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D E C I S I O N
of 7 March 1997

Case Number: T 0387/94 - 3.3.4

Application Number: 84900782.8

Publication Number: 0131623

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
Chimeric genes suitable for expression in plant cells

Patentee:
Monsanto Company

Opponents:
Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.
Imperial Chemical Industries PLC, Legal Department: Patents
Pioneer Hi-Bred International Inc.
Biocem
Unilever PLC
Agricultural Genetics Company Ltd.
Mogen International N.V.

Headword:
Chimeric genes in plant cells/MONSANTO

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Main and first auxiliary request:
"Novelty - (yes)"
"Inventive step - (no)"
Second auxiliary request:
"Novelty - (yes)"
"Inventive step (yes)"

Decisions cited:
T 0649/92, T 0455/91, T 0500/91

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0387/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 7 March 1997

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 11 March 1994 concerning maintenance of European patent No. 0 131 623 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 131 623 (application No. 84 900 782.8) relating to "Chimeric genes suitable for expression in plant cells" was granted on international application No. PCT/US84/00048 of 16 January 1984 claiming priorities from US 458 414 of 17 January 1983 and US 485 568 of 15 April 1983, for ten Contracting States with ten claims.

Independent claims 1 and 5 read:

"1. A chimeric gene capable of expressing a polypeptide in plant cells comprising in sequence:

(a) a promoter region from a gene which is naturally expressed in plant cells;

(b) a 5' non-translated region;

(c) a structural coding sequence encoding a neomycin phosphotransferase polypeptide; and

(d) a 3' non-translated region of a gene naturally expressed in plant cells, said region encoding a signal sequence for polyadenylation of mRNA; said promoter being heterologous with respect to the structural coding sequence."

"5. A chimeric gene capable of expressing a polypeptide in plant cells comprising in sequence:

(a) a promoter region from a plant virus;

(b) a 5' non-translated region;

(c) a structural coding sequence;

(d) a 3' non-translated region of a gene naturally expressed in plants, said region encoding a signal sequence for polyadenylation of mRNA, said structural coding sequence being heterologous with respect to said promoter region.

Dependent claims 2 to 4 specified further embodiments of the gene of claim 1. Dependent claims 6 to 9 specified further embodiments of the gene of claim 5. Dependent claim 10 was directed to a culture of microorganisms identified by ATCC accession number 39265.

II. Notices of opposition were filed against the European patent by seven parties (Opponents 01 to 07).

Revocation of the patent was requested on the grounds of Article 100(a) and (b) EPC.

III. In the course of the procedure, one hundred and fifty three documents were filed. Those of the documents which were relied on by the parties and are referred to in the present decision are:

(6): Chilton et al., Stadler Symp.13, pages 39 to 51, 1981,

(9): Colbère-Garapin et al., J.Mol.Biol.150, pages 1 to 14, 1981,

(13): Depicker et al., J.Mol & Appl.Genet.1, pages 561 to 573, 1982,

(15): Dix et al., Molec.gen.Genet.157, pages 285 to 290, 1977,

(17): Fraley et al., Miami Winter Symp. "Advances in Gene technol.; Molecular Genetics of plants and animals" 20, pages 211 to 221, 1983,

(19): Gardner, R., "Genetic engineering of plants - An agricultural perspective", Kosuge et al. (Eds), pages 121 to 142, 1982,

(22): Guilley et al., Cell 30, pages 763 to 773, 1982,

(28): Jimenez et al., Nature 287, pages 869 to 871, 1980,

(29a): Transcript of an oral presentation of J.D. Kemp which took place on 16 to 19 May 1982 at the Symposium: "Genetic Engineering: Applications to agriculture" held at the Agricultural Research Center of the U.S Department of Agriculture in Beltsville, Maryland, U.S.A,

(34): Leemans et al., "Mol.Biol. of Plant Tumors", Chap.21, pages 537 to 545, 1982,

(37): Matzke et al., J.Mol.& Appl.Genet. 1, pages 39 to 49, 1981,

(38): Meagher et al., "Genome organization and Expression in Plants" Leaver (ed) NATO Advance Study Inst.Series 29, pages 63 to 75, 1980,

(56): EP-A 0 290 799,

(62): Beck et al., Gene 19, pages 326 to 335, 1982,

Tab 11: Dudley et al., Virol.117, pages 19 to 28, 1982,

Tab 30: Corden et al., Science 209, pages 1406 to 1414, 1980.

