DECISION
of 23 October 2003

Case Number: T 1070/00 - 3.3.8
Application Number: 89202060.3
Publication Number: 0357119
IPC: C12N 15/52
Language of the proceedings: EN

Title of invention:
A method for enhancing production of secondary metabolites using clustered biosynthetic genes

Patentee:
DSM N.V.

Opponents:
(01) SmithKline Beecham plc
(02) UNILEVER N.V.

Headword:
Antibiotic clustered genes/DSM

Relevant legal provisions:
EPC Art. 54(3),(4), 123(2)

Keyword:
"Main request and auxiliary request - added subject-matter (no)"
"Novelty (no)"

Decisions cited:
T 1099/99

Catchword:
-
Case Number: T 1070/00 - 3.3.8

DECISION
of the Technical Board of Appeal
of 23 October 2003

Appellant: SmithKline Beecham plc
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New Horizons Court
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
31 May 2000 concerning maintenance of European patent No. 0357119 in amended form.

Composition of the Board:
Chairman: L. Galligani
Members: P. Julia
S. C. Perryman
**Summary of Facts and Submissions**

I. European patent No. 0 357 119 with the title "A method for enhancing production of secondary metabolites using clustered biosynthetic genes" was granted with 14 claims on the basis of the European patent application No. 89 202 060.3, with priority dates 11 August 1988 and 21 April 1989.

II. Two notices of opposition were filed requesting the revocation of the patent under Article 100(a) EPC (lack of novelty and inventive step), Article 100(b) EPC (insufficiency of disclosure) and Article 100(c) EPC (added subject-matter). The patent was maintained in amended form by the opposition division on the basis of a main request containing 16 claims, wherein claim 1 read as follows:

"1. A DNA construct comprising at least two clustered genes including an individual regulatory region for each gene which are directly or indirectly involved in the biosynthetic pathway of the production of a secondary metabolite."

Claims 2 to 7 were dependent on claim 1 and defined specific embodiments thereof. Claim 8 was directed to a vector comprising the DNA construct of claims 1 to 7, whereas claims 9 to 11 were directed to transformed hosts comprising these DNA constructs or the vector of claim 8. Independent claim 12 related to a (chromosome walking) method for the isolation of penicillin biosynthetic genes, whereas claim 13 and 14 related, respectively, to DNA constructs comprising a gene obtainable by said method and to transformed hosts.
comprising the DNA construct of claim 13. Claims 15 and 16 were directed to methods for obtaining, enhancing or improving the production or yield of a (antibiotic) secondary metabolite using the DNA constructs of claims 1 to 7.

III. The appellant (opponent 01) filed an appeal against the decision of the opposition division. Neither the patentee (respondent) nor opponent 02 (party as of right under Article 107 EPC) made any comments on the statement setting out the grounds of appeal.

IV. The board sent a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal indicating its preliminary opinion.

V. Both the appellant and the respondent filed observations relating to the board's communication. The respondent further filed a main request, which corresponded to the request accepted by the opposition division, and five additional auxiliary requests.

VI. Oral proceedings took place on 23 October 2003. They were attended by the appellant and the respondent. Opponent 02, although duly summoned, did not attend them. During the oral proceedings the respondent withdrew all previous auxiliary requests and filed a new auxiliary request comprising 8 claims.

VII. Independent claims 1 and 2 of the auxiliary request corresponded to claims 15 and 16 of the main request with several amendments and they read as follows:
"1. A method for enhancing the production of a secondary metabolite in a microbial host comprising:
   preparing a DNA construct comprising at least two clustered genes including an individual regulatory region for each gene which are directly or indirectly involved in the biosynthetic pathway of the production of a secondary metabolite;
   transforming a candidate host with this DNA construct;
   cloning the resulting transformants; and
   identifying clones producing said secondary metabolite at a higher level than said candidate host."

"2. A method for providing improved yield of an antibiotic secondary metabolite comprising:
   growing a transformed host comprising an extra copy of a sequence comprising a DNA construct comprising at least two clustered genes including an individual regulatory region for each gene which are directly or indirectly involved in the biosynthetic pathway of the production of a secondary metabolite, resulting in an enhanced production of said antibiotic; and
   isolating the resulting antibiotic product."

Claims 3 to 7 were dependent on claims 1 or 2 and further defined the DNA constructs as in claims 2 to 6 of the main request, whereas claim 8 corresponded to the method of claim 12 of the main request.

VIII. The following documents are referred to in the present decision:
IX. The appellant's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Main request

Articles 123(2),(3) and 84 EPC

The requirement to have "an individual regulatory region for each gene" in the clustered genes of the claimed DNA constructs had no basis in the application as filed. This feature was disclosed in reference to the general prior art and for DNA fragments identified from fungi or bacteria that could be used as possible source for the DNA constructs of the patent. However, it was neither recognised as an essential feature of the invention nor generalised to DNA constructs or fragments other than from fungi or bacteria.

Article 54(3),(4) EPC

Document D14 disclosed the deposited cosmid clone pCX3.2 with a 38 kb insert of chromosomal DNA from
Penicillium chrysogenum. Figure 6(b) of this document identified the presence of the isopenicillin N synthetase (IPNS) and the tripeptide ACV synthetase (ACVS) genes in this insert, both genes being clustered in the manner as defined by the patent in suit. The presence of an individual regulatory region for each gene was an implicit feature. The 38 kb DNA insert had been obtained from a fungi and, as stated in the patent in suit, when the genomic DNA was from a fungus, each gene had normally its own independent transcriptional initiation regulatory region. Even if the ACVS gene had only been identified by hybridization and the fragment shown in Figure 6(b) only comprised a partial ACVS gene, the cosmid clone pCX3.2 comprised the complete ACVS gene as shown by complementation studies. The absence of a full characterization of the DNA region in-between the ACVS and the IPNS genes in order to exclude the presence of non-related genes was irrelevant as this characterization was also missing in the patent in suit. Figure 6(b), the cosmid clone pCX3.2 and the ACVS and IPNS cluster were already disclosed in the priority document D21. Thus, document D14 was entitled to its priority, and affected the novelty of the main request under Article 54(3),(4) EPC.

Auxiliary request

Articles 123(2), (3) and 84 EPC

Apart from the objection raised for the main request, which was maintained for this auxiliary request, no other objections were raised under these Articles.
Article 54(3),(4) EPC

The cosmid clone pCX3.2 was able to confer the ability to produce penicillin to non-producing fungi such as Neurospora crassa and Aspergillus niger. The absence of experimental evidence demonstrating an increase in penicillin production was irrelevant. The teaching of document D14 was directed to improve the production of penicillin and thus, a method for enhancing or improving the production of this antibiotic using antibiotic-producing fungi was already disclosed in document D14. Thus, also the auxiliary request lacked novelty.

X. The respondent's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Main request
Articles 123(2),(3) and 84 EPC

The reference in the application as filed to "each gene will have its own independent transcriptional regulatory region" was a basis for a monocistronic organisation. The term monocistronic was not only used in the context of a fungal genome but also in a much broader context, such as for bacteria or even without any limitation at all.

Article 54(3),(4) EPC

According to the established practice of the Boards of Appeal, a document could take away the novelty of
claimed subject-matter only if this subject-matter was directly and unambiguously derivable from said document.

Document D14 disclosed that the ACVS and the IPNS genes were closely located in P. chrysogenum. However, these genes were only identified using hybridization probes from a different microorganism, namely Flavobacterium. This Flavobacterium ACVS probe had been obtained (by chromosome walking) using a Flavobacterium IPNS region which itself had only been identified using an IPNS hybridization probe from yet another microorganism (Streptomyces). None of these probes had been fully characterized, let alone the corresponding genes. Furthermore, the Flavobacterium ACVS probe, which was derived from a contiguous, short DNA fragment in the Flavobacterium, was found to hybridize to three different regions spread over a large DNA fragment in P. chrysogenum. Thus, the results and technical evidence from these hybridization studies were totally inconclusive and ambiguous. There was no information on the actual localization of both the ACVS and the IPNS genes, their regulatory regions, transcription sites, etc.. Moreover, there was no information at all on the intermediate region between these genes and there was no actual evidence that other non-related genes were absent in-between the ACVS and the IPNS genes. Thus, in the light of document D14, the skilled person could not have concluded with certainty that the ACVS gene was actually present in the disclosed DNA fragments and there was no direct and unambiguous evidence that the ACVS and the IPNS genes were clustered in the manner as defined in the patent in suit.
The complementation assays also did not support the presence of the ACVS gene in a conclusive manner as only three out of five transformants were found to be positive and they had a very broad penicillinase sensitivity. Preparations 14 and 15 of document D14 (not entitled to the claimed priority) did not overcome these deficiencies as they used P. chrysogenum as recombinant host and thus, the elevated ACVS activity could be due to an increase of endogenous ACVS activity produced by a possible regulator, conditions of the assay, selected transformants, etc.. Post-published documents showed that the DNA fragment of Figure 6(b) and the plasmid vector pPEN3 (preparation 15) comprised an incomplete ACVS gene. Thus, the technical evidence provided by document D14 was not conclusive and the skilled person could not have derived in a direct and unambiguous manner the subject-matter which was claimed.

**Auxiliary request**

*Articles 87 and 88 EPC*

The subject-matter of claims 1 and 2 of this request was acknowledged not to be entitled to the first priority date but only to the second priority date.

*Articles 123(2),(3) and 84 EPC*

The line of argumentation put forward for the main request was further maintained for the auxiliary request.
Document D14 was concerned with the ACVS enzyme and with the increase of the production of this enzyme. Even if there was a general reference to increasing the production of penicillin, this enhancement was neither exemplified nor shown in the document. All the examples only referred to elevated levels of ACVS enzyme and most of them were performed using penicillin non-producer hosts (N. crassa and A. niger). The production of ACVS enzyme could not be equated to the production of penicillin. Fungi transformation did not always result in increased production of recombinant product (disadvantageous or disruptive recombination, etc.) and thus, it was required to purposively screen and select transformants producing higher amounts of said product. However, there was no reference to the identification of clones producing secondary penicillin metabolite in higher levels than non-transformed hosts and there was no disclosure of any method for screening such clones in document D14.

XI. The appellant requested that the decision under appeal be set aside and the patent revoked.

XII. The respondent (patentee) requested as main request that the appeal be dismissed and as auxiliary request that the decision under appeal be set aside and the patent be maintained on the basis of the auxiliary request filed during oral proceedings on 23 October 2003.
Reasons for the Decision

Main request

Articles 123(2), (3) and 84 EPC

1. Claim 1 differs from granted claim 1 in that it requires the presence of an individual regulatory region for each gene, wherein the word "individual" has been introduced into granted claim 1. This amendment restricts the claimed DNA constructs to those comprising monocistronic clustered genes and excludes genes clustered in a polycistronic manner. Thus, the requirements of Article 123(3) EPC are fulfilled.

2. The application as filed refers to general DNA fragments used for producing the claimed DNA constructs. It is stated that depending on the source of these fragments various expression cassettes may be constructed, in particular with "genomic DNA from a bacterium, the fragment containing a mono- or polycistronic coding region may include its own transcriptional initiation regulatory region ... Where genomic DNA is from fungus, normally only one gene will be associated with a transcriptional initiation regulatory region, so that each gene will have its own independent transcriptional initiation regulatory region" (page 5, lines 40 to 46). On page 4, lines 26 to 27, there is a general reference to identified DNA fragments "which include sequences which are mono- or polycistronic" without a limitation to any specific source. Thus, there is a basis for general monocistronic clusters independently of the source of the DNA fragments used. The word "individual" finds a basis in the expression "its own independent", which
reflects a monocistronic organization of a gene with its own independent, individual regulatory region. Thus, the requirements of Article 123(2) EPC are considered to be fulfilled.

3. No objections have been raised under Article 84 EPC and the board sees none.

*Article 54(3), (4) EPC*

4. Document D14 discloses a BamHI DNA fragment from Streptomyces clavuligerus comprising the expandase gene responsible for the initial penicillin ring-expansion of the cephalosporin biosynthetic pathway. This 3kb BamHI DNA fragment of pBROC137 (cf Figure 2(c)) is further subcloned and screened for expandase activity (cf pBROC141, Figure 3). A fragment of pBROC141 is then used as hybridization probe for isolating an homologous DNA fragment from the Gram-negative bacteria Flavobacterium sp. SC 12,154 (cf pBROC143, Figure 1(b)), which is subcloned and screened for expandase activity too (cf pBROC148, Figure 4). By using an hybridization probe comprising the isopenicillin N synthetase (IPNS) gene from Penicillium chrysogenum, pBROC143 is also shown to comprise a DNA fragment having a high degree of homology with said IPNS gene - being the IPNS enzyme responsible for the conversion of isopenicillin N to penicillin N.

5. A BamHI fragment of pBROC143 is further used as an hybridization probe for isolating cosmids pBROC155 and pBROC156 (about 35 kb), which comprise the genomic DNA from Flavobacterium occurring next to the IPNS, expandase and epimerase genes of pBROC143. By probing
total chromosomal DNA from P. chrysogenum with fragments of pBROC155 and, assuming that the only antibiotic genes that P. chrysogenum (penicillin-producer but not cephalosporin) has in common with Flavobacterium (cephalosporin-producer but not penicillin) are those concerned with the biosynthesis of isopenicillin N from its constituent amino acids (ie IPNS and tripeptide ACV synthetase genes), it is possible to identify two fragments of pBROC155 which comprise the gene involved in the biosynthesis of the ACV tripeptide (TPS/VE, two contiguous BamHI fragments of 3.0 and 2.2 kb) and the previously identified IPNS gene (CXI, 6.3 kb BamHI fragment) (cf Figure 1(a)).

6. Document D14 further discloses the isolation of clone pCX3.2 from a cosmid gene library of P. chrysogenum. Cosmid clone pCX3.2 has been deposited under the terms of the Budapest Treaty and comprises a 38 kb insert of genomic DNA from P. chrysogenum. By cross-hybridization studies with the TPS/VE and IPNS fragments from Flavobacterium (cf point 5 supra), pCX3.2 is shown to comprise both an ACV synthetase region and the IPNS gene (cf Figure 6(b)). The presence of ACV synthetase activity is demonstrated by showing that the transformation by pCX3.2 of an Aspergillus nidulans strain NPA5 - with a mutation that blocks the ACV synthesis - results in the production of penicillin.

7. All this information is found in the priority document D21. Figure 6(b) of document D21 identifies a 13.5 kb DNA(I) fragment of pCX3.2 comprising the ACVS region closely linked to the IPNS gene. This DNA(I) fragment, which is said to be a specific embodiment of the invention (cf page 5, second full paragraph), is
characterized by its restriction map, a specific (kb) length and the presence of these ACVS and IPNS genes. Furthermore, this DNA(I) fragment is explicitly identified as carrying a "cluster" (cf page 10, second full paragraph and page 35, first paragraph). Document D21 not only discloses the deposited pCX3.2 and this DNA(I) fragment but it further shows the presence of five shorter fragments, namely pGXS10, pGXS11, pGX-C1, pGXEL1 and pCYX4, wherein the two latter ones are identified as comprising, respectively, the ACVS gene (pGXEL1) and the IPNS gene (pCYX4). These fragments are also characterized by their specific restriction maps, (kb) lengths and presence of the identified genes and they are made readily available to the skilled person by the deposited pCX3.2.

8. In the light of this disclosure, the board considers that the ACVS and IPNS cluster from P. chrysogenum is clearly characterized in document D14 and its priority document D21 (9 December 1987). Moreover, the ACVS and IPNS cluster is identified as a cluster in a DNA construct having all the features that define the subject-matter as claimed.

9. The respondent has argued that the presence of a DNA construct with a cluster such as the claimed one is not clearly and unambiguously derivable from document D14, in particular due to a lack of a clear and unambiguous evidence for: (i) the presence and location of the ACVS and IPNS genes, (ii) the absence of any intermediate (non-related) gene in-between the ACVS and IPNS genes and (iii) the presence of an individual regulatory region for each the ACVS and the IPNS genes. The board,
however, cannot agree with the respondent's argumentation for the following reasons:

9.1 In contrast to Figures 1 to 5, wherein the (epimerase, expandase) genes identified by hybridization are not indicated as such in any restriction fragment, Figure 6 shows the clustered position of the ACVS and IPNS genes in the restriction fragments of both Flavobacterium and P. chrysogenum (cf Figures 6(a) and 6(b)). There is nothing in document D14 suggesting that the position of these genes in Figure 6 and, more particularly in the DNA(I) fragment of Figure 6(b), should be understood as being only hypothetical or provisional.

9.2 It has been argued that, whereas in Flavobacterium the ACVS gene is identified in a short, contiguous 5.5 kb BamHI fragment (cf Figure 6(a)), in P. chrysogenum this ACVS gene is spread over a longer 8 kb EcoRI fragment with three non-contiguous hybridization regions (cf Figure 6(b)) and that this difference would immediately raise doubts in the mind of the skilled person who would conclude that the position of the ACVS gene in pCX3.2 is not reliably identified. This line of argumentation, however, cannot be followed. In the light of the known differences between prokaryote and eukaryote genomes, such as the presence of introns, sequence duplications, etc. a different hybridization pattern cannot be seen as surprising but only as reflecting the normal difference between prokaryote (Flavobacterium) and eukaryote (Penicillium) genes. The complementation studies demonstrate the presence of the ACVS gene in pCX3.2, whereas the hybridization studies show that there is only one region in pCX3.2 hybridizing to an ACVS probe, namely one closely
clustered to the IPNS gene. There is no reason to doubt on the presence and the position of the ACVS gene in pCX3.2 as shown in Figure 6(b).

9.3 The IPNS gene from P. chrysogenum is easily identified by its (known) restriction map in the 1.4 kb XbaI-BglII fragment of pCYX4 (cf page 260, right-hand column and Figure 2 of document D27). In a similar manner, pGXE1 comprising the ACVS region, and pGXS11 and pGXS10 comprising two contiguous DNA fragments covering said ACVS region, are also available to the skilled person (cf point 7 supra), who can, if necessary, check the information disclosed in Figure 6(b). In fact, document D14 uses the 8.0 kb EcoRI fragment from pGXE1 to obtain the plasmid vector pPEN3 which shows, as expected, elevated levels of ACVS activity in P. chrysogenum transformants (cf page 18, preparation 15 page 18). Even if pPEN13 does not enjoy priority rights - preparation 15 is not found in document D21 - it, nevertheless, confirms the characterization of the pGXE1 fragment, already present in the priority document D21 as well as pGXS11 and pGXS10. Thus, there is no reason for the skilled person to consider the information of Figure 6(b) as regards the presence and location of the ACVS and the IPNS as being doubtful or ambiguous.

9.4 In this respect too, Figure 6(b) discloses two pCX3.2 fragments covering the intermediate region along the ACVS and the IPNS genes, namely pGX-C1 and pGXS11. The board fails to find any suggestion in document D14 for the presence of an intermediate gene in-between the disclosed ACVS and IPNS genes, let alone a functionally non-related gene as defined in the patent in suit (cf...
There is no intermediate gene shown in Figure 6(b) and there is no reason for the skilled person to expect one in this particular region. The board notes that even the patent in suit, without providing any further technical evidence (such as the complete nucleotide sequence of this intermediate region), explicitly acknowledges that the "ACVS gene(s) is also clustered to the (IPNS plus AT) gene cluster" (cf page 9, line 27 of the patent in suit) and thus, clustered in the manner as defined in the patent itself. No technical evidence has been put forward to contradict this. To accept that document D14 does not clearly and unambiguously disclose the absence of an intermediate non-related gene would be to apply a different standard to the disclosure of this prior art than to the patent in suit which would be contrary to the established case law (cf T 1099/99 of 4 December 2002).

9.5 Similarly, as regards the presence of an individual regulatory region for each of the ACVS and IPNS genes, the skilled person in reading document D14 has to assume, as the patent in suit has also done, that being the source genomic DNA from fungus, "normally only one gene will be associated with a transcriptional initiation regulatory region, so that each gene will have its own independent transcriptional initiation regulatory region" (cf page 5, lines 44 to 46 of the patent in suit). No technical evidence has been put forward to contradict this assumption and, as stated in point 9.4 supra, the same standard has to be apply for both the prior art and the patent in suit.
9.6 In the present case, however, the position of the 5' flanking region of the P. chrysogenum IPNS gene and its transcription initiation site are known from document D27 (cf Figure 2), as it is also rightly reflected by the presence of the IPNS transcription arrow in Figure 6(b) of document D14. The 5' flanking regions of the closely related IPNS genes from A. nidulans and C. acremonium are highly homologous and known from the prior art too (cf page 175, right-hand column, second full paragraph and Figure 4 in document D18). Thus, the assumption of an individual regulatory region for the IPNS gene is not contradicted by any prior art document on file. Moreover, the complementation studies disclosed in document D14 - as well as in the priority document D21 - demonstrate a successful transcription and translation of the ACVS gene present in pCX3.2. The fact that the IPNS translation arrow in Figure 6(b) runs in a direction opposite to the ACVS gene, implicitly indicates the presence of an individual regulatory region for the ACVS gene, even if the position of this regulatory region is not localized in Figure 6(b). This information is further supported by the elevated levels of ACVS activity found in P. chrysogenum transformants after transformation with plasmid vector pPEN3 which, as stated in point 9.3 supra, comprises the pGXE1 fragment shown in Figure 6(b) and not the 5' flanking (regulatory) region of the IPNS gene.

9.7 It has further been argued that the results of the complementation assays with pCX3.2 shown in document D14 are ambiguous as they are said to vary "from slightly less than wild type to slightly greater than the non-producing controls" (cf page 17, lines 4 to 6).
However, document D14 refers to possible reasons thereof, such as decreased growth rates, inefficient expression of heterologous genes, etc. and concludes, nevertheless, that these results indicate that the gene cluster of pCX3.2 can restore the ability to produce penicillin. Reference has also been made to post-published documents as showing that fragment pGXE1 does not comprise the complete ACVS gene but only a (5' and 3') truncated ACVS gene. Thus, the presence of an elevated ACVS activity found with pPEN3 must allegedly be due to other reasons, such as an enhanced expression of endogenous ACVS gene from the transformed P. chrysogenum. This additional information is, however, not directly derivable from document D14 and, even if assuming that pGXE1 does not comprise the complete ACVS gene, this result does not rule out the presence of an individual regulatory region for the ACVS gene. In fact, this information is not considered to be relevant as the deposited pCX3.2 actually comprises all the additional 5' and 3' flanking regions of the ACVS gene – as shown in Figure 6(b) – and thus, the complete ACVS gene.

9.8 None of the prior art documents on file contradicts the technical evidence provided by document D14 and directly conveyed to the skilled person, namely the presence in the DNA construct pCX3.2 of the ACVS and IPNS genes clustered in the manner as defined in the patent in suit (cf Figure 6(b)). Moreover, there is no post-published prior art document on file demonstrating that this information directly derivable from document D14 – and its priority document D21 – is wrong or misleading.
10. Therefore, the board concludes that the claimed subject-matter does not fulfil the requirements of Article 54(3),(4) EPC.

Auxiliary request

Articles 123(2),(3) and 84 EPC

11. Apart from the objection raised under Article 123(2) EPC for the main request (cf point 2 supra), which has been maintained for this request, no further objections have been raised under Articles 123(2),(3) and 84 EPC. The board sees none and, in line with the argumentation followed for the main request, which is considered to apply to this request too, the requirements of all these Articles are considered to be fulfilled.

Article 54(3),(4) EPC

12. The teachings of document D14 are neither limited to scientific research nor to the specific ACVS gene and enzyme. Document D14 refers to the general use of "the DNA of the invention ... in many areas of industrial activity" (cf page 7, line 58), wherein the DNA according to the invention includes the deposited pCX3.2 (cf page 6, lines 16 to 24). In particular, it is explicitly stated that "recombinant vectors containing said DNA may be of value, when transformed into suitable hosts, in the production of genetically modified micro-organism which synthesize increased amounts of valuable antibiotics" (emphasis added by the board) (cf page 8, lines 2 to 6). More particularly, claim 14 comprises a method of producing penicillin from a naturally penicillin-producer host using a vector as claimed in claim 9, ie the designated pCX3.2.
In the light of this disclosure, the board considers that the identification of clones producing increased or higher levels of penicillin is implicitly comprised in the method of document D14.

13. The board further notes that whereas claim 1 of this request explicitly requires the above indicated step of identifying clones producing secondary metabolite at a higher level, this step is absent in the method of claim 2 which only requires growing the transformed host comprising an extra copy of a sequence comprising a DNA construct with the clustered genes so as to have an enhanced production of antibiotic and isolating the resulting antibiotic product. Thus, such a method is clearly disclosed in document D14.

14. Thus, the board considers that the requirements of Article 54(3),(4) EPC are not met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar:                             The Chairman:

A. Wolinski                             L. Galligani