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# D E C I S I O N
of 21 January 1998

**Case Number:** T 0639/95 - 3.3.4

**Application Number:** 88908449.7

**Publication Number:** 0329770

**IPC:** C12P 7/62

**Language of the proceedings:** EN

**Title of invention:**
Method for producing novel polyester biopolymers

**Applicant:**
Massachusetts Institute of Technology

**Opponent:**
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**Headword:**
Biopolymers/MIT

**Relevant legal provisions:**
EPC Art. 83
EPC R. 67

**Keyword:**
"Disclosure - sufficiency (no) - undue burden"
"Reimbursement of appeal fee (no)"

**Decisions cited:**
T 0226/85, T 0292/85, T 0048/85, T 0281/86, T 0060/89, T 0158/91, T 0500/91, T 0886/91, T 0694/92, T 0296/93

**Catchword:**
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Case Number: T 0639/95 - 3.3.4

# D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 January 1998

Appellant: Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, MA 02139 (US)

Representative: Bassett, Richard Simon
ERIC POTTER & CLARKSON
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 23 February 1995 refusing European patent application No. 88 908 449.7 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
J.-C. Saisset

## Summary of Facts and Submissions

I. European patent application No. 88 908 449.7 published as international application WO 89/00202 (EP-A-0 329 770) with title "Method for producing novel polyester biopolymers" was refused by the examining division with decision issued on 23 February 1995 according to Article 97(1) EPC on the ground that the invention as claimed in claims 1 to 12 filed on 15 December 1994 was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Claim 1 on file read as follows:

"A method for constructing polyhydroxybutyrate (PHB) or related biopolymers in a host comprising: providing genes encoding the enzymes beta-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxybutyrate synthetase, providing portions of DNA controlling the expression of said genes, providing a host for expression of said genes, wherein said synthetase gene is introduced into said host, and expressing said genes, and providing substrates for said enzymes, wherein the action of said enzymes on said substrates produces a polymer having a polyester backbone."

Dependent claims 2 to 6 concerned embodiments of the method according to claim 1. Claim 7 was a product-by-process claim directed to the resulting biopolymer. Independent claim 8 concerned "A rDNA sequence hybridizing to a gene encoding polyhydroxybutyrate synthetase". Claims 9 to 12 were directed to a system for synthetising polyhydroxybutyrate (PHB).

II. The examining division considered that the technical information given in the patent application was not

sufficient to enable a person skilled in the art to carry out the claimed invention, in particular because the gene encoding PHB synthetase, which was an essential feature of the claimed method, was not disclosed. The examining division questioned also the novelty of claim 7.

III. The appellants lodged an appeal against this decision and with the statement of grounds filed a statement by Dr S. Baumberg. With letter dated 16 September 1997, the appellants filed as a new request claims 1 to 11 identical to the claims rejected by the examining division, except for claim 7 which was deleted with consequent renumbering of the other claims. Arguments were put forward in support of the allowability of these claims under the terms of Article 83 EPC. With reference to a number of decisions of the boards of appeal, in particular T 292/85 (OJ EPO 1989, 275), T 281/86 (OJ EPO 1989, 202) and 296/93 (OJ EPO 1995, 627), the appellants maintained that there was no requirement under Article 83 EPC that the invention be actually carried out before the priority date, but merely that is sufficiently disclosed. They admitted that the present application did not refer to any vector or plasmid containing the PHB synthetase gene and that the said gene should be considered as an essential technical feature of the invention because the skilled person needs it in order to perform the invention. However, as stated also in the declarations of Drs. Peoples and Baumberg, the identification and isolation of the gene in question was enabled by the patent application.

The appellants, with reference to the minutes of oral proceedings before the examining division, further complained that they had not been given the possibility to thoroughly present their case during oral proceedings and that evidence of sufficiency they had

submitted had not been taken into consideration. In their view, this represented a substantial procedural violation. In this context, they referred to the decision T 48/85 of 18 November 1986 in which the appeal fee was reimbursed as the examining division had refused to consider evidence which could have led to reverse its attitude.

