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D E C I S I O N
of 3 May 2000

Case Number: T 0354/97 - 3.3.4

Application Number: 83301269.3

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Language of the proceedings: EN

Title of invention:
Expression, processing and secretion of heterologous protein by yeast

Patentee:
GENENTECH, INC.

Opponent:
DSM Gist Holding B.V.
The Green Cross Corporation

Headword:
Protein secretion/GENENTECH

Relevant legal provisions:
EPC Art. 123(2)(3), 83, 54

Keyword:
"Main and second auxiliary requests - added subject-matter (yes)"
"First and third auxiliary requests - novelty (no)"
"Fourth auxiliary request - sufficiency of disclosure (yes)"

Decisions cited:
T 0014/83, T 0292/85, T 0019/90, T 0187/91, T 0409/91, T 0435/91, T 0931/91, T 0612/92, T 0694/92, T 0637/97

Catchword:

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Case Number: T 0354/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 3 May 2000

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 27 January 1997 revoking European patent No. 0 088 632 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Kinkeldey
Members: F. L. Davison-Brunel
W. Moser

Summary of Facts and Submissions

I. The appeal is against the decision of the Opposition Division to revoke the patent in suit under Article 102(1) EPC because the main request (claims as granted) failed to fulfill the requirements of Article 123(2) EPC, and the description did not provide an enabling disclosure with regard to the subject-matter of the first and second auxiliary requests then on file (Article 83 EPC).

II. Submissions were filed by the Appellants (Patentees) as well as by the Respondents I and II (Opponents 02 and 04) and a communication was sent by the Board to express its provisional non-binding opinion. The Appellants filed one main request and five auxiliary requests with their last written submission. During oral proceedings, a new auxiliary request 4 was filed in replacement of the earlier one.

The claims of the main request were the claims as granted but for the deletion of claims 11 and 12 and the subsequent renumbering of claim 13 as claim 11. Claim 1 read as follows:

"1. A process for obtaining mammalian protein heterologous to a yeast organism as a product of yeast expression, processing and secretion, which process comprises culturing viable yeast cells transformed with an expression vehicle functionally harboring DNA encoding said mammalian protein together with a heterologous signal peptide therefor, said heterologous signal peptide being heterologous to the yeast and not normally being produced or employed by said yeast organism, said culturing resulting in secretion of said

mammalian protein into the medium of the culture."

Claims 2 to 10 related to further features of said process. Claim 11 was directed to a specific yeast expression vector.

Auxiliary request 1 differed from the main request in that the term "mammalian protein" was replaced by the term "human protein" in each claim which contained it.

Auxiliary request 2 differed from the main request in that claim 11 was deleted.

Auxiliary request 3 differed from the main request by deletion of claim 2. Furthermore, claim 1 read as follows:

"1. A process for obtaining protein heterologous to a yeast organism as a product of yeast expression, processing and secretion, which process comprises culturing viable yeast cells transformed with an expression vehicle functionally harboring DNA encoding said protein together with a heterologous signal peptide therefor, said heterologous signal peptide being heterologous to the yeast and not normally being produced or employed by said yeast organism, said culturing resulting in secretion of said protein into the medium of the culture wherein the protein is human growth hormone; bovine growth hormone; human fibroblast; human immune or human or hybrid leukocyte interferon; human serum albumin; or human insulin."

Auxiliary request 4 differed from the main request in that claim 1 read as follows:

"1. A process for obtaining human protein heterologous to a yeast organism as a product of yeast expression, processing and secretion, which process comprises culturing viable yeast cells transformed with an expression vehicle functionally harboring DNA encoding said human protein together with a heterologous signal peptide therefor, said heterologous signal peptide being heterologous to the yeast and not normally being produced or employed by said yeast organism, said culturing resulting in secretion of said human protein into the medium of the culture, and further comprising the step of recovering said human protein from the medium of the culture."

Corresponding claims were filed for the Contracting State AT.

III. The following documents are referred to in this decision:

(P1) : EP-A-0 043 980,

(P24) : GB 2 068 969,

(P26) : Lemontt et al., DNA, Vol. 4, No. 6, 1985, pages 419 to 428,

(P33) : Ammerer et al., Recombinant DNA - Extract from report on Cleveland Symposium on macromolecules, A. Walton et al.,Eds, Elsevier Scientific Publishing Co., 1981, pages 185 to 197,

(P37) : EP-A- 0 079 739,

(P41) : Kohara et al., Biosci. Biotech. Biochem., Vol. 58, No. 4, 1994, pages 779 to 781,

(P42) : Cabezon et al., Proc.Natl.Acad.Sci.USA, Vol. 81, 1984, pages 6594 to 6598,

(P45) : Declaration of R.W. Schekman dated

28 October 1996,

(P55) : Nishizawa et al., Appl.Microbiol.Biotechnol., Vol. 38, 1993, pages 624 to 630,

(P60) : Livi et al., The J. of Biol.Chem., Vol. 266, No. 23, 1991, pages 15348 to 15355,

(P61) : Izumoto et al., Gene, Vol. 59, 1987, pages 151 to 159,

(P62) : Jigami et al., Gene, Vol. 43, 1986, pages 273 to 279,

(P65) : Nakamura et al., Gene, Vol. 50, 1986, pages 239 to 245,

(P66) : Kondo et al., Biochim. et Biophys. Acta, Vol. 1243, 1995, pages 195 to 202,

(P72) : Bröker et al.,Biochim. et Biophys. Acta, Vol. 908, 1987, pages 203 to 213,

(P73) : Sleep et al., Bio/Technology, Vol. 8, 1990, pages 42 to 46,

(P74) : Etcheverry et al., Bio/Technology, Vol. 4, 1986, pages 726 to 730,

(A1) : WO 93/ 15204,

(A10) : EP-A-0 301 670,

(A11) : Stepien et al., Advance in Gene Technology: Human Genetic Disorders, Proc. of the 16th Miami Winter Symposium, 16-20 January 1984. W.A.Scott et al., Eds, Cambridge University Press,

(A16) : Ohi et al., Mol.Gen.Genet, Vol. 243, 1994, pages 489 to 499,

IV. The submissions in writing and at oral proceedings by the Appellants insofar as they are relevant to the present decision can be summarized as follows:

Main and second auxiliary requests:

Article 123(2) EPC:

These requests contain claims directed to the expression of mammalian proteins. The objection that such a disclosure could not be found in the application as filed was not justified because the concept of mammalian proteins would immediately come to the mind of the skilled person reading the application:

- on page 5, six of the examples of proteins to be expressed were human proteins, human beings the most important group of mammals. Viral antigens from mammalian viruses were also mentioned. The expression of interferon and growth hormone of human, ie. of mammalian, origin was exemplified.

- on page 16, the function and processing of human interferon proteins was discussed under the heading "secretion signals of mammalian interferon genes". In the same manner, the term "mammalian" was made use of on page 27, line 11 to qualify cells. The skilled person would thus have understood that it equally applied to the proteins to be produced.

  Prior art such as document (P33) made it clear that the generalisation from proteins of specific mammals to mammalian proteins was natural to the skilled person.

First auxiliary request:

Article 123(2) EPC:

In this request, the term "human protein" was

substituted for the term "mammalian protein". All arguments presented in relation to this latter term equally applied to the earlier, all the more so, that the term "human" was disclosed in the application as filed in the context of the proteins to be expressed.

Article 83 EPC, sufficiency of disclosure:

The state of the art on file showed that at least 21 different proteins and polypeptides were successfully secreted by yeasts using heterologous signal sequences. In contrast, there were only very few isolated instances of failures and very few simple steps were necessary to remedy them.

For example, the evidence that human serum albumin (HSA) could not be secreted in the culture medium using its own prepro-leader sequence was inconclusive (document (P74)). In addition, HSA was shown to be secreted in the culture medium of the yeast Kluyveromyces lactis (document (A1)) and Pichia pastoris (document (A16)) using its own prepro-HSA leader sequence, and also from that of Saccharomyces cerevisiae (document (P73)) using a modified prepro-HSA leader sequence, the modification of which did not alter the natural properties of the prepro-sequence in terms of secretion.

In the same manner, the failure reported in document (P41) to secrete human growth hormone (HGH) using an artificial signal sequence was irrelevant as the patent in suit showed that said secretion was obtained when using the signal sequence of interferon.

Finally, although document (P26) related to the failure

to secrete tissue plasminogen activator (tpA) in S.cerevisiae using its own signal sequence, document (A10) described the secretion of tpA in the culture medium of K.lactis using the HSA signal sequence.

Document (P45) which only contained speculations as to the reasons why secretion might be difficult was not relevant since the person skilled in the art had the disclosure of the patent in suit for guidance.

The present case was not analogous to previous cases dealt with in decisions T 612/92 (of 28 February 1996) and T 694/92 (OJ EPO 1887, 408), where the competent boards concluded to lack of sufficient disclosure. Neither were the findings of lack of sufficiency in decisions T 409/91 (OJ EPO 1994, 653) and T 435/91 (OJ EPO 1995, 188) directly applicable as there was no evidence that entire categories of proteins or of signal sequences existed with which the invention could not be carried out. The case was rather of the kind dealt with in T 292/85 (OJ EPO 1989, 275), where it was stated that the failure of one isolated example did not go against sufficiency, and in T 636/97 (of 28 March 1998), where sufficiency was acknowledged when no major conceptual leap was required to apply the teachings of the patent in its generality.

Article 54 EPC; novelty:

Document (P37) described the expression of HSA cDNA in E.coli while mentioning that it could also be produced in yeasts. Although the cloning of the pre-albumin cDNA sequence was described, there was doubt that this DNA had in fact been used for expression and, thus, there was no clear evidence that the HSA protein had been

expressed in yeast using an heterologous signal sequence. Furthermore, it was not sure that HSA was secreted in the culture medium since it had been obtained from the inside of the host cells. This disclosure was not so unambiguous as to be detrimental to novelty.

Third auxiliary request:

The same reasoning applied with regard to the novelty of claim 1 over document (P37) as with regard to that of claim 1 of the first auxiliary request over the same document.

Fourth auxiliary request:

Article 54 EPC; novelty:

The subject-matter of claim 1 was novel over the teaching of document (P37) as said document did not disclose that the human protein produced is recovered from the medium of the culture.

V. The submissions of Respondents I and II were essentially as follows:

Main and second auxiliary requests:

Article 123(2) EPC:

The concept of mammalian proteins was not disclosed in the application as filed: on page 5, many proteins to be expressed were listed which were not (or not necessarily) of human origin such as viral antigens, immunogens, enzymes, etc ... Thus, "mammalian protein"

was only one generalised selected group and was not mentioned as such.

The characteristics of being mammalian was disclosed as a feature of the cells which naturally produced interferon (page 27) and as a feature of the signal sequences to be used in the claimed process (page 16). There was no reason to extend this distinctive characteristic to the protein to be expressed whereas this protein was merely characterized in the application as filed by the feature that it should be heterologous to the host (page 1). It was not allowable to use external documents to assist in understanding what kind of generalisation was included in a patent.

First auxiliary request:

Article 123(2) EPC:

Replacing the term "mammalian protein" by the term "human protein" in auxiliary request 1 did not make this request allowable under Article 123(2) EPC since there was no indication in the application as filed that the generalisation to human proteins was to be preferred over any of the other possible types of generalisations.

Article 83 EPC, sufficiency of disclosure:

The scope of protection of claim 1 was extremely broad covering as many as 600 yeast strains, numerous signal sequences and all possible genes. In contrast, the patent in suit provided only three examples.

The state of the art on file showed that the teachings

of the patent in suit were not generally applicable: documents (P41), (P42), (P55) and (P26) described failures to express HGH, alpha-antitrypsin, nerve growth factor (NGF) and tpA in S.cerevisiae. There was no example of the secretion of HSA in S.cerevisiae using its own prepro leader sequence (document (P73)). With other leader sequences, the level of expression was poor (document (P74)). Later successes at expressing some of these proteins depended on further developments of the techniques such as setting up transformation systems for potentially useful yeasts.

Document (P45) was relevant to understand how complex the mechanism of secretion was. In fact, the skilled person who did not achieve expression could attribute this failure to no less than four different causes: the nature of the signal sequence used, the yeast strain, the nature of the protein to be expressed and the experimental conditions. Undue experimentation was involved in finding which parameters to change to carry out the invention.

The case law to be applied to the present case was that of decisions T 409/91 and T 435/91 (see point IV supra), where it was stated that the claimed invention had to be reproducible over the whole scope of the claims, and that of decision T 931/91 (of 20 April 1993), where sufficiency of disclosure was acknowledged when only a few attempts were required to change failure into success (which was not the case here), as well as that of decision T 694/92 (see point IV supra), where the necessity to achieve a proper balance between the scope of protection and the actual contribution to the art was emphasized. Decision T 292/85 (see point IV supra) was not applicable as the claimed subject-matter

was not a broad, hitherto undisclosed concept.