IV. The opposition division issued an interlocutory decision within the meaning of Article 106(3) EPC whereby the patent was maintained on the basis of an auxiliary request comprising claims 1 to 4 and 10 as granted.

V. The opposition division considered that the specification disclosed the invention of all claims as granted in an enabling manner so that the requirements of Article 83 EPC were fulfilled.

Novelty of all claims as granted was acknowledged under Article 54 EPC over documents (6) and (56) as neither of these documents disclosed a chimeric **neo** gene (feature (c)), in an unambiguous manner.

In view of the requirements of Article 56 EPC, inventive step, document (34) was considered the closest prior art to the subject-matter of claims 1 to 4 and 10, as it suggested constructing a chimeric **neo** gene to allow for direct selection of transformed plant cells. It was decided that the combination of document (34) with documents (9) or (28) which disclosed that a chimeric **neo** gene had successfully been expressed in mammalian or yeast cells would not necessarily have led to a reasonable expectation of success for expression in plants because at the priority date of claims 1 to 4 and 10, no foreign genes of any kind had ever been expressed in this host.

The closest prior art to the subject-matter of granted claims 5 to 9 which were considered to enjoy priority rights only from the second priority application was identified as document (17) which disclosed the **nos-**

neo-nos chimeric gene. The underlying problem was identified as the provision of alternative chimeric genes for expression in plant cells and the solution thereof was identified as a chimeric gene expressed from the CaMV promoters. This solution was found to be obvious in view of document (19) which suggested that the CaMV promoters may prove valuable for the construction of selectable markers. Reasonable expectation of success would be expected since at the priority date of claims 5 to 9, foreign genes had already been expressed in plants.

Consequently, only the auxiliary request no longer containing these claims was allowable.

VI. Appeals were lodged against the decision of the opposition division by the Patentee (Appellant I) and Opponents 2, 3, 4, 5 and 7 (Appellants II, III, IV, V and VII respectively). Appellant I filed one auxiliary request together with the grounds of appeal.

VII. All Appellants filed answers to their respective submissions. Appellant I filed two further auxiliary requests.

VIII. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the boards of appeal, setting out the issues to be discussed further.

IX. All Appellants filed answers to the Board's communication. Appellant I filed eight further auxiliary requests in addition to the two previous auxiliary requests.

X. Oral proceedings were held on 6 and 7 March 1997. At these proceedings, five new auxiliary requests were submitted intended to replace all previous auxiliary requests.

New Auxiliary Request I contained seven claims. Independent claims 1 and 5 read as follows:

"1. A chimeric gene capable of expressing a **neomycin phosphotransferase** polypeptide in plant cells **conferring antibiotic resistance to the plant when inserted into the plant genome**, comprising in sequence:

(a) a promoter region from a gene which is naturally expressed in plant cells;

(b) a 5' non-translated region;

(c) a structural coding sequence encoding neomycin phosphotransferase I or II; and

(d) a 3' non-translated region of a gene naturally expressed in plant cells, said region encoding a signal sequence for polyadenylation of mRNA; said promoter being heterologous with respect to the structural coding sequence." (emphasis by the Board)

"5. A chimeric gene capable of expressing a polypeptide in plant cells comprising in sequence:

(a) **a full-length transcript** promoter region **isolated from cauliflower mosaic virus;**

(b) a 5' non-translated region;

(c) a structural coding sequence;

(d) a 3' non-translated region of a gene naturally expressed in plants, said region encoding a signal sequence for polyadenylation of mRNA, said structural coding sequence being heterologous with respect to said promoter region."