IV. The appellants requested that the decision under appeal be set aside and the patent be granted with the claims 1 to 11 filed on 16 September 1997 and as auxiliary request to remit the case to the first instance. They further requested the reimbursement of the appeal fee.

V. At the end of oral proceedings held before the present board, the Chairperson announced that the debate was closed, that no further submissions would be admitted in the proceedings and that the decision would be issued in writing.

## Reasons for the Decision

*Article 83 EPC*

1. Article 83 EPC requires that the disclosure of a claimed invention must be "sufficiently clear and **complete** for it to be carried out by a person skilled in the art" (emphasis added). According to the established case law of the boards of appeal, this means that a skilled person, having read the description, should be able at the filing date, also on the basis of common general knowledge, to perform the invention with undue burden and without needing inventive skill within the whole area claimed. Although a reasonable amount of trial and error is permissible

when it comes to the sufficiency of disclosure in an unexplored or difficult field, there must then be available adequate instructions in the specification or on the basis of common general knowledge which would lead the skilled person necessarily and directly towards success through the evaluation of initial failures or through an acceptable statistical expectation rate in case of random experiments (cf. decision T 226/85, OJ EPO 1988, 336, item 8 of the reasons). This does not necessarily mean that it should be proven that the invention was actually carried out at the filing date. However, the written description of the invention should be such as to enable the person skilled in the art to make it and use it without undue difficulties. This is also in line with case law referred to by the appellants (cf. section III, first paragraph above).

2. The level of skill of the skilled person in question is the same that is applied when considering the question of inventive step (cf. decisions T 60/89, OJ EPO 1992, 268 and T 694/92,OJ EPO 1997, 408). This means, in accordance with the established case law (cf. eg decisions T 886/91 of 16 June 1994 and T 500/91 of 21 October 1992), that the said skilled person can only be expected to carry out experimental work by routine means within the framework of the existing knowledge, not to perform scientific research in areas not yet explored.

3. As set out eg in decision T 158/91 of 30 July 1991 (cf. point 2.3 of the reasons), the question of sufficient disclosure, be it of a prior art document or a patent application in question, has to be examined in each case on its own merits. An examination as to sufficiency of a disclosure depends on the correlation of the facts of the case to certain general parameters such as, for example, the character of the technical

field, the average amount of effort necessary to put into practice a certain written disclosure in that technical field, the time when the disclosure was presented to the public and the corresponding common general knowledge, the amount of reliable technical details disclosed in a document.

4. In the present case, in order to perform the claimed invention with undue burden the skilled person should have had readily available the starting materials, these being in particular the genes encoding the enzymes beta-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxybutyrate synthetase, and should have encountered no undue difficulties in achieving the desired result, ie in preparing polyhydroxybutyrate (PHB) biopolymers in a transformed host.

5. The examining division in the decision under appeal acknowledged that in respect of the genes encoding the enzymes beta-ketothiolase and acetoacetyl-CoA reductase, which are two of the three genes required to perform the invention, the disclosure is sufficient. However, the examining division gave reasons why in its opinion the skilled person was not given by the specification enough technical details and information in respect of the gene encoding polyhydroxybutyrate synthetase the availability of which is crucial for putting into practice the claimed invention.

6. The appellants agree that:

(a) the PHB synthetase gene is an essential technical feature of the invention;

(b) neither a gene encoding PHB synthetase nor the said enzyme had been disclosed before the priority date; and

(c) the present application does not describe any vector or plasmid containing the said gene.

They further admit that the isolation and the identification of the PHB synthetase gene is not described with the same amount of technical details and information given in respect of the thiolase and reductase genes. However, they submit that this was not necessary because, by following the protocol given on pages 30 to 32 of the description and taking into account the detailed description of the isolation and characterisation of the other two genes, a skilled person would have had no difficulties in obtaining the PHB synthetase gene by routine techniques and could have thus performed the invention without undue burden. In support of their contention, the appellants rely on the four declarations by Dr Oliver P. Peoples (one of the inventors in the present case) and on the statement of 31 May 1995 by Dr Simon Baumberg.

7. The board has thus to decide whether the arguments and evidence put forward by the appellants are sufficiently convincing to confute the reasons given in the decision under appeal so as to lead to its setting aside.

8. For this, it must essentially be decided whether the enablement requirement is met in respect of the isolation of a DNA encoding PHB synthetase, this being one of the essential starting materials for carrying out the method according to claims 1 to 6 and preparing the means of claims 7 to 11.

9. In order to isolate such DNA the skilled person would have referred in particular to pages 30 to 32 of the description which relates to the "Identification of the Z.ramigera PHB synthetase gene". In this part of the specification the skilled person would have found neither a written description of the gene, nor of the

product coded for, nor of a plasmid or vector containing the said gene. In addition to some initial information on the reaction catalysed by the enzyme, the skilled person would have found here a general outline of experimental steps to be followed in order to isolate the gene in question consisting essentially in the following instructions:

(i) isolate PHB negative mutants of Z. ramigera by transposon mutagenesis using a conjugal transfer system based on derivatives of the broad host range plasmid pRK290 described by Ditta et al. (Proc. Natl. Acad. Sci. USA, Vol. 77, 1980, pages 7347 to 7351) (cf. page 30, third paragraph, first sentence);

(ii) identify the mutants by the sudan black screening technique (page 30, third paragraph, third sentence) and screen them by Southern hybridization analysis using $^{32}P$-labelled Tn5 as a probe to identify the location of the gene (cf. page 31, third paragraph, third sentence);

(iii) achieve complementation analysis by using the cosmid library described by Easson et al (1987), J.Bacteriology (N.B.: an incomplete reference is given in the specification) (cf. page 31, last sentence at the bottom). Screen for complementation of the mutants by growing, harvesting, and lysing the cells to release and characterize PHB and determine the different enzyme activities (see passage bridging pages 30 and 31);

(iv) carry out subcloning of the synthetase complementing sequences on a smaller three to five kb restriction fragment for DNA sequencing and analyse them by computer, utilizing the

codon usage data from thiolase and reductase as the Zooglea standard in order to locate the protein coding regions and regulatory sequences (cf. page 32, first paragraph).

In respect of the above protocol, the skilled person was further informed that:

(a) "When the Sudan black screening technique was applied to Z. ramigera, at least two Tn5 sudan black negative (PHB negative) mutants were identified and characterized." (cf. page 31, second paragraph, first sentence);

(b) "Construction of Tn5 mutant libraries is facilitated by using an exopolysaccharide negative strain, Z. ramigera S99, described by Easson et al (1987) submitted to the Journal of Bacteriology to overcome the problems of polysaccharide interference with the conjugation process and the screening procedure." (cf. page 31, second paragraph, second sentence);

(c) "Methods for mutating and isolating Z. ramigera strains is described in our co-pending application U.S. serial No. 035,604, filed April 7, 1987, by Easson et al, entitled "Method to Control and Produce Novel Biopolymers." (cf. page 31, second paragraph, third sentence).

(d) "A complete library of PHB$^-$ mutants defective in each step of the pathway has been established. A similar Tn5 mutant library of A. eutrophus H16 has also been constructed." (cf. page 31, third paragraph, first two sentences).

Moreover, as pointed out by the appellants, the skilled person would have also referred back to other parts of the description useful for carrying out the above protocol, eg to pages 11 and 12 in respect to the isolation of a Z. ramigera library and to the figures with the DNA sequences of the thiolase and reductase genes. In fact, it is stated on page 31, third paragraph, third sentence: "From the knowledge of the genomic organization of the thiolase and the reductase genes, it is relatively straightforward to screen PHB synthetase mutants...".

10. The board has to decide whether the quality and quantity of experimentation needed to perform the claimed invention based on the guidance provided by the specification was "**undue**" for a person of ordinary skill at the time the disclosure was presented.

11. One of the factors to be initially considered is whether any relevant information in relation to prior art incorporated by reference in the description is missing or incomplete. In this context, the board observed at oral proceedings that:

(i) the reference to Easson et al. on page 31 (see point 9, items iii) and b) supra) was, firstly, incomplete and, secondly, published after the priority date;

(ii) the US serial application referred to on page 31 (see point 9, item c) supra) was published long after the filing date (14 August 1990; cf. US-A-4 948 733);

(iii) it was not clear whether the reference to Ditta et al. on page 30 was in relation to plasmid pRK290 or to its derivatives (see point 9, item (i) supra).

12. In reply thereto, the appellants submitted at the oral proceedings that the prior art references on page 31 (cf. items i) and ii) in point 11 above) were not at all necessary for the skilled person in order to perform the protocol as outlined, because - as shown by Dr Peoples in his fourth declaration - for the construction of Tn5 mutant libraries the skilled person did not have to use an exopolysaccharide negative strain and, furthermore, the preparation of a cosmid library and methods for mutating and isolating a Z. ramigera strain were nothing out of the ordinary.

As regards the reference to Ditta et al. (cf. item iii) in point 11 above), the appellants submitted that it described indeed the derivatives of plasmid pRK290 referred to in the patent application so that no further development or adaptation of its teaching was necessary. The appellants, however, were unable to provide copy of the reference.

13. In the board's judgement, the incompleteness of the references on page 31 of the description (cf. items i) and ii) in point 11) represented a first hurdle for the skilled person which contributed to increase the amount of effort necessary to put into practice the protocol for identifying and isolating the PHB synthetase gene. This is because the skilled person, when realising that, due to the incompleteness of the information given in the description, he or she could not rely on the promised explicit guidance based on the said prior art references, was left to his or her own resources to find an alternative route in order advance experimentally. This involved additional burden. In fact, the burden for devising an alternative route based on one's own resources is certainly higher than that necessary for working experimentally according to a described recipe.

As regards the reference to Ditta et al., it is noted that it describes the construction of pRK290, its properties as cloning vector and its use in constructing a gene bank of Rhizobium meliloti, nothing being said about **derivatives** thereof. Since the appellants, who are assumed to known the contents of the references relied upon in the description, when asked at the oral proceedings, did not have any doubts that the reference is question described the derivatives meant on page 30 of the description, there is no reason for the board to offer them an opportunity to comment in the sense of Article 113(1) EPC on this finding of facts. In the board's judgement, the skilled person, when confronted with the lack of detailed information on the derivatives of pRK290 referred to in the experimental plan on page 30 of the description, was again left to his or her own resources to find a route in order advance experimentally and fill this gap of information. This further contributed to increasing the burden in putting into practice the experimental plan for identifying and isolating the PHB synthetase gene.

14. As regards the procedural steps of the experimental plan indicated on pages 30 to 32 of the description, it is noted that they are indicated in a very general way. The said plan outlines only the main steps that the appellants intended to follow or followed in order to achieve the identification, cloning and expression of the PHB synthetase gene (see in point 9 supra, items i to iv), very little or nothing at all being presented in terms of results and no details being given which could facilitate the skilled person to repeat the work with less trouble (eg the description of specific genome fragments used as a probe or of any DNA sequence of the gene itself or an indication of its location within the genome). To be informed eg that "From the knowledge of the genomic organization of the thiolase

and the reductase genes, it is relatively straightforward to screen PHB synthetase mutants..." (cf. page 31, third paragraph, third sentence) is of no assistance for the skilled person who is left to his or her own resources to find out which DNA portions can lead necessarily and directly toward success. All the experimental steps indicated involve a good amount of trial and error in an unexplored area with no guarantee of success. Of them, in particular the step of the isolation of PHB negative mutants by transposon mutagenesis (see item i) in point 9 supra) is based on a random technique aimed at inactivating the gene looked for by insertion of a bacterial transposon. This is not simply a routine matter as success does not come only from one's own abilities or efforts. Unless success is achieved in this step, the skilled person cannot proceed to the next step. The successful achievement of complementation in a later step (see item iii) in point 9 supra) presupposes the presence of the relevant gene in the cosmid library which is prepared and success in obtaining its expression. Also this is not matter of triviality. Unless this step is carried out successfully, the skilled person cannot proceed to the further steps of subcloning the complementing DNA sequences, analysing them and locating in them the coding regions so as to then use them in the method of according to claims 1 to 6 and the means of claims 7 to 11. The mere listing of the latter experimental steps to be followed is also per se not informative enough.

15. Although it can be said that at the priority date of the present application, all the techniques referred to were to some extent manageable, it cannot be said that it was a trivial exercise to put them in practice in the sequence outlined by the complex experimental plan given on pages 30 to 32 of the description. Each individual step therein presented the skilled person

with some degree of difficulties and uncertainties. What is remarkable is the discrepancy between the lack of technical details in respect of the procedural steps to be taken according to the general plan and the complexity of the plan as a whole. Thus, even if each individual experimental step per se can be considered as being feasible with a certain amount of trial and error, the total amount of experimental effort necessary to successfully advance step by step towards the desired final goal may still be regarded as **undue** for a skilled person. In the board's judgement, this is the case for the complete experimental protocol at issue here considered integrally from the perspective of the task set, also in consideration of the information gaps referred to above in respect of the prior art incorporated by reference (see point 13 supra).

16. As regards the expert declarations submitted by the appellants in support of the issue of enablement, they cannot change the board's view on the matter for the reasons given hereinafter.

17. In his statement, Dr Baumberg merely expresses **an opinion**, no experimental data being provided. This opinion is prudently formulated essentially by paraphrasing the experimental protocol reported on pages 30 to 32 of the description. The use of expressions like "would require only commonly available knowledge and experimental techniques", "it would therefore be a routine task...", "would have required nothing further than modest effort", "this knowledge would in turn be useful" or "would be easily replicated by any person with standard appropriate skills" shows that the statement is not founded on the experience of repeating the experimental protocol. This is not sufficient to overcome the board's objections as outlined in points 11 to 15 supra.

18. As for the declarations of Dr Peoples, their persuasive value has to be judged in the light of the fact that he is one of the inventors. Dr Peoples, in comparison to the skilled person, has the advantage of being the inventor and, thus, of having access to "inside" information, this being measures and ways which were not necessarily accessible to the skilled person. Dr People knew, for example, what was meant by derivatives of pRK290, as shown also by the fact that in repeating the experiments he made use of the specific plasmid pRK602 which is not described in the patent specification (cf. all declarations). Furthermore, he had full access to the information which is incomplete or lacking on page 31 of the description (cf. point 13 supra). He could also rely on a whole series of specific means such as, among many others, the spontaneous streptomycin resistant strain of **A.eutrophus** 11599S1 (cf. eg first declaration), the plasmid constructs pLAFR3, pLA29, pLA40, pLA41, pLA42 (cf. eg first declaration), pAeT10 (cf. eg third declaration), pAeT29, pLZ2 (cf. eg fourth declaration) which are not described in the specification. The argument put forward by the appellants that the said specific means were not decisive and that the skilled person, based on the protocol given in the description, would have devised equally valid alternative means is not convincing in the light of the analysis made in points 11 to 15 supra.

19. In conclusion, the arguments and evidence put forward by the appellants do not convince the board that the enablement requirement is met in respect of the isolation of a DNA encoding PHB synthetase. The amount of experimentation needed to perform the claimed invention based on the guidance provided by the specification was "**undue**" for a person of ordinary skill at the time the disclosure was presented. Thus, the requirements of Article 83 EPC are not satisfied.

*Reimbursement of the appeal fee*

20. Rule 67 EPC provides for the possibility of reimbursement of the appeal fee "where the Board of Appeal deems an appeal to be allowable". In the present case, as the appeal is dismissed, the first condition for the reimbursement of the appeal fee is not fulfilled.

## Order

**For these reasons it is decided that:**

1. The appeal is dismissed.

2. The request for reimbursement of the appeal fee is rejected.

The Registrar: The Chairperson:

D. Spigarelli U. M. Kinkeldey