Article 54 EPC, novelty:

Claim 1 lacked novelty under Article 54(3)(4) EPC in view of document (P37) which disclosed the expression of the complete cDNA coding for prepro-HSA in yeast. Since this cDNA comprised the DNA encoding the HSA secretion signal polypeptide, the culturing of the transformed yeast cells inevitably led to secretion of albumin into the medium.

Third auxiliary request:

The same reasoning applied with regard to the lack of novelty of claim 1 over document (P37) as with regard that of claim 1 of the first auxiliary request over the same document.

Fourth auxiliary request:

Article 54 EPC, novelty:

Claim 1 lacked novelty over document (P37) as this document disclosed, in addition to a process leading to the secretion of HSA in the yeast culture medium, that the purification of said HSA could be accomplished by using procedures well known in the art.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of one of the following claim requests:

(a) main request filed on 31 March 2000: claims 1 to 11 for all designated Contracting States, except

AT, and claims 1 to 11 for the Contracting State AT; or

(b) first auxiliary request filed on 31 March 2000: claims 1 to 11 for all designated Contracting States, except AT, and claims 1 to 11 for the Contracting State AT; or

(c) second auxiliary request filed on 31 March 2000: claims 1 to 10 for all designated Contracting States, except AT, and claims 1 to 10 for the Contracting State AT; or

(d) third auxiliary request filed on 31 March 2000: claims 1 to 10 for all designated Contracting States, except AT, and claims 1 to 10 for the Contracting State AT; or

(e) fourth auxiliary request filed during oral proceedings: claims 1 to 10 for all designated Contracting States, except AT, and claims 1 to 10 for the Contracting State AT; or

(f) fifth auxiliary request filed on 31 March 2000: claims 1 to 9 for all designated Contracting States, except AT, and claims 1 to 9 for the Contracting State AT.

The Respondents I and II requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main and second auxiliary requests

Article 123(2) EPC; added subject-matter:

2. Claim 1 of both the main request and the second auxiliary request was objected to under Article 123(2) EPC for being directed to a process for obtaining **mammalian** proteins, whereas, in the application as filed, mammalian proteins were not disclosed as a category of proteins to be expressed.

3. The Board agrees that proteins characterised as being mammalian are not mentioned expressis verbis in the application as filed but, in accordance with the case law of the boards of appeal (see for example, T 187/91, OJ EPO 1994, 572), considers it necessary for reaching a decision to assess whether the category of mammalian proteins is nonetheless directly and unambiguously derivable from said application, such that a reader of the description of the application as filed could reasonably have expected that a claim could be directed to this class of proteins.

4. On page 4 of the application as filed, it is stated that "the invention is based upon the discovery that yeast organisms can be caused to express, process and secrete protein **that is normally heterologous to the yeast organism**." On page 5, the protein to be expressed is once more defined as **heterologous to the yeast**. In addition, on lines 21 to 29, categories of desirable proteins are disclosed. Said proteins are regrouped according to their function: hormones, enzymes...; their properties: immunogens... ;or their structure: glycoproteins. In some categories, examples are given where the proteins are further characterized by their

origin: human, bovine, but also viral. In the Board's judgment, it is not possible to deduce from the way these proteins are classified that mammalian proteins were indeed the category of proteins to be expressed. This is true, even if the examples provided in the application as filed are of the expression of human leukocyte interferon and human growth hormone (i.e of mammalian proteins), taking into account that on page 5, these proteins are defined as belonging to the categories of interferons and hormones respectively.

5. Thus, it is apparent from the application as filed that about all proteins were considered, and selecting a particular group which is not envisaged therein amounts to a non-disclosed selection.

6. One argument presented by the Appellants in favour of the category of mammalian proteins being unambiguously, albeit implicitly, disclosed in the application as filed was that two parameters of the process namely, the secretion signals and the type of cells which naturally secrete proteins, were characterized as "mammalian" on page 16 and page 29 of the application as filed, respectively, and that, therefore, the term mammalian would have been extended by the skilled reader to the protein to be expressed . This argument does not convince the Board as it is not self evident that the characterising feature of some entities mentioned in the application as filed may necessarily be taken as a characterising feature of others. The further argument drawn in particular from document (P33) that in the prior art the term "human" or "bovine" was used interchangeably with the term mammalian is not decisive in the present case. The common general knowledge of the skilled person would,

of course, have it that humans or cattle are mammalians. Yet, the possibility of using the latter word for the earlier ones obviously depends on the facts at hand. Here, the situation is that proteins from neither humans nor cattle were identified as representative of the category of mammalian proteins within the framework of the invention.

7. For these reasons, the main and second auxiliary requests are refused as the subject-matter of their claim 1 does not fulfill the requirements of Article 123(2) EPC.

First auxiliary request

Article 123(2)(3) EPC; added subject-matter, broadened scope of the claims:

8. The objection raised in relation to claim 1 of the first auxiliary request was that this claim related to a process for obtaining human proteins, whereas the category of "human proteins" was not disclosed in the application as filed.

9. The situation is, however, distinctly different from that discussed above under points 2 to 6. Many references are made throughout the application as filed to human proteins to be expressed: on page 5, lines 22 to 25: human growth hormone, human interferons, human serum albumin and human insulin are mentioned; and on pages 30 and 37 the secretion of human interferon and human growth hormone is exemplified. Accordingly, the Board considers that, in the application as filed, the term "human" appears in relation to the proteins to be expressed in such a way that the category of human

proteins is clearly and unambiguously derivable from said application. The requirements of Article 123(2) EPC are fulfilled.

10. The requirements of Article 123(3) EPC are also fulfilled as the category of human proteins is narrower than that of mammalian proteins.

Article 83 EPC: sufficiency of disclosure

11. Claim 1 is directed to the production of human proteins in any yeast strain using any heterologous secretion signal sequence. Its scope of protection is, thus, very wide. Yet, in accordance with the case law of the EPO with regard to sufficiency of disclosure (see for example, T 19/90, OJ EPO 1990, 476), this mere fact is not in itself a ground for considering the patent as not complying with the requirements of Article 83 EPC. To reach a decision on this issue, it is necessary to assess whether the invention may be performed over the whole area claimed without undue burden or application of inventive skill.

12. The teaching in the description of the patent in suit is that, in order to carry out the claimed process, it is necessary in a first instance to isolate the DNA encoding the desired protein and to clone it into a plasmid vector suited for expression in yeast, in functional combination with the DNA encoding a secretion signal peptide heterologous to the yeast, then to transform the construct into the yeast cells wherein the protein is expressed, processed and secreted. The relevant disclosure on how to accomplish the basic task of constructing the relevant plasmids is provided on page 5, lines 16 to 18 and page 7, lines 47

to 48 by reference to specific documents of the state of the art. A protocol for the transformation of S.cerevisiae is described on pages 4 and 5. The secretion in S.cerevisiae of human interferon and human growth hormone is exemplified. In the Board's judgment, the skilled person wanting to secrete proteins in the yeast culture medium would have been able to follow the provided information as a matter of routine experimentation. And, indeed, evidence that human proteins can be secreted by the claimed process is readily found in post-published documents (P60) to (P62), (P65), (P66), (P72) and (A11) which describe the secretion from yeast of interleukin 1, pancreatic secretory trypsin inhibitor, lyzozyme, salivary alpha-amylase, vascular permeability factor, antithrombin and insulin, respectively.

13. The Respondents I and II pointed out to documents (P74), (P26) and (P41), where HSA, tpA and HGH are reported to be secreted in the periplasmic space of S.cerevisiae rather than in the culture medium using their natural secretion signals (HSA and tpA) or an artificial signal sequence (HGH), as well as to document (P42), which discloses the failure of producing human alpha-antitrypsin, as evidence that the claimed process could not be carried out over the whole scope of the claim.

14. The Board cannot consider document (P41) as evidence that HGH is not secreted in the culture medium by the claimed process, since the patent in suit teaches on pages 36 to 38 that it is secreted in the culture medium when a signal sequence derived from the interferon genes is used. As for HSA and tpA, documents (P73), (A18) and document (A10) show that they are

secreted in the culture medium by using other secretion signals than their own and/or different yeast strains such as P.pastoris and K.lactis. This implies that, if secretion in the culture medium is not obtained directly, it may nonetheless be achieved by changing the above mentioned parameters. The question is, thus, whether the patent in suit contains sufficient information for the skilled reader to be able to do so without undue burden and application of inventive skills.

15. On page 3, lines 34 to 37 of the patent in suit, it is stated: ""Heterologous signal polypeptide" refers to such polypeptides not normally produced or employed by a yeast system and may be selected from the signal polypeptide native to the heterologous protein under consideration, or other heterologous (signal) polypeptide functionally linked to the heterologous protein under consideration". On page 5, lines 31 and 32, it is stated: "Various yeast strains can be employed--see Lodder et al., The Yeasts, a Taxonomic Study, North Holland Publ.Co., Amsterdam."
Thus, the patent in suit draws the skilled person's attention to the possibility of using yeast strains and signal sequences different from those specifically disclosed in the patent specification.

16. As already stated under point 12 supra, the Board does not consider that, at the filing date, undue burden was involved in carrying out the necessary experimental steps leading to secretion, including vector construction and yeast protoplast transformation. The Appellants argued in relation to transformation that improved protocols were used when expressing tpA in K.lactis (document (A10)) and HSA in P.pastoris

(document (A16)). Yet, there is no evidence on file that the results obtained according to these documents would not have been obtained when using the usual transformation method. In this context, it is noted that document (A16), page 493 discloses that P.pastoris can be transformed by the spheroplast method first described in 1978.

17. It is important that secretion was achieved every time the skilled person, faced with an initial failure, chose to make use of other secretion signals and/or yeast strains (see point 14, supra). Consequently, the failure observed with human alpha-antitrypsin (document (P42)) is no convincing proof that the claimed process is not reproducible with this protein, because no efforts were made to correct said failure. The authors of document (P42) explain on page 6598 that the observed failure could "result from strain variation or from intrinsic properties of the molecules". These possible causes for failure are those which can be alleviated by the remedies mentioned above in relation to tpA and HSA.

18. Document (P45) discusses why the mechanisms involved in secretion may be complex. Yet, it is not relevant to enablement since the person skilled in the art had the disclosure of the patent in suit for guidance.

19. In the course of their pleadings, both the Appellants and the Respondents I and II made reference to numerous decisions of the boards of appeal concerning sufficiency of disclosure: more specifically to T 409/91, T 435/91, T 612/92, T 292/85, T 694/92, T 931/91 (see points IV and V supra) and T 14/83 (OJ 1984, 105; also cited in T 931/91).

20. In the cases T 409/91 and T 435/91, it was readily apparent from the teachings provided in the specification of the patents in question that the invention as claimed would not be reworkable over its whole scope. In T 612/92, there existed factual evidence in the post-published prior art that the invention could not be carried out over a large area of the claims. The facts upon which these decisions are based are thus obviously different from those in the present case in view of the findings under points 12, 15 and 16, supra.

21. Other cited decisions address the question of what should be the technical contribution by the claimed invention for sufficiency of disclosure to be acknowledged, taking at the same time into account the essence of said invention and the manner in which it was claimed. Thus, in T 292/85, the essence of the invention was found to be a new technique and the board held that the description of one way of carrying out this technique enabled the skilled person to perform the invention without undue burden over a broad range as long as there were suitable variants known to the skilled person which would provide the same effect for the invention. In T 694/92 the board held that more than one example might be necessary in order to support claims of a broad scope, in cases where the gist of the claimed invention consisted of the achievement of a given technical effect by known techniques in different areas of application. In the Board's judgment, the subject-matter of the patent in suit is different from that in both these cases because it is neither a new technique in the sense given to the term in T 292/85, as the technical effect of secreting heterologous proteins in the culture medium of yeast cells was

already known from 1981 (see document (P45), page 2), nor is there only one example disclosed to support the broad claim.

22. There is factual evidence in the present case that the claimed process is workable although, in few cases, success was not reached at first try. Thus, the situation is rather analogous to that encountered in the case T 14/83 (see supra) where it is stated under point 6 of the decision,: "However, occasional lack of success of a claimed process does not impair its feasibility in the sense of Article 83 EPC if, e.g., some experimentation is still to be done to transform the failure into success, provided that such experimentation is not undue and does not require inventive activity."

23. For these reasons, the Board concludes that the requirements of Article 83 EPC are fulfilled.

Article 54 EPC: novelty:

24. Document (P37) is relevant to novelty under Article 54(3)(4) EPC. It is concerned with the expression of the gene encoding HSA in E.coli and yeasts. It discloses that the translated region of said gene contains, in addition to the open-reading frame for mature HSA, a signal peptide which is cleaved when the protein is secreted (page 2, line 16 to page 3, line 15). In Example 7, the expression of the HSA gene in yeast cells is contemplated but not disclosed expressis verbis. Constructs were made, whereby the main body of the HSA gene is inserted into yeast expression vectors. Information on how to obtain expression is given by way of reference to the state of

the art (lines 31 to 32). In the Board's judgment, this teaching provides a technical disclosure at the same technical level as that provided by the patent in suit with regard to the cloning in yeast cells of mammalian DNA sequences in general for the purpose of secretion. They are, thus, considered enabling (see also point 12, supra).

25. By carrying out the expression of the HSA gene in yeasts in the manner contemplated in document (P37), secretion of HSA in the culture medium will necessarily follow. Thus, document (P37) is damaging to the novelty of claim 1, as it provides a process for the secretion of a human protein in the yeast culture medium.

26. Auxiliary request 1 is, thus, rejected for failing to fulfill the requirements of Article 54 EPC.

Auxiliary request 3

27. Claim 1 relates to a process for obtaining specific proteins which are listed as desirable to obtain on page 5 lines, 22 to 28 of the application as filed. The requirements of Article 123(2) EPC are fulfilled. Those of Article 123(3) EPC are also fulfilled as the scope of the claim is narrower than that of the granted claim 1 which related to mammalian proteins in general. Furthermore, claim 1 also meets the requirements of Article 84 EPC.

28. Claim 1 comprises the production of human serum albumin with which document (P37) is specifically concerned. Thus, the findings under points 24 and 25 supra of lack of novelty of the subject-matter of claim 1 of auxiliary request 1 over document (P37) apply mutatis

mutandis to the subject-matter of this claim 1.

29. Auxiliary request 3 is, thus, rejected for lack of novelty.

Auxiliary request 4

Article 123(2)(3) EPC; added subject-matter, enlargement of the scope of the granted claims:

30. Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 1, which was found allowable under Article 123(2)(3) EPC (cf. points 8 to 10 supra), by the addition of the process feature "...and further comprising the step of recovering said human protein from the medium of the culture". A process comprising this feature is disclosed in the application as filed, for example, on page 4, lines 18 to 24. The requirements of Article 123(2) EPC are, thus, fulfilled.

31. The requirements of Article 123(3) EPC are also fulfilled as the scope of claim 1 is narrower than that of the corresponding granted claim 10, which related to the recovery from the culture medium of mammalian proteins in general.

Article 83 EPC; sufficiency of disclosure:

32. The findings of sufficiency of disclosure in relation to the claims of auxiliary request 1 (see points 11 to 23, above) apply mutatis mutandis to the claims of auxiliary request 4. In the Board's judgment, the additional step of recovering the human protein from the medium is within the skilled person's ability as it

is a process which is carried out every time a protein is produced. No arguments have been presented to the contrary.

Article 54 EPC; *novelty:*

33. As already stated (see point 24, supra), document (P37) does not disclose expressis verbis a process whereby HSA is secreted in the culture medium of yeast cells. This necessarily implies that there is no disclosure in this document of HSA being recovered from said medium. The Respondents I and II drew the Board's attention to the passage on page 11, lines 7 to 9 where it is stated that "The purification of human serum albumin can be accomplished by using procedures well known in the art". However, in the Board's judgment, this sentence, which is written in the context of producing HSA in E.coli as well as in yeasts, does not necessarily imply that HSA is recovered from the culture medium before purification, there being the other possibility that it may be recovered from the host cells themselves. Accordingly, document (P37) does not destroy the novelty of claim 1 of auxiliary request 4. No further novelty objections were raised against any of the claims of auxiliary request 4. The Board is convinced that no other documents on file are damaging to the novelty of the claims of this auxiliary request.

34. The requirements of Article 54 EPC are, thus, fulfilled.

35. The conclusions reached in terms of formal requirements (points 30 and 31, supra), sufficiency of disclosure (point 32, supra) and novelty (point 33, supra) equally apply to the auxiliary request 4 for the Contracting

State AT.

Article 56 EPC; inventive step:

36. The Opposition Division has not yet decided the issue of inventive step. The Board does not consider it appropriate to carry out the examination of inventive step itself at this stage of the proceedings, but decides to use its discretionary power under Article 111(1) EPC to remit the case to the Opposition Division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division for further prosecution on the basis of claims 1 to 10 for all designated Contracting States, except AT, and claims 1 to 10 for the Contracting State AT, filed as fourth auxiliary request during oral proceedings.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey