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D E C I S I O N
of 17 September 1998

Case Number: T 0794/94 - 3.3.4

Application Number: 78300596.0

Publication Number: 0001929

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Plasmid for transforming bacterial host to render it capable of polypeptide expression

Patentee:
Genentech, Inc.

Opponents:
Roussel Uclaf
Eli Lilly and Company
Biogen Inc.
Novartis AG Patent and Trademark Dept.
Boehringer Mannheim GmbH Patentabteilung
Gist-brocades NV
Hoechst Aktiengesellschaft

Headword:
Plasmid/GENENTECH

Relevant legal provisions:
EPC Art. 56, 83, 84, 123
EPC R. 57a

Keyword:
"Main request and first auxiliary request - not admitted into proceedings"
"Second auxiliary request - inventive step (no)"

Decisions cited:
T 0095/83, T 0153/85, T 0127/85, T 0292/85, T 0406/86, T 0295/87, T 0694/92, T 0829/93, G 0009/91

Catchword:
Criteria for admission of late filed requests during oral proceedings

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Case Number: T 0794/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 17 September 1998

Appellant: (Proprietor of the patent)
Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco
California 94080 (US)

Representative:
Armitage, Ian Michael
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP (GB)

Respondent I: (Opponent 01)
Roussel Uclaf
35, Bd des Invalides
75007 Paris (FR)

Representative:
Bourgouin, André
Département des Brevets
Roussel Uclaf
B.P. no 9
93230 Romainville (FR)

Respondent II: (Cpponent 02)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis
Indiana, 46285 (US)

Representative:
Fisher, Adrian John
Carpmaels and Ransford
43 Bloomsbury Square
London WC1A 2RA (GB)

Respondent III: (Opponent 03)
Biogen Inc.
14 Cambridge Center
Cambridge, Massachusetts 02142 (US)

Representative:
Bannerman, David Gardner
Withers & Rogers
4 Dyer's Buildings
Holborn
London EC1N 2QP (GB)

Respondent IV: (Opponent 04)
Novartis AG
Patent and Trademark Dept.
Klybeckstrasse 141
4002 Basel (CH)

Respondent V: (Opponent 05)
Boehringer Mannheim GmbH
Patentabteilung
Sandhofer Strasse 116
68298 Mannheim (DE)

Representative:
Schreiner, Siegfried
Boehringer Mannheim GmbH
Werk Penzberg
Abt. RE-TB
Postfach 11 52
82372 Penzberg (DE)

Respondent VI: (Opponent 06)
Gist-brocades NV
Wateringseweg 1
P.O. Box 1
2600 MA Delft (NL)

Representative:
Swinkles, Bart Willem
c/o Gist-Brocades N.V.
Patents & Trademarks Department
Wateringseweg 1
P.O. Box 1
2600 MA Delft (NL)

Respondent VII: (Opponent 07)
Hoechst Aktiengesellschaft
Zentrale Patentabteilung
Gebäude F 821
65926 Frankfurt am Main (DE)

Representative:
Jaenichen, Hans-Rainer Dr.
Vossius & Partner
Postfach 86 07 67
81634 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 22 July 1994 revoking European patent No. 0 001 929 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: R. E. Gramaglia
S. C. Perryman
F. Davison-Brunel
W. Moser

Summary of Facts and Submissions

I. European Patent No. 0 001 929 (application No. 78 300 596.0) relating to a plasmid for transforming a bacterial host to render it capable of polypeptide expression was granted on the basis of 16 claims after appeal proceedings (decision T 292/85, OJ EPO 1989, 275). The priority date was 8 November 1977. The claims as granted read as follows:

"1. A recombinant plasmid suited for transformation of a bacterial host wherein the plasmid comprises a homologous regulon, heterologous DNA, and one or more termination codon(s), the heterologous DNA encoding a desired functional heterologous polypeptide or intermediate therefor which is not degraded by endogenous proteolytic enzymes, said DNA being positioned in proper reading frame with said homologous regulon between said regulon and the termination codon(s), whereby on translation of the transcription product of the heterologous DNA in a suitable bacterium, the resulting expression product is said desired functional polypeptide or intermediate therefor in recoverable form.

2. A recombinant plasmid according to claim 1, wherein the regulon is essentially identical to a regulon ordinarily present in the chromosomal DNA of the bacterial host.

3. A recombinant plasmid according to claim 1 or 2, wherein the said heterologous DNA comprises cDNA.

4. A recombinant plasmid according to claim 1 or 2, wherein the said heterologous DNA comprises organic synthesis-derived DNA.

5. A recombinant plasmid according to any one of the preceding claims, wherein the plasmid is a bacterial plasmid.

6. A recombinant plasmid according to any one of the preceding claims, wherein the regulon comprises *Escherichia coli* lac or the *Escherichia coli* tryptophan promoter-operator system.

7. A recombinant plasmid according to any one of the preceding claims, wherein the heterologous DNA codes for a functional polypeptide as such and the heterologous DNA is immediately preceded by a translational start codon.

8. A recombinant plasmid according to any one of claims 1 to 6, wherein the heterologous polypeptide is a mammalian hormone or an intermediate therefor.

9. A process for the production of a recombinant plasmid as defined in any one of the preceding claims which comprises treating a length of double stranded DNA comprising an intact replicon and in sequence, (a) a regulon for controlling transcription and translation in a bacterial host and (b) a restriction endonuclease recognition site, with a suitable restriction endonuclease to form a DNA fragment that comprises the replicon and the regulon, and ligating thereto in proper reading frame with said regulon heterologous DNA encoding a functional heterologous polypeptide or intermediate therefor which is not degraded by endogenous proteolytic enzymes, said heterologous DNA having a terminal nucleotide grouping which is ligatable to said DNA fragment, to give said recombinant plasmid.

10. A bacterium transformed with a recombinant plasmid according to any one of claims 1 to 8.

11. A bacterial culture comprising a transformed bacterium according to claim 10.

12. A process for the bacterial production of a functional heterologous polypeptide or intermediate therefor comprising growing a bacterial culture as defined in claim 11 to bring about expression of said polypeptide or intermediate in recoverable form and recovering said polypeptide or intermediate.

13. A process according to claim 12 for producing an immunogenic substance comprising a polypeptide hapten, comprising:

(a) providing a recombinant plasmid containing a homologous regulon, and in proper reading frame therewith, a heterologous DNA sequence encoding the hapten, a DNA sequence encoding a second amino acid sequence sufficient in size to render the product of DNA expression immunogenic and one or more termination codons;

(b) growing a bacterium transformed with the recombinant plasmid, occasioning expression of a conjugate polypeptide consisting essentially of the amino acid sequence of the hapten and the second amino acid sequence; and

(c) testing the conjugate polypeptide for its ability to raise antibodies against said hapten.

14. A process according to claim 12 for producing an immunogenic substance comprising somatostatin, comprising:

(a) providing a recombinant plasmid containing a homologous regulon, and in proper reading frame therewith a heterologous DNA sequence encoding the somatostatin, and a DNA sequence encoding a second amino acid sequence sufficient in size to render the product of DNA expression immunogenic and one or more termination codons; and

(b) in a bacterium transformed with the recombinant plasmid, occasioning expression of a conjugate polypeptide consisting essentially of the somatostatin and the second amino acid sequence.

15. A process according to claim 13 or 14, wherein the expression product comprises in excess of about 100 amino acids.

16. A process according to claim 13 or 14, wherein the expression product comprises in excess of about 200 amino acids."

II. Notices of opposition were filed by the present seven respondents I to VII (opponents 01 to 07) all requesting the revocation of the European patent as a whole, on the grounds of Article 100(a) and (b) EPC (all respondents) and of Article 100(c) EPC (respondents I, II and IV). Oral proceedings took place on 18 November 1993. Maintenance of the patent was argued for on the basis of a main request and three auxiliary requests. At the end of the oral proceedings

the decision of the four member Opposition Division to the effect that none of the requests was allowable for lack of inventive step and that the patent was to be revoked was announced. The written decision to this effect was posted on 22 July 1994.

III. The appellant (patentee) lodged an appeal against this decision filing a notice of appeal, paying the fees and filing on 1 December 1994 a statement of grounds asking for maintenance of the patent to be considered on the basis of a main request and six auxiliary requests.

IV. The following documents are cited in the present decision:

(OD51) Oral disclosure by Dr Herbert Heyneker at the Department of Biochemistry and Biophysics of the University of California, San Francisco, on Tuesday 11 October 1977, with the title "Expression in **E. coli** of a chemically synthesized gene coding for the gene somatostatin."

(D101) Transcript relating to the deposition made on 31 July 1992 by the witness Dr Heyneker before the United States District Court, Southern District of Indiana, Indianapolis Division, Vol. V, pages 555 to 574 and 615 (Respondent II's Exhibit B submitted with the letter of 16 August 1993).

(D1) Polisky et al., Proc. Natl. Acad. Sci. USA, Vol. 73, pages 3900 to 3904 (1976)

(D3) Summary of W. Gilbert's talk at the Eli Lilly 16th Insulin Symposium on 24 to 25 May 1976, Indianapolis, Indiana, USA, published in 1976 in Nucleic Acid Recombinant Memoranda, Memo Nar 40/4, 1st paragraph.

(D7) Itakura et al., Nature, Vol. 198, pages 1056 to 1063 (December 1977)

(D12) Goeddel et al., Nature, Vol. 281, pages 544 to 548 (October 1979)

(D15) Murray et al., Proceedings of the 10th FEBS Meeting, pages 193 to 207 (1975)

(D16) Atkins, Nature, Vol. 262, pages 256 to 257 (1976)

(D36) Vosberg, Hum. Genet., Vol. 40, pages 1 to 72 (1977)

(D111) Summary of Dr Riggs' presentation at the symposium "Chemically Engineered Insulin-Ten Years Perspective" held on 1 December 1988 at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, California, USA.

V. A change of representative of the appellant was notified to the EPO on 19 March 1998.

VI. On 7 April 1998, the board sent a communication accompanying the summons to oral proceedings, indicating doubts as to whether the requests then on file met the requirements of Article 123(2) EPC.

VII. On 2 September 1998 the appellant withdrew all its existing requests on file, and submitted a new main claim request and six new auxiliary claim requests, together with twenty-four pages of submissions. The claims of all the requests put forward included the restriction that the heterologous DNA encoding a desired functional heterologous polypeptide or intermediate therefor be devoid of a fusion part conferring resistance to proteolytic degradation in the host, as well as the feature "said desired functional heterologous polypeptide or intermediate therefor being sufficiently large so as not to be degraded by endogenous proteolytic enzymes in the host".

VIII. Respondent I indicated that it would not be represented at oral proceedings.

IX. Oral proceedings took place on 16 and 17 September 1998. Respondent III, although duly invited, did not attend the oral proceedings. After hearing submissions on the requests filed with the letter of 2 September 1998, the board indicated its preliminary view that all the requests contained matter violating Article 123(2)EPC, but also indicated that the appellant would be allowed to file not more than three further requests to replace these and to take account of the points discussed. The appellant accordingly withdrew the requests filed on 2 September 1998, and on 16 September 1998 submitted a new main claim request, and 1st and 2nd auxiliary claim requests. After hearing further submissions the board gave its decision that the main claim request and the 1st auxiliary claim request were not admitted into the proceedings, but afforded the appellant an opportunity to amend the 2nd auxiliary claim request filed on 16 September 1998, which consisted of six claims, in response to the matters discussed. On 17 September 1998 the appellant withdrew said 2nd auxiliary claim request and filed a

new 2nd auxiliary claim request containing three further claims in addition to the six claims of the previous 2nd auxiliary claim request. The board only admitted into the proceedings the 2nd auxiliary claim request containing the amended claims 1 to 6.

X. The claims 1, 2 and 9 of the **main claim request** read:

"1. A recombinant plasmid suited for transformation of a bacterial host, wherein the plasmid comprises:

(a) a homologous regulon,

(b) a DNA coding sequence, in proper reading frame with the homologous regulon, to be expressed under the control of said homologous regulon to produce a polypeptide expression product,

(c) one or more termination or stop codons immediately following the sequence (b),

the DNA coding sequence (b) comprising a heterologous structural gene coding for a desired functional heterologous polypeptide or intermediate therefor, and optionally sequence encoding additional protein, so that the polypeptide expression product is the desired functional heterologous polypeptide or intermediate therefor, optionally containing additional protein, in recoverable form;

wherein the polypeptide expression product including additional protein is sufficiently large so as not to be degraded by endogenous proteolytic enzymes in the bacterial host, and said additional protein (if present) is **other than a sequence of ß-galactosidase** sufficient to provide such proteolytic protection **in E coli as the bacterial host**. (Emphasis by appellant)

"2. A recombinant plasmid according to claim 1, wherein said DNA coding sequence (b) comprising a heterologous structural gene coding for a desired functional polypeptide or intermediate therefor is free of sequence encoding additional protein and immediately preceded by a translational start codon."

"9. A process for the production of a recombinant plasmid suited for transformation of a bacterial host, wherein the plasmid comprises:

(a) a homologous regulon,

(b) a DNA coding sequence, in proper reading frame with the homologous regulon, to be expressed under the control of said homologous regulon to produce a polypeptide expression product,

(c) one or more termination or stop codons immediately following the sequence (b),

the DNA coding sequence (b) comprising a heterologous structural gene coding for a desired functional heterologous polypeptide or intermediate therefor, and optionally sequence encoding additional protein, so that the polypeptide expression product is the desired functional heterologous polypeptide or intermediate therefor, optionally containing additional protein, in recoverable form;

wherein the polypeptide expression product including additional protein is sufficiently large so as not to be degraded by endogenous proteolytic enzymes in the bacterial host;

said process comprising:

(i) treating a length of double-stranded DNA comprising an intact replicon and in sequence,
(1) a regulon for controlling transcription and translation in a bacterial host and
(2) a restriction endonuclease recognition site,
with a suitable restriction endonuclease to form a DNA fragment that comprises the replicon and the regulon, and

(ii) ligating thereto in proper reading frame with said regulon DNA encoding said desired functional heterologous polypeptide or precursor therefor which is not degraded by endogenous proteolytic enzymes, said heterologous DNA having a terminal nucleotide grouping which is ligatable to said DNA fragment,

to give said recombinant plasmid."

Claim 1 of the **1st auxiliary claim request** reads:

"1. A recombinant plasmid suited for transformation of a bacterial host, wherein the plasmid comprises:

(a) a homologous regulon,

(b) a DNA coding sequence, in proper reading frame with said homologous regulon, to be expressed under the control of said homologous regulon to produce a polypeptide expression product,

(c) one or more termination or stop codons immediately following the sequence (b),

the DNA coding sequence (b) encoding a desired polypeptide from a heterologous structural gene, **free of sequence encoding additional protein**, so that the expression product is the desired functional heterologous polypeptide or intermediate therefor, in recoverable form." (emphasis by appellant).

Claims 1 to 6 of the **2nd auxiliary claim request** read:

"1. A recombinant plasmid suited for transformation of a bacterial host, wherein the plasmid comprises a homologous regulon and heterologous DNA, the heterologous DNA encoding a desired functional mammalian polypeptide or mammalian intermediate therefor, which is not degraded by endogenous proteolytic enzymes, the DNA being immediately preceded by a start codon and immediately followed by one or more termination or stop codon(s), whereby said desired functional mammalian polypeptide or intermediate therefor is neither preceded nor followed by additional protein, said DNA being positioned in proper reading frame with said homologous regulon between said regulon and the termination codon(s), whereby on translation of the transcription product of the heterologous DNA in a suitable bacterium, the resulting expression product is said desired functional mammalian polypeptide or mammalian intermediate therefor in recoverable form.

2. A recombinant plasmid according to claim 1, wherein the regulon is essentially identical to a regulon ordinarily present in the chromosomal DNA of the bacterial host.

3. A recombinant plasmid according to claim 1 or 2, wherein the said heterologous DNA comprises cDNA.

4. A recombinant plasmid according to claim 1 or 2, wherein the heterologous DNA comprises organic synthesis-derived DNA.

5. A recombinant plasmid according to any one of the preceding claims, wherein the plasmid is a bacterial plasmid.

6. A recombinant plasmid according to any one of the preceding claims, wherein the regulon comprises the Escherichia coli lac or the Escherichia coli tryptophan promoter-operator system.

XI. In support of the patentability of the subject-matter of the claim requests on file, the appellant argued essentially as follows:

Article 83 EPC

- There was a complete teaching in the patent in suit as to how to express non-fusion mammalian proteins. Not only did the patent in suit provide all the technical details such as appropriate host cells, vectors, DNA joining techniques, the source of DNA, expression control regions and selective cleaving agents, but it also taught that if the protein turned out to be unstable, it should be conjugated. If it is stable, no conjugation is necessary.

Article 56 EPC

- Before the priority of the patent in suit it could not be taken for granted by the scientific community that unfused heterologous proteins could be expressed in bacteria and that the product would have been stable (see document (D15), page 205, central paragraph, document (D16) and document (D36), bottom of page 38)

- From Dr Heyneker's oral disclosure (OD51) the skilled person would have been aware that in an endogenous/heterologous fusion protein, the endogenous portion provided protection for the very small heterologous peptide. The strategy of even trying to express a heterologous protein directly had not been contemplated or discussed at that meeting. The skilled person would have been led to extend the ß-galactosidase protein rather than eliminate it, because Dr Heyneker's oral disclosure conveyed to the skilled person the prejudice that mammalian proteins could not be expressed as such in bacteria.

- In contrast to this, the patent in suit provided written and detailed guidance for the skilled reader to directly express unfused foreign proteins in view of the technical teaching that they were stable provided they were sufficiently large.

- It was true that the first direct expression of a mammalian protein was made later on in 1979 by the Goeddel's team (see document (D12)), however, the patent in suit already provided the essential

intellectual contribution that led to the direct expression of mammalian proteins in bacteria. This technical contribution was that size alone was a critical factor for the stability of the expression product.

XII. The respondents argued essentially as follows:

Article 123(2) EPC

- Under this heading objection was raised against the expression in claim 1 of the main request "sufficiently large so as not to be degraded by endogenous proteolytic enzymes in the bacterial host" as finding no basis in the application as filed, and similarly to the term "mammalian" in the 2nd auxiliary request.

Article 83 EPC

- As far as direct expression of mammalian proteins was concerned, the patent in suit provided as much or as little technical information as did the oral disclosure by Dr Heyneker (OD51). Therefore, either the patent in suit was enabling for direct expression and then the disclosure (OD51) was also enabling and a bar to patentability, or both were not enabling.

- The technical effect relied upon by the appellant that mammalian proteins could be expressed as such, provided that they were sufficiently large to resist proteolysis, was doubtful because protein degradation by enzymes also depended on other factors such as the conformation, not only the on size thereof (see for confirmation document (D7), page 1062, bottom of r-h column: "whether large").

Article 56 EPC

- There was only one sentence on page 10, lines 22 to 26 of the application as filed relating to direct expression. The intellectual contribution provided by the patent in suit was merely the idea as such of direct expression. However, document (D15) (see last paragraph of page 205) already disclosed direct expression at a theoretical level. Document (D3) disclosed a plasmid comprising a "portable lac promoter" ready to accept any eucaryotic DNA sequence to be expressed. Thus the skilled person would have had a reasonable expectation of success that a mammalian protein could be expressed directly using the lac promoter. Another approach could have been to replace the DNA used by Polisky (see document (D1)) with a DNA encoding a functional eucaryotic protein.

- If the technical teaching provided by the patent in suit was to be understood as: "the direct expression of a heterologous polypeptide was possible if the heterologous polypeptide was sufficiently long", this information could not be deduced from the oral disclosure (OD51) but it also could not be deduced from the application as filed. Thus, the patent in suit did not solve any technical problem vis-à-vis what the skilled person could have already solved in the light of the oral disclosure (OD51) supplemented with the common general knowledge.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main or first auxiliary claim request submitted on 16 September 1998 or the first two pages containing claims 1 to 6 of the second auxiliary claim request submitted on 17 September 1998.

XIV. The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

2. *Admission of late requests*

2.1 Principles applicable

2.1.1 The principles applicable to the admission into the proceedings of new requests filed at a late stage have long been established. Thus in decision T 95/83 (OJ EPO 1985, 075) it was stated in point 8 of the reasons:

"In paragraph 2.2. of the official "Guidance for appellants and their representatives" published in 1981 (OJ EPO 6/1981, 176) and recently republished with a note that it applies mutatis mutandis to appeals in opposition proceedings (OJ EPO 8/1984, 376), the Boards of Appeal have sought to make it clear that if it is desired to submit amendments to the description, claims or drawings of a patent application or a patent "this should be done at the earliest possible moment". In the paragraph referred to, applicants for patents and patentees are specifically warned to bear in mind that a Board may disregard amendments not submitted in good

time before oral proceedings. For the avoidance of doubt in future cases, the Board takes the opportunity of saying that it is only in the most exceptional circumstances, where there is some clear justification both for the amendment and for its late submission, that it is likely that an amendment not submitted in good time before oral proceedings will be considered on its merits in those proceedings by a Board of Appeal."

2.1.2 The present guidelines for parties to appeal proceedings and their representatives (OJ EPO 1996, 342) have words to the same effect in Section 3.3 on the submission of amendments and auxiliary requests. The mere fact that the board has sent a communication setting a time limit for response, does not mean that a multiplicity of new requests raising quite new issues from any mentioned in the communication will automatically be allowed into the proceedings. As was stated in decision T 153/85 (OJ EPO 1988, 001) in point 2.1 of the reasons:

"...The appeal procedure of Articles 108, 110 and 111 EPC is designed to ensure that as far as possible the oral proceedings are brief and concentrated, and that the appeal is ready for decision at the conclusion of the oral proceedings. Alternative claims ought to be submitted for consideration during the stage of examination of the appeal, which is primarily conducted by the rapporteur. The filing of alternative claims at a later point in time, such as during the oral proceedings, when the examination stage has been substantially completed, is contrary to the prescribed procedure... The submission of alternative claims at an oral proceeding is liable to disrupt it, which is clearly undesirable...In all normal circumstances, an appellant has ample time and opportunity, both during the proceedings at first instance and during the appeal proceedings, to consider and formulate the full range

of claims that he may desire, well prior to the oral hearing. Therefore the closer to the oral hearing that alternative claims are filed, the greater the risk that they will be disregarded. However, in principle, having regard to the particular circumstances of a particular case, a Board may exceptionally decide to consider late-filed claims, provided both the Board and all parties to the appeal proceedings have sufficient opportunity to give all necessary consideration to the allowability of such claims."

2.1.3 Whether additional requests are to be admitted into the proceedings is a matter for the discretion of the board concerned, in the light of the particular circumstances. This is established jurisprudence. Thus, for example, in decision T 829/93 of 24 May 1996, it has been said at point 5 of the reasons:

"The Board concurs with the statements made in the decisions T 127/85 (OJ 1989, 271), T 295/87 (OJ 1990, 470) and T 406/86 (OJ 1989, 302) to the effect that admitting amendments during opposition proceedings is a matter of discretion under Rules 57(1) and 58(2) EPC, and amendments should only be admitted if they can influence the decision on issues under Article 100 EPC or arise in relation to matter to be amended in consequence of such issues. New Rule 57a EPC corresponds to this established case law. This judgment is in line with the general principles expressed by the Enlarged Board of Appeal in its decision G 9/91 (OJ 1993, 408) (see in particular paragraphs 9 and 10 of the reasons), where emphasis is put on the fact that the opposition proceedings constitute only an exception to the rule that a European patent after grant is no longer within the competence of the EPO. Thus, the possibility of amendments at this stage is justified only as an answer to grounds for opposition endangering the patent."

No guidelines which fetter the discretion of the boards can be given, because the admission of late requests is too much a matter depending on the actual situation in each case. Proprietors must keep in mind that it is in the discretion of the boards to refuse to allow into the proceedings sets of claims not submitted at the earliest opportunity in an appeal, namely with the statement of grounds where the patentee is the appellant. Opponents, however, cannot rely on this discretion being exercised adversely to the patentee, if the board considers that there has been an opportunity to adequately consider the issues raised by a new set of claims, however late in the proceedings it was submitted.

2.1.4 This board has not infrequently been prepared to allow new claim requests filed at a very late stage, even during lengthy oral proceedings. However, this has been due not to any deviation from the existing jurisprudence of the boards on the admission of late requests as set out above, but to a recognition that the exceptional problems sometimes involved in patents in the field of genetic engineering where the presence in a single patent of different independent claims to DNA, protein, vectors, modified bacteria, antibodies and processes involving all these, can make formulation of a suitable request difficult, and accordingly amount to exceptional circumstances justifying late submission of requests formulated to meet objections which have already been considered at length. It is preferable for the board to be able to decide on the basis of substantive issues in respect to a reformulated request, than to refuse a patent because no set of claims originally put forward as a whole meets the requirements of Article 123(2) (fair basis) and 84 (clarity) EPC. However, there is no right to file an endless succession of new requests in substitution for requests found inadmissible or unallowable by the

board. Proceedings must come to an end some time. Repeated failure of a proprietor to find a formulation which meets both the requirements of Article 123 EPC on fair basis and Article 84 EPC on clarity when attempting to overcome objections under Articles 54, 56 and 83 EPC, suggests that there is no patentable subject matter.

2.2 Advisable action when putting forward requests

2.2.1 If it can quickly be checked that requests meet the requirements of Articles 123 and 84 EPC, and are necessary and appropriate to meet a ground for opposition, the chances of such a request being accepted even at a very late stage are much improved. To achieve this it is advisable to put forward not just a clean copy of the claims, but a copy of the claims as granted showing precisely by what verbal additions and deletions the claims of the new request are derived from the claims as granted. In addition, for each amendment all passages in the original description which are relied on as providing a fair basis for that amendment should be stated, and it should be stated what ground of opposition (for example, lack of novelty over a prior publication) that amendment serves to avoid. If done systematically, this would also avoid obviously hopelessly unsatisfactory requests even being put forward.

2.2.2 The boards take a conservative view on what amendments are appropriate, in order to avoid an unnecessary multiplication of the issues in dispute and lengthening of the procedure. While the proprietor might wish to completely reformulate the claims in order to bring out what is considered to be the invention, such free formulation is only possible when drafting the application text originally, with a more limited opportunity during examination. It is not appropriate

in appeal proceedings in inter partes proceedings. Clarity is not a ground for opposition, so it cannot by itself be a ground for changes by the proprietor. The general legal presumption is that a change in terminology implies a change in meaning. In inter partes proceedings if the terminology is changed this should be to avoid a ground of opposition. If no different meaning is intended, the wording of the granted claims should be changed as little as possible to avoid new issues being raised unnecessarily.

2.2.3 The guidelines referred to in point 2.2 above also make clear at Section 3.2 that appeal proceedings are essentially a written procedure, and the arguments of parties should be developed in writing, and not left to the oral proceedings. This is a further reason why claim requests should be submitted at the earliest opportunity. Otherwise the opponents cannot be expected to put their objections in writing, and the proprietor deprives himself of any opportunity of receiving written comments by the board.

2.2.4 The addition of dependent claims which do not correspond to any claims as granted, cannot remove a ground of opposition but may well give rise to new objections and issues that would require discussion. Thus such addition cannot be necessary and appropriate, and a request containing additional dependent claims is likely to be refused admission into the proceedings. For a fuller discussion see decision T 829/93 (supra).

2.3 Main claim request

2.3.1 The main claim request put forward at the oral proceedings corresponds substantially to the main claim request filed on 2 September 1998 which was intensively debated during the first part of oral proceedings before the board. As a result of the discussion, the

latter request was amended to delete claims dependent on claim 1 not corresponding to any claims as granted, and also amended to overcome some objections raised during the said oral proceedings.

2.3.2 However, this new main claim request remains open, inter alia, to other objections mentioned during the oral proceedings, namely:

- contrary to the requests put forward with the statement of grounds, the appellant is now again claiming fusion proteins,

- there is no basis for the term "structural" contained in the phrase "heterologous structural gene" in claims 1 and 2, and the meaning and purpose of this term are unclear,

- claim 9 as granted and in the requests filed with the statement of grounds was dependent on claim 1. Now it is put forward as an independent claim, the fair basis for which is disputed by some of the respondents.

- Claim 9 also uses the term "precursor" for which there is no basis in the claims as granted or the application as filed.

2.3.3 In view of new, unresolved issues that the main claim request raises, the board cannot consider it to be a clearly allowable request, such as might be admitted into the proceedings at such a late stage, and the board exercises its discretion under Article 114(2) EPC not to admit this claim request into the proceedings.

2.4 1st auxiliary claim request

2.4.1 The 1st auxiliary claim request put forward at the oral proceedings, corresponds substantially to the 4th auxiliary claim request filed on 2 September 1998 amended to overcome some objections discussed during the oral proceedings on 16 September 1998.

2.4.2 However this 1st auxiliary claim request remains open, inter alia, to other objections mentioned during the oral proceedings, namely:

- there is no basis for the term "structural" contained in the phrase "heterologous structural gene" in claim 1, and the meaning and purpose of this term are unclear,

- all reference to "not degraded by endogenous proteolytic enzymes" has been deleted from claim 1, which raises issues as to the scope of the claim.

2.4.3 In view of new, unresolved issues that this 1st auxiliary claim request raises, the board cannot consider it to be a clearly allowable request, such as might be admitted into the proceedings at such a late stage, and the board exercises its discretion under Article 114(2) EPC not to admit this claim request into the proceedings.

3. *2nd auxiliary claim request*

As can be seen in points 3.1 to 3.2 infra, the claims of this request do not suffer from the deficiencies pointed out in points 2.3.2 and 2.4.2 supra. Therefore they can be admitted into the proceedings.

3.1 Article 123(2) and (3) EPC

3.1.1 Claim 1 is based on a combination of claims 1 and 7 as granted, together with a restriction to the heterologous DNA encoding a mammalian polypeptide or mammalian intermediate therefor, and the DNA being immediately preceded by a start codon and immediately followed by one or more termination or stop codons whereby said desired mammalian polypeptide or intermediate therefor is neither preceded nor followed by additional protein. The changes made restrict the scope of claim 1 compared to claim 1 as granted, so that the requirement of Article 123(3) EPC is satisfied.

3.1.2 The homologous regulon is no longer stated as including a translational start codon, but the requirement that the DNA is immediately preceded by a start codon and is positioned in proper reading frame between said regulon and the termination codon(s) amounts to the same feature being required, so the amendment has a basis.

3.1.3 The reference to "termination or stop codon(s)" means exactly the same as the reference to "termination codon(s)". The change should not have been made, but as it clearly raises no new issue it can be ignored as de minimis, without refusing to allow the set of claims into the proceedings.

3.1.4 The change from heterologous to "mammalian" finds a basis on page 11, line 24. Mammalian is one category falling into the generic term heterologous (to bacteria) explicitly disclosed on page 11, lines 24 of the application as originally filed, and the sub-categories mammalian hormones, and other mammalian peptides are also explicitly disclosed on page 11,

lines 21 to 22 of the application as originally filed (cf. "enzymes, serum proteins and ß-endorphins"). The category mammalian polypeptide is thus implicitly disclosed to the person skilled in the art.

3.1.5 Claim 1 can thus be considered to have a fair basis in the application as originally filed. Claims 2 to 6 raise no separate issues on fair basis. The request thus also satisfies the requirements of Article 123(2) EPC.

3.2 Article 84 EPC - clarity

3.2.1 Some of the respondents objected that the meaning of mammalian intermediate was not clear. This term has to be interpreted in the light of the description pursuant to Article 69 EPC. In particular the passage on page 11, lines 28-30 makes clear that intermediate refers to polypeptides that are made naturally in mammalian cells and there cleaved to a shorter active form. Given this description the board considers that no objection under Article 84 EPC to the claims as amended arises.

3.3 Article 54 EPC

3.3.1 All the parties agreed that the subject-matter of the claims of the second auxiliary request satisfies the requirements of Article 54 EPC and the board agrees as well.

3.4 Articles 83 and 56 EPC

3.4.1 Claim 1 now refers to a plasmid suited for direct expression of a desired functional mammalian polypeptide or intermediate therefor which is not degraded by endogenous proteolytic enzymes. While page 10 ("Where the structural gene is to be inserted in a cloning vehicle for expression as such, the gene

is preceded by a "start" codon (e.g., ATG) and immediately followed by one or more termination of stop codons (see Fig. 2)") provides a verbal basis for such a plasmid, there is no example in the specification of direct expression of mammalian proteins.

3.4.2 As regards the technical means for arriving at the plasmid of claim 1 useful for direct expression of mammalian proteins, such as appropriate host cells, vectors, DNA joining techniques, the source of DNA, expression control regions and selective cleaving agents, the specification gives no detail beyond what was already known from the prior art. The prior art is represented by the prior oral disclosure by Dr Heyneker of the research results relating to somatostatin expression (OD51). The board accepts document (D101) as providing reliable evidence of this oral presentation. Document (D101) reveals that Dr Heyneker showed to the public slide 001151 (see document (D101), page 567, lines 12 to 16: "I do recall using slide 001151"), which gave details of the construction of the vector that was used to successfully express somatostatin, i.e., the same vector disclosed in the patent in suit for expressing the ß-galactosidase-somatostatin fusion protein. Other means available from the prior art to arrive at the claimed plasmid are the suggested expression cassette of document (D3), namely the plasmid comprising a "portable lac promoter" ready to accept any eucaryotic DNA sequence to be expressed, and the "methods and means of forming recombinant cloning vehicles and transforming organisms" referred to in the specification (see page 4, lines 8 to 37), admittedly belonging to the prior art.

3.4.3 As for the technical teaching that non-fusion mammalian proteins are stable upon expression provided they are sufficiently large, which the appellant maintains that the patent in suit conveys to the skilled person, the

board, in spite of a close scrutiny of the whole application as filed, is unable to derive this technical teaching either explicitly or implicitly. The only deduction in relation to the somatostatin and insulin polypeptides mentioned that the skilled person can make, is that these require to be fused to some longer endogenous polypeptide if they are to avoid digestion. Nothing is said as to which, if any, mammalian polypeptides could avoid being degraded if DNA coding only for these is inserted as required by claim 1.

In a different context (see section XI supra), the appellant argued that the skilled person attending Dr Heyneker's presentation on the research results relating to somatostatin expression (OD51) would have viewed the endogenous ß-galactosidase protein as a protective carrier for the heterologous polypeptide (cf. the expression in document (111), last page: "burying somatostatin at the end of ß-galactosidase") and that **no more than this** could have been deduced from this presentation. These considerations strengthen the board's view that the skilled person cannot deduce from the patent in suit more than the teaching that somatostatin and insulin require a long protective endogenous protein if they are to avoid proteolysis.

3.4.4 In view of the above finding, the board is unable to formulate any problem in relation to claim 1, for which it can be said that it has been solved by the novel information. It can also not be said that the actual contribution to the state of the art made by the disclosure of the patent in suit consists of providing experimental support for the direct expression of mammalian proteins, i.e., the technical contribution is not a new technique but the successful completion of an experiment known at a theoretical level from the prior art, as in the case dealt with in decision T 694/92 (OJ

EPO 1997, 408). This is because the direct expression of mammalian proteins is not exemplified in the patent in suit. Therefore, either the skilled person could make what is claimed in claim 1 already on the basis of the prior art, or both the prior art and the patent in suit contain insufficient information to realize what is claimed in claim 1. Thus claim 1 must fail either as the requirements of Article 83 EPC have not been fulfilled, or for lack of inventive step (Article 56 EPC). In the absence of clear evidence that the equivalent information provided by the prior art, or by the patent in suit, is insufficient to allow the skilled person to carry out the invention, the board finds that claim 1 lacks an inventive step. The 2nd auxiliary claim request too has also to be rejected and the appeal dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Spigarelli L. Galligani