the novelty of the claimed subject-matter. Novelty is therefore acknowledged.

*Inventive step (Article 56 EPC)*

6. Even though document (1), due to its lack of technical teaching, cannot prejudice novelty, this does not imply that the document does not constitute prior art under Article 54(2) EPC. It has thus to be considered when discussing inventive step. The Board regards document (1) as the appropriate starting point in the prior art as it tells the skilled person of the problem to be solved, namely the provision of a method and means for the transformation of Penicillium chrysogenum, and suggests an approach for solving this problem, albeit that the skilled person cannot rely thereupon to actually solve the problem.

7. Claims 1 to 11 at issue are directed to a method and means for solving the underlying technical problem. Example 3 substantiates the validity of the proposed approach by demonstrating the applicability of the trpC gene from a wild-type prototrophic strain of Penicillium chrysogenum as a selection marker in a plasmid complementing an auxotrophic trpC mutant strain of Penicillium chrysogenum. The description indicates that other candidate markers can also be used (pyr4, argB, and $NO^{-3}$reductase). Although no further specific examples are given, the Board is satisfied that the information provided in the application allows the claimed method to be carried out and the claimed plasmids to be obtained. The respondents had at no stage challenged this. The Board is thus satisfied that the underlying technical problem is solved by the proposed method over the whole area claimed.

8. It is noted that the patent in suit does not disclose a generally applicable technique new in itself, but rather makes the suggestion that the general approach already used for the transformation of other fungi (see eg documents (4), (14), (17)), in particular the experimental approach used for Aspergillus nidulans (see document (4)), will also work for Penicillium chrysogenum. Document (4) discloses the transformation of an auxotrophic trpC mutant strain of Aspergillus nidulans with a plasmid carrying a wild-type trpC gene from a prototrophic strain of Aspergillus nidulans.

9. The relevant question in respect of inventive step is what the skilled person, on the basis of the information given in document (1), would have done to find a practicable solution to the problem. In looking for a solution, the skilled person might indeed have considered document (4), but it should be objectively established whether at the priority date there were indications that this method offered any reasonable prospect of success when applied to Penicillium chrysogenum. As pointed out in the case law (see eg T 296/93, OJ EPO 1995, 627; T 923/92 of 8 November 1995 and T 694/92 of 8 May 1996, to be published in the OJ EPO), a line of action will not be obvious if the skilled person at the priority date was not in a position, on the basis of existing knowledge, to embark on this line of action with a reasonable expectation of success. As stated in decision T 296/93 (above), a "reasonable expectation of success" should not be confused with the "hope to succeed".

10. The appellants argue in favour of inventive step essentially on the basis of the total unpredictability as to how one might successfully develop a selectable transformation technique for Penicillium chrysogenum, due to:

- The known difficulty of forming and selecting heterokaryons in Penicillium chrysogenum;

- The almost complete lack of knowledge about the genetics of Penicillium chrysogenum;

- The known lack of meiosis in Penicillium chrysogenum.

11. As apparent from the prosecution of the European patent application No. 87 201 761 (see letter dated 2 December 1992, page 3 in document (24)), the respondents, in contrast with their initial submissions in the present case (cf. opinion of Dr C. A. M. J. J. van den Hondel dated 30 June 1994), also support the view that in early 1986 it was not possible for the average skilled person in the art to tackle problems arising in the development of efficient gene-transfer systems for Penicillium chrysogenum based on complementation of auxotrophic mutants, due to:

- The poor genetic characterisation of Penicillium chrysogenum;

- The difficulties inherent in handling of industrial strains, eg generation and regeneration procedures of protoplasts;

- The limited number of cloned genes available at the time for complementation, relative to the large number of auxotrophic mutations known;

- The difficulties known in handling and maintaining particular auxotrophic strains due to their auxotrophy.

Although the above statements were made by the respondents in support of their contention that the teaching of the patent in suit was not applicable for complementing an auxotroph Penicillium chysogenum to prototrophy in general, but only in respect of the specific trpC marker (see loc. cit. page 2; incidentally, it should be noted that the patent in suit has not been opposed by the respondents on the grounds of insufficiency of disclosure (Article 100(b) EPC); see also point 7 above), the respondents' statements are taken as illustrative of the state of the art at the priority date.

12. The above submissions by both the appellants and the respondents thus indicate that the skilled person wishing to solve the underlying technical problem as defined above (see point 6) was entering a quite unexplored area of fungal genetics. This implies that the skilled person would not have been able to reasonably predict that the technique already known for the transformation of other fungi, in particular

for Aspergillus nidulans, would have worked also for Penicillium chrysogenum.

13. This conclusion is at variance with the position of the opposition division which in its line of reasoning for denying inventive step started from document (4) and did not take document (1) into account. According to the opposition division, the skilled person, although not having a 100% guarantee that the process applied in document (4) for Aspergillus nidulans would have worked for Penicillium chrysogenum, had a reasonable expectation that it would work, on the basis of the fact that transformation had been achieved with a number of other fungi such as Aspergillus nidulans (see documents (13), (18) and (22)), Aspergillus niger (see documents (15) and (19)), Cephalosporium acremonium (see document (21), Neurospora crassa (see document (17)) and Podospora anserina (see document (14)). From this, according to the opposition division, the skilled person would have derived the suggestion that transformation of Penicillium chrysogenum by the same method was possible. In the view of the opposition division, the absence of meiosis in Penicillium chrysogenum would not have prevented the skilled person from applying the teaching of document (4) to Penicillium chrysogenum because prior art document (19) demonstrated in respect of Aspergillus niger, which also lacked meiosis, that the transforming DNA could indeed integrate into the genome. As for the difficulty of forming and selecting heterokaryons, the opposition division held that prior art

document (8) indicated to the skilled person a way of selecting heterokaryotic transformants in Penicillium chrysogenum.

14.1 In the Board's judgement, the skilled person faced with the underlying technical problem would have first considered the contents of document (1). As already stated (see point 5 above), he or she would not have been able to derive therefrom any information for repeating the experiment described and thus achieve directly a solution to the underlying technical problem. As acknowledged also by the opposition division in examining the technical teaching of this document (see point 5 above), the skilled person would not have been able to compensate through common general knowledge the total absence of useful technical information in the document in question. Moreover, the fact that the actual poster presentation had been retracted with the request to cancel even the publication of the abstract (see letter of Dr. B. P. Koekman dated 22 March 1985 in document (24)) would have made the skilled person wonder inter alia whether the announcement in the abstract of the successful transformation of Penicillium chrysogenum had any sound scientific basis. Under these circumstances, it can be said that document (1) per se did not provide any certainty that the transformation of Penicillium chrysogenum was readily possible without any difficulty. At most, the unsubstantiated report of document (1) would have fostered in the skilled person the "hope to succeed" because somebody else had possibly somehow succeeded.

14.2 As already stated above (see point 9), in looking for a solution to the underlying technical problem, the skilled person might indeed have considered document (4). The fact that gene transfer had been achieved in a number of fungal species indicates that the experimental approach disclosed in document (4) was "obvious to try" for the skilled person faced with the problem of providing a method and means for the transformation of Penicillium chrysogenum. It can thus be said that, at least on paper, the technique of document (4) would have been a method under consideration. However, as it is sometimes the case (see eg the case of T 923/92 or T 694/92 supra), this does not necessarily mean that the skilled person would have had a reasonable expectation of success when embarking on such a project. In early 1986, although transformation systems had been developed for some fungi such as yeast, Neurospora crassa and Aspergillus nidulans, not much or no information was available concerning transformation of fungi in widespread commercial use such Aspergillus niger or Penicilli. This is confirmed eg by the later document (3), published in October 1986, where it is stated (see page 158):

"At present there is not much information available concerning the transformation of biotechnological relevant fungi. This may be because on the one hand technical experience is lacking or on the other hand (and this is most probable) many efforts undertaken by industrial laboratories are not published.

Otherwise it is not understandable that there is no information available for *Penicilli* producing the most known antibiotic Penicillin".

Later document (12), published in 1987 and reporting transformation of Penicillium chrysogenum, states (see introduction on page 639): "Transformation systems in which a nutritional mutant is transformed by the equivalent wild-type gene have been described for *Neurospora crassa* (...) and *Asperigillus nidulans* (...). One of the difficulties in developing similar transformation systems for fungi of industrial importance has been the unavailability of mutants which are genetically well characterised."

14.3 The complexity and diversity of these eukaryotic organisms as well as the limited knowledge about their molecular genetics rendered the extrapolation of data and conclusions on gene transfer from one genus or species to another problematic. The lack of a sexual cycle in most biotechnologically important fungi constituted another obstacle in the carrying out of genetic work (see eg document (15), first paragraph of the introduction). Under these circumstances, it can be stated that the transformation of yet another fungi was perceived in the art as an achievement in its own right. As regards in particular Penicillium chrysogenum, this species was genetically poorly characterised. Apart from the unsubstantiated report in document (1), auxotrophic strains or plasmids of this species were not available (see affidavit dated 4 June 1994 by Dr PeÁalva). The genetics of this fungal species was at

the priority date a quite unexplored area and thus the skilled person entering it was undoubtedly faced with a number of uncertainties and problems. In the Board's view, the skilled person, being in the dark about the genetics of Penicillium chrysogenum, would have been quite uncertain about the outcome of the envisaged application of the technique of document (4), even in the light of document (1). The report by document (8) of the occurrence of parasexual recombination in Penicillium chrysogenum would not have increased the degree of confidence of the skilled person that the technique applied to Aspergillus nidulans would work as such in Penicillium chrysogenum. In fact, document (8) showed that heterokaryon formation in Penicillium chrysogenum required a particular technical approach different from that used in Aspergillus. Thus, if anything, this would have pointed away from document (4) and left the skilled person in uncertainty as to what to do. Thus, the technical circumstances of the present case are such that it cannot be said that the skilled person, although possibly having some hope to succeed, would have had a reasonable expectation of success in the sense set out in the case law (see point 9 above) when envisaging the application of the experimental approach of document (4) to Penicillium chrysogenum, even if he or she selected to use the technique suggested there.

15. For these reasons the Board concludes that the subject-matter of claims 1 to 11 on file involves an inventive step (Article 56 EPC), and the appeal should be allowed.

## Order

**for these reasons it it 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 patent on the basis of claims 1 to 11 as filed on 8 July 1994.

The Registrar: The Chairperson:

L. McGarry U. Kinkeldey