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**D E C I S I O N**  
**of 16 May 2001**

**Case Number:** T 0725/99 - 3.3.4

**Application Number:** 85114855.1

**Publication Number:** 0184086

**IPC:** C12N 15/31

**Language of the proceedings:** EN

**Title of invention:**

Novel non-reverting salmonella live vaccines

**Patentee:**

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

**Opponent:**

Connaught Laboratories Limited  
Medeva plc

**Headword:**

Live vaccines/LELAND STANFORD JUNIOR UNIVERSITY

**Relevant legal provisions:**

EPC Art. 123(2)

**Keyword:**

"Main and auxiliary requests - added subject-matter - yes"

**Decisions cited:**

T 0630/92, T 0514/88, T 0288/92, T 0187/91, G 0001/93

**Catchword:**

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Case Number: T 0725/99 - 3.3.4

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.4**  
**of 16 May 2001**

**Appellant:** THE BOARD OF TRUSTEES  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 10 May 1999  
revoking European patent No. 0 184 086 pursuant  
to Article 102(1) EPC.

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey  
**Members:** F. L. Davison-Brunel  
V. Di Cerbo

## Summary of Facts and Submissions

I. The appeal lies from the decision of the Opposition Division to revoke the European patent No. 0 184 086 filed under No. 85 114 855.1 with the title "Novel, non-reverting Salmonella life vaccines" which was granted with 16 claims for all Designated Contracting States.

Claims 1 and 9 read as follows:

"1. A method for preparing a live non-virulent vaccine from a virulent pathogenic cellular microorganism, which vaccine is substantially incapable of reverting to virulence in a vertebrate host susceptible to said microorganism while providing for a strong immune response said method comprising

introducing a non-reverting mutation **in at least two independent genes in one biosynthetic pathway** to form a non-virulent mutant which is auxotrophic for a metabolite normally unavailable in said vertebrate host and

isolating said non-virulent mutant which is auxotrophic for said metabolite." (emphasis added by the Board).

"9. A live non-virulent cellular microorganism comprising a non-reverting mutation **in at least two independent genes in one biosynthetic pathway**, said non-virulent microorganism being auxotrophic for a metabolite normally unavailable in a vertebrate host." (emphasis added by the Board).

Claims 2 to 7 related to further features of the method of claim 1. Claim 8 was directed to a microorganism made according to anyone of the methods of claims 1 to 7. Claims 10 to 15 related to further features of the microorganism of claim 9. Claim 16 was directed to a vaccine comprising said microorganism.

- II. The patent was, inter alia, opposed under Article 100(c) EPC. The Opposition Division decided that there was no basis in the application as filed for a method comprising the introduction of a non-reverting mutation in **at least two independent genes in one biosynthetic pathway**, a feature of the claims as granted which was introduced into the claims during an appeal procedure (T 630/92 of 22 February 1994) in the course of the examination proceedings.
- III. The Appellants (Patentees) filed an appeal. The Board sent a communication under Article 11(2) of the Rules of procedure of the Boards of appeal, setting out its preliminary non-binding opinion.
- IV. Oral proceedings took place on 16 May 2001. During oral proceedings, the Appellants filed an auxiliary request, the claims of which were identical to the granted claims but for the fact that the expression "in at least two independent genes" in claims 1 and 9 was replaced by the expression "in more than one independent genes".
- V. The submission in writing and during oral proceedings by the Appellants can be summarized as follows:
- The general subject-matter of the patent was life vaccines made from microorganisms wherein at least

one biosynthetic pathway was blocked. The skilled person would understand from the references in the application as filed to "at least one pathway" (for example, on page 5, lines 30 to 32 and page 11, lines 2) that the invention could be carried out in one pathway. Furthermore, he/she was taught that the block was to be non-reverting and non-leaky (page 7, lines 29 to 32, page 9, lines 23 to 26, page 11, lines 9 to 13). Then one or two techniques were suggested to isolate the relevant mutated strain, of which one was to introduce two or more independently mutated genes into a single host strain (page 15, lines 3 to 11). Thus, having made the first choice of working in one biosynthetic pathway only, the skilled person was implicitly but unambiguously led by the patent specification to create mutations in two independent genes in one biosynthetic pathway. The subject-matter of claim 1 was already disclosed in the application as filed. The requirements of Article 123(2) EPC were fulfilled.

- If the pre-grant decision of an Examining Division and, a fortiori, of a Board of Appeal on a specifically examined issue was to be set aside in opposition, the burden of proof was on an Opponent to provide one or more compelling objective reasons to show why the earlier decision was wrong. For reasons of fairness and justice to the Patentee, such an adverse decision should only be taken in the most extreme circumstances. Inasmuch as the Article 123(2) EPC question was already decided by an Examining Division and by a Board of Appeal on the same facts, these decisions should be allowed to stand. Obtaining different answers

in pre- and post-grant proceedings was bad for the patent applicants who spent time and money getting, maintaining and defending the patent. It encouraged the filing of divisional applications simply in order to provide a route for making an alternative amendment, which would not offend Article 123(3) EPC in the event of an adverse post-grant decision on a pre-grant amendment. If the Board was not of this opinion, the following questions should be submitted to the Enlarged Board of Appeal:

*"1. In post-grant consideration of an amendment made before grant, and explicitly acknowledged by the Examining Division, or ruled by a Board of Appeal pre-grant, as meeting Art 123(2), should the prima facie assumption that the Examining Division (or a Board of Appeal pre-grant) examined the issue to the appropriate standard, so that the onus in post-grant proceedings is on an opponent to show that the pre-grant decision was wrong because it clearly overlooked a significant fact before it ?"*

*"2. In particular, in respect of Art 123(2) issues, is the standard of "beyond all reasonable doubts" appropriate to determining whether an amendment meets this requirement of the EPC ?"*

*"3. If the answer to questions 1 and 2 is in the affirmative, does this mean that, in the post-grant situation envisaged in question 1, the onus is on an opponent to show beyond all reasonable doubt that the amendment does add subject-matter contrary to Art.123(2)?"*

VII. The submissions in writing and during oral proceedings by the Respondents (Opponents 1 and 2), insofar as they are relevant to the present decision are summarized as follows:

- The entire thrust of the patent application was towards mutating genes in two different pathways as could be appreciated from reading the original claims and examples.
- The original application did not disclose the "two genes in one pathway" invention as a matter of language:
  - Language referring to the presence of "at least one" biosynthetic pathway was simply an indication that any singular or plural number of biosynthetic pathways were involved and was not in reality language which expressly disclosed one biosynthetic pathway. Blocking a plurality of pathways was best according to the teaching on page 11, lines 2 to 3.
  - The specific combination of gene count, mutation count and pathway count defined in the claims was a novel selection taken from three lists.
  - The passage on page 6, lines 17 to 23 was at best a generic disclosure of creating at least one non-reverting mutation in one or more genes in one or more biosynthetic pathways. Read in the context of the patent specification, it appeared that what was envisaged was one mutation created in a gene in a first pathway and a second mutation created in a gene in a



second pathway.

- The passage on page 15, lines 22 to 26 seemed contrary to the claimed subject-matter because it suggested blocking at least two biosynthetic pathways by mutating one gene.
  
- The original application did not disclose the "two genes in one pathway" invention as a matter of substance:
  - The passage bridging pages 7 and 8 described three reasons why it was desirable to make two mutations. These reasons were only consistent with the concept of making two mutations in two different pathways.
  
  - The skilled person would not have thought of introducing two mutations in the same pathway because of the difficulties of screening for such double mutants.
  
- The question of added subject-matter should be assessed to a rigorous standard to ensure that an applicant cannot escape the purpose of Article 123(2) EPC as set forth by the Enlarged Board of Appeal in the decision (G 1/93, OJ EPO 1994, 541) ie. to ensure that an applicant cannot gain an unwarranted advantage by obtaining patent protection for something which he had not properly disclosed and, may be, not even invented on the date of filing of the application.

In this decision, the Enlarged Board of Appeal also made clear that the interests of the public

were of paramount importance in the assessment of whether the requirements of Article 123(2) EPC were fulfilled.

VII. The Appellants requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or on the basis of the set of claims filed during the oral proceedings (first auxiliary request), auxiliarily, that three questions filed during the oral proceedings be referred to the Enlarged Board of Appeal.

The Respondents requested that the appeal be dismissed.

## Reasons for the Decision

### *Main request*

1. The issue to be decided is that of compliance of claim 1 with the requirements of Article 123(2) EPC. In accordance with the case law of the Boards of Appeal such as, for example, decisions T 514/88 (OJ EPO 1992, 570) and T 288/92 (of 18 November 1993) and T 187/91 (OJ EPO 1994, 572), an amendment is allowable under this article if it can be directly and unambiguously derived from the application as filed. In the present case, it is necessary to decide whether or not the application as filed provides an explicit or implicit but clear and unambiguous disclosure that the claimed process may be carried out by introducing a non reverting mutation in **at least two independent genes** in **one biosynthetic pathway**. It is, therefore, the information concerning the number of mutated genes **in**

**relation to the number** of biosynthetic pathways which must