(Emphasis by the Board)

Claim 4 of New Auxiliary Request II was identical to claim 5 of New Auxiliary Request I. Claim 1 of New Auxiliary Request II differed from claim 1 of New Auxiliary Request I in that part (a) of the claim read:

"a promoter region from a ribulose-1,5-bis-phosphate carboxylase small subunit gene".

Claims 2, 3, 5 and 6 of New Auxiliary Request II read as follows:

"2. A gene of claim 1 in which the 3' non-translated region is selected from a gene from the group consisting of the genes from the T-DNA region of Agrobacterium tumefaciens.

3. A gene of claim 1 in which the 3' non-translated region is from the nopaline synthase gene of Agrobacterium tumefaciens.

5. A gene of claim 4 in which the 3' non-translated region is from a nopaline synthase gene.

6. A culture of microorganisms identified by ATCC accession number 39265."

X. The submissions in writing and during oral proceedings by Appellant I were as follows:

Main request, claim 1:

Novelty

The two features of the claimed gene that it be chimeric and capable of being expressed clearly distinguished it from the construct pTiT37 disclosed in Figure 1 of document (6). In this construct, the **nos** promoter was separated from the structural sequence of the **neo** gene by part of the **nos** coding sequence and a region of 107 nucleotides which contained the bacterial **neo** promoter and two reading frames. This was not a structure which answered the definition of a chimeric gene. Furthermore, it was most unlikely that such a piecemeal DNA molecule would be transcribed and translated which implied that an active neomycin phosphotransferase polypeptide would not be obtained.

Figure 2 of document (6) was a generic scheme on how to provide a chimeric gene for expression into plants. The subject-matter of claim 1 could only be read into it if one admitted that document (6) not only clearly pointed to the **neo** gene as the marker of choice but also provided knowledge of its structure so that the scheme of Figure 2 could be implemented. Yet, the structure of the **neo** gene was not disclosed in document (6) nor was it part of the state of the art at the publication date of said document. Therefore, this document did not clearly and unambiguously disclose the claimed subject-matter and, thus, did not destroy novelty.

Inventive step

There were two steps in the invention: firstly the expression of foreign genes into plants whereas such expression had not been obtained before and, secondly, the provision of a very superior plant selection system. Documents (6) and (9) were relevant closest prior art to these two steps respectively.

Document (6) may have rendered obvious the concept of isolating a chimeric gene for expression in plants. However, the authors themselves considered the task to be problematic (pages 43 and 45). The same uncertainties existed with regard to expression which led the Board in T 649/92 (to be published in OJ EPO) to acknowledge the inventive step of a technology closely related to the subject-matter of the present patent.

Document (34) provided additional evidence that the expression of a chimeric gene into plant cells, in this instance the dihydrofolate reductase gene, was not necessarily straightforward. In document 29(a), the authors did not obtain translation of the chimeric gene, they had constructed nor could they give a firm reason for their failure. Difficulties could be expected in obtaining neomycin resistant transformed cells because of the mode of action of the neomycin antibiotic in said cells.

Document (9) indicated that a chimeric **neo** gene could be made into a superior selection system, showed this, but only for animal cells. To deduce therefrom that a chimaeric neo gene could equally be used as a selection system in plants was too big a mental step to be undertaken by the average person skilled in the art as defined in the case law of the EPO (T 455/91, OJ EPO 95, 684, T 500/91 of 21 October 1992). Furthermore, it was not justified to equate the success obtained with animal cells with a reasonable expectation of success that the system would also work in plant cells as the two types of cells were too different.

New Auxiliary requests I and II, claim 1

The same reasoning applied to claim 1 of New Auxiliary request I as to claim 1 of the main request. No

arguments needed to be provided in relation to the patentability of claim 1 of New Auxiliary request II, which was not being challenged.

New Auxiliary request II, claim 4:
Articles 123(2) and 84 EPC

The expression "full length transcript promoter" was clear to the skilled person. This promoter initiated transcription of the whole of the CaMV DNA i.e. of an mRNA with a sedimentation coefficient of 35S (32S). The 35S (32S) promoter was described in the application as filed on pages 49 and 50.

Inventive step

The claim enjoyed priority rights from 15 April 1983. Document (17) was to be regarded as the closest prior art. It disclosed the expression in plant cells of a foreign coding sequence in the form of a chimeric gene under the control of the Ti **nos** promoter, but did not suggest isolating any alternative promoters for use in chimeric genes. Many promoters other than the CaMV 35S promoter were known in the art (Ti, plant and animal promoters), which might have been equally suitable.

At the time the invention was made, there was not enough scientific information available on the biology of plant viruses to permit predictions whether virus encoded trans-acting factors were required for viral transcription to occur. The relevance of in vitro transcription studies carried out in Hela cells (document (22)), to the mechanism of in vivo transcription had already been questioned (document Tab(30)).

The 35S promoter would not have been chosen because it behaved unlike any other promoter. Its broad host range

would have been considered most surprising and its remarkable strength could not have been predicted by reference to any documents on file.

Document (9) had also been cited as closest prior art. However, the same reasoning applied as developed with regard to the inventive step of claim 1 (see supra).

XI. The submissions in writing and during oral proceedings by Appellants II to V and VII were as follows:

Main request, claim 1
Novelty

Document (6), Figure 1 described a chimeric gene with the features cited in claim 1 (a) to (d). This gene would be expected to express the **neo** determinant in plants. Even if it did not, it would nonetheless fall within the definition of the claimed construct as the extra feature of this construct that it was "capable of expressing" was found in the pre-characterising portion of the claim i.e. could not be regarded as a limiting feature. Furthermore, the fact that the chimeric gene of Figure 1 contained additional DNA between the promoter and the **neo** structural sequence was not a structural property excluded by the claim.

Document (6), Figure (2) also provided a scheme for making a chimeric gene as in claim 1. Page 43 suggested to use the **nos** promoter region and the **neo** gene would have been chosen of necessity. The person skilled in the art would therefore have had no difficulties in putting that scheme into practice. Document (6) should, thus, be considered as novelty destroying.

Inventive step of claim 1

Document (6) could be considered as the closest prior

art. Starting from its teachings, in particular on Figure 2 and page 43, it was obvious how to proceed to obtain the claimed chimeric gene especially since the sequences of the **neo** gene and of the **nos** promoter were already known. The authors of document (6) themselves expressed reasonable expectation of success. Document (34) also suggested using a chimeric gene as in claim 1 to achieve expression in plant cells. Document (29a) described the transcription of a chimaeric gene into plant cells. The authors clearly identified why translation had not taken place which enabled the person skilled in the art to avoid this problem.

The invention was the last predictable step in applying genetic engineering to all living organisms. The **neo** determinant had previously been used as selective marker in bacteria, yeast and animal cells. In particular, document (9) disclosed that a chimeric construct which comprised the same elements as the now claimed chimeric gene was expressed in animal cells and, thus, could also be regarded as closest prior art. It provided the motivation to try the chimeric construct as a means for expression in plant cells. Combining its teachings with those of document (6) describing the usefulness of the nos promoter or documents (19) or (38) suggesting the use of CaMV promoters made the subject-matter of claim 1 non inventive.

New Auxiliary request I

The same reasoning with regard to novelty and inventive step equally applies to claim 1 of the Auxiliary Request I.

New Auxiliary Request II
Articles 123(2) and 84 EPC

The expression "full length transcript promoter" was not found in the application as filed. Furthermore, it was unclear. The requirements of Articles 123(2) and 84 EPC were not fulfilled.

Inventive step

Documents (17) or (9) could equally be considered as closest prior art. Document (17) disclosed the expression of the neo resistance determinant in plant cells from the nos promoter. Although many eucaryotic promoters were already known in the art, very few if any would have been considered a reasonable alternative to the **nos** promoter for use in chimeric gene expression in plant cells but for the CaMV promoters, the use of which had already been suggested in documents (19) and (38).

In the same manner, the problem of chimeric gene expression had been solved in animal cells with animal virus promoters (Document (9)) and it was obvious to try the equivalent technology in plant cells with CaMV vectors. Only routine experimentation was required in both cases.

Document (22) showed that the CaMV promoters were active in isolation, in vitro, in the Hela cells transcriptional system. Thus, the skilled person would have been confident that transactivation factors were not necessary for the CaMV promoters to be active in vivo and that the unusual structure of the 35S transcript would not prevent it from working in isolation.

The strength of the CaMV promoter could not be taken into account to justify inventive step as there was no support in the patent in suit for a beneficial effect due to this promoter. If it was nonetheless taken into account, it would have to be acknowledged as obvious in view of the prior art which pointed out the abundance of CaMV transcripts in infected plant cells and to the quantitative superiority of the 35S promoter versus the 19S promoter.

XII. Appellant I (Patentee) requested that the decision under appeal be set aside and that the patent be maintained as main request as granted or as auxiliary requests on the basis of one of the sets of claims headed New Auxiliary Request I to V respectively submitted at the oral proceedings on 7 March 1997.

XIII. Appellants II to V and VII (Opponents) requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Sufficiency of disclosure

1. In the course of appeal proceedings, none of the Appellants II to V and VII argued any longer that the requirements of Article 83 EPC were not fulfilled. The Board has no reason not to agree with the findings of the Opposition Division that the invention was sufficiently disclosed. Sufficiency of disclosure is acknowledged.

Main request, claim 1

Novelty:

2. Claim 1 is directed to a chimeric gene capable of expressing a polypeptide. This feature, although being of a functional nature, nonetheless, reflects the structure of the gene because the structure of a gene is an essential element governing its expression.

3. Document (6) was cited as a novelty destroying document. Figure 1 depicts the steps of a method of Matzke and Chilton to isolate a schematically represented plasmid, engineered pTiT37, where the coding sequence of the neomycin phosphotransferase polypeptide is located within a DNA fragment containing the promoter of the nos gene which is naturally expressed in plant cells. On page 43, it is stated that the neo determinant is **not** expressed when the neo gene is made chimaeric by the method of Matzke and Chilton. To the Board, this implies that, in pTiT37, the position of the neo determinant relative to the nos promoter is not such as to enable expression. Therefore, pTiT37 must be structurally different from any of the plasmids of claim 1, the structure of which necessarily enables expression. It is, thus concluded that the pTiT37 plasmid is not novelty destroying for the subject-matter of claim 1.

4. Figure 2 of document (6) describes a generic scheme for construction of a chimeric gene effective in plant cells. On page 43, it is **envisaged** to put this scheme into practice with the regulatory sequence of the **nos**

gene. The coding sequence of the foreign gene to be expressed is not specified. Thus, there is no disclosure in document (6) of what is claimed. The content of this document could only be discussed under the heading of inventive step.

5. The Board concludes that novelty may be acknowledged.

Inventive step:

6. The closest prior art was identified alternatively as either document (6) or (9). Document (6) (Figure 2) discloses a scheme to achieve foreign gene expression in plant cells which involves coupling the structural part of the foreign gene to be expressed to a promoter recognized by the plant cells' machinery. The authors indicate their intention to carry out the experiment with the **nos** promoter. The **neo** gene is mentioned as one of the genes which had already been used when trying to express foreign genes in plant cells (page 43).

7. Starting from this closest prior art, the objective technical problem to be solved can be defined as expressing chimeric genes into plant cells.

8. The solution consists in putting into practice the generic scheme disclosed in document (6), by constructing a chimeric gene where the **neo** determinant is linked to a promoter recognized by the plant cells' machinery. This solution has been accepted as obvious to try by all Appellants.

9. The question which remains to be decided is whether a reasonable expectation of success existed that the chimeric gene would be expressed in plant cells.

10. In this context, it is worth noticing that the authors of document (6), while discussing the difficulties associated with such an experiment nonetheless feel reasonably confident that it will work (page 46, last par.). In the same manner, the authors of document (34) trying to express the methotrexate resistance coding sequence from the bacterial transposon Tn7 in plant cells suggest that other bacterial genes could equally be used. Such statements certainly are indicative that the task of expressing foreign genes into plants was not perceived as unduly difficult.

11. At the priority date, the sensitivity of plant cells to kanamycin, the DNA sequences of the **neo** gene and of at least one promoter known to be active in plant tissues (the **nos** promoter) were known from documents (15), (62) and (13). The techniques of joining DNA sequences together into a chimeric gene and the methods for transforming plant cells were general common knowledge. Moreover, the teachings of document (29a)) showed that a chimaeric construct with the phaseolin coding sequence under the control of a Ti promoter could be transcribed in plant cells. An explanation is given why this transcript was not translated, providing guidance to the skilled person as to which problems to avoid in order to get translation.

12. In the Board's opinion, most of the way to expressing chimeric genes in plant cells had already been travelled and the person skilled in the art would have had a reasonable expectation of success that the expression of the neo coding sequence could be achieved.

13. Appellant I argued to the contrary in the specific case of the neomycin resistant determinant in view of the mode of action of the neomycin which exerted its toxicity at the level of the chloroplasts. If this

antibiotic could not be inactivated by the neomycin phosphotransferase synthesized in the transformed plant cells before reaching the chloroplasts, the transformants would die.

14. However, it is not apparent on the basis of the facts on file that this concern was shared by the scientific community at the priority date. Thus, the Board cannot accept that it would have been considered as affecting reasonable expectation of success.

15. In decision T 694/92 (supra), inventive step was acknowledged for a claim which presented much similarity to present claim 1, as it was directed to a dicotyledonous plant cell capable of expressing the phaseolin gene from its own promoter. The facts on the cases, however, differ in one fundamental aspect: the nature of the promoter. In the earlier case, the claimed specific promoter was a highly regulated promoter which could not have been expected to function in undifferentiated plant tissues. On the contrary, in the present case, the nos promoter was known to be active in such tissues. Thus, the reasoning in decision T 694/92 is not applicable in the present case.

16. The Board concludes that the main request must be rejected for lack of inventive step over the combination of document (6) with document (29a)). In view of this finding, there is no need to review the arguments presented with regard to inventive step in connection to document (9).

New Auxiliary Request I

17. Compared to claim 1 of the main request, claim 1 of the New Auxiliary Request I is amended in that the polypeptide to be expressed is restricted to the one encoded by the structural sequence of a gene encoding a

neomycin phosphotransferase polypeptide. Support for this amendment can be found on pages 37 to 39 of the patent application as originally filed. The requirements of Article 123(2)(3) are fulfilled.

18. This amendment does not make the claim unclear (Article 84 EPC).

19. Since the reasoning with regard to the inventive step of claim 1 of the main request (see points 9 to 18, supra) was based on prior art where the polypeptide to be expressed was neomycin phosphotransferase, it applies equally to claim 1 of the New Auxiliary Request I. Like the main request, this request is, thus, rejected for lack of inventive step.

New Auxiliary Request II, claims 1 to 3 and 6

20. Claim 6 is identical to granted claim 10 (claim 26 as originally filed). Claims 1 to 3 correspond to granted claims 2 to 4 with the amendment that the polypeptide to be expressed is the neomycin phosphotransferase polypeptide. Support for this amendment can be found on pages 37 to 39 of the patent application as originally filed. It amounts to a limitation of the subject-matter of the granted claims and does not make the claims unclear. The requirements of Article 123(2)(3) and Article 84 EPC are fulfilled.

21. The patentability of these claims has not been challenged by any of the Appellants on any grounds for opposition under Article 100(a) EPC. Thus, they need not be further discussed within the framework of this appeal.

Claims 4 and 5

Articles 123(2)(3) and 84 EPC

22. Claim 4 differs from granted claim 5 in feature (a) which has been amended to a "full length transcript promoter isolated from cauliflower mosaic virus". Although the expression "full length transcript promoter" cannot be found in the application as filed, the example on page 49 and 50 of said application describes a chimeric gene with "a promoter region which causes transcription of the 32S CaMV mRNA". At the filing date of the application, it was already known from document (19) that it was the full transcription of the CaMV DNA which gave rise to the 32S mRNA (also known as 35S RNA depending on the way the sedimentation coefficient had been measured). It is the Board's view that the person skilled in the art would have no difficulties in understanding that the expression "full length transcript promoter" related to "the promoter region which causes transcription of the 32S mRNA" as originally filed. Accordingly the Board concludes that the requirements of Article 84 and 123(2) EPC are fulfilled by claim 4.

23. The same conclusion is reached for dependent claim 5 corresponding to granted claim 5.

24. The amendment amounts to a reduction in scope of the granted claims 5 and 7. The requirements of Article 123(3) are also fulfilled.

Inventive step

25. It was unanimously agreed at oral proceedings that the priority date of claims 4 and 5 was the filing date of the second priority application (15 April 1983). Therefore the closest prior art can either be seen as

document (17) which is the transcription of an oral presentation which took place in the time interval between the filing of the first and second priority application or as document (9).

26. Document (17) is concerned with the use of a chimeric gene to confer antibiotic resistance on plant cells. It describes a chimeric gene where the bacterial neo resistance determinant is under the control of the Ti plasmid nos promoter. The authors mention that previous attempts to express foreign genes from bacterial, fungal, animal and plant origin have failed and hypothesize that the reasons therefor may be the inability of the expression controlling regions of said genes to function in said cells. Doubts are thus cast on the potential suitability of alternative promoters. The nos promoter appears as **the** satisfactory solution to gene expression in plant cells.

27. Starting from this prior art, the objective problem to be solved might be considered as the provision of alternative promoters for use in chimeric gene expression in plant cells.

28. The solution provided is the full length transcript promoter (35S promoter) from the CaMV virus. From the examples given in the patent specification, the Board is satisfied that the problem has been solved.

29. Whether even the very formulation of this problem from document (17) was within the ability of the person skilled in the art needs to be investigated.

30. The person skilled in the art in the field of biotechnology is well defined by the case law of the Boards of Appeal (T 455/91, T 500/91, see supra). His/Her attitude is considered to be conservative. "He/She would never go against an established prejudice, nor try to enter unpredictable areas nor take uncalculable risks".

31. Accordingly, it is the Board's opinion that the above stated problem which consists in finding alternative solutions to an already quite satisfactory solution, when previously tested alternatives have failed, would not come to the mind of the person skilled in the art. Natural conservatism would make him or her satisfied with the current solution (no incentive to try). Intrinsic cautiousness would prevent him or her from seriously contemplating entering an area of research already known to be fraught with difficulties.

32. In the course of oral proceedings, the Board's attention was drawn to documents (19) and (38) which suggest that the CaMV promoters may possibly be of use in constructing chimeric marker genes. Seeing that these mere **suggestions** are to be balanced against the above stated **facts** that a satisfactory solution to gene expression in plant cells was available and that failures had been observed in all previously tested alternatives, the Board considers that even the combination of these documents with document (17) would not have been sufficient to lead the person skilled in the art to consider that he or she had a reasonable prospect of finding an alternative.

33. It has also being argued that Document (9) could be considered as closest prior art. It describes the expression of the bacterial neo determinant in animal cells under the control of animal viral promoters.

34. Starting from this prior art, the problem to be solved can be defined as adapting to plant cells the technology set up to achieve expression of chimeric genes in animal cells. As previously stated in paragraph 28, the Board finds satisfactory the solution provided which consists in linking the 35S promoter of CaMV virus to the coding sequence of the gene to be expressed.

35. In T 455/91 (supra), the then competent Board found that, inspite of his or her conservative attitude, the person skilled in the art would regard a transfer of technology from one field to a neighbouring field as nothing out of the ordinary. That case however concerned a small modification in the translation start signals recognized by the yeast machinery. That modification was known from the bacterial art **and** it was clear from previous experiments with deletion mutants that it would not negatively affect translation. Thus, the neighbouring fields were very close. In the present case, the technical situation is much less well defined. It is clear from the documents on file that little information was available at the relevant priority date on the mechanisms of gene expression in plant and animal cells and the implications of this knowledge in the case where the genes to be expressed were not an intrinsic part of the genomes of said cells had not been researched. The reasoning used in decision T 455/91 cannot thus be applied in this case.

36. However, since the use of CaMV promoters in the construction of chimeric genes had already been suggested in documents (19) and (38), the Board accepts that the combination of any of these documents with document (9) made the construction of chimeric genes with CaMV promoters obvious to try.

37. The question which remains to be answered is whether the skilled person would have had a reasonable expectation of success that the claimed chimeric gene with the CaMV 35S promoter would express in plant cells.

38. Document (22)(page 769) discloses an **in vitro** experiment to test the ability of the 35S promoter to initiate transcription in the presence of human Hela cells extracts and the mammalian RNA polymerase II. It is found that under these conditions, the 35S promoter is capable of initiating transcription. The characteristics of the **in vivo** transcription of the CaMV DNA from the 35S promoter are described in document (Tab 11). The location and structure of the 35S promoter is most peculiar as said promoter is part of the 3' end of its own in vivo transcript. This in vivo transcript is in itself unusual in that it initiates some 600 base pairs upstream of a break in the transcribed DNA strand. It contains a transcription stop signal shortly downstream of the transcription start site and is so large that its messenger function is questioned (page 26).

39. The significance of in vitro data for in vivo transcription is discussed in document (Tab 30) in the case where transcription is driven by an animal viral promoter in Hela cells. The authors point out that the in vitro Hela cells system is very inefficient in providing **specific** transcription, as the mammalian RNA polymerase II most probably recognizes the sole TATA box and mRNA start point as a promoter sequence. They indicate that the situation may be complicated further in vivo. Reference is made to the possibility that some additional transcription factors may be required if only because "the in vivo transcribed DNA should be organized into some form of chromatin structure not present in the in vitro system...".

40. The person skilled in art would, thus, be reluctant to equate an in vitro to an in vivo transcription in case of a "standard" animal promoter. He/She was also aware from document (Tab 11) that the 35S promoter and its in vivo transcript were disctinctly different from classical eucaryotic promoters and messenger RNAs. It is, thus, the Board's opinion that the skilled person would not have considered the in vitro data as providing a reasonable expectation of success that in vivo, the 35S promoter would be able to initiate the transcription of a "conventional" piece of DNA.

41. Reference has also been made to Document (6) which suggested that the results obtained in animal cells were encouraging pointers that chimeric genes would also be expressed in plants. Yet, document (6) is not concerned with animal cells work nor does it suggest adapting to plant cells the expression system used in animal cells. To the Board, the above suggestion cannot be considered as more than an optimistic speculation reflecting an eagerness that an expression system may be found.

42. The Board concludes that document (9) even in combination with any of documents (19) and (38) and document (22) does not destroy inventive step.

43. In view of these findings, the arguments for and against basing inventive step on promoter strength need not be reviewed.

44. The requirements of Article 56 EPC are fulfilled by the claims of New Auxiliary Request II.

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 patent on the basis of the set of claims headed New Auxiliary Request 2 submitted at the oral proceedings on 7 March 1997 and a description to be adapted.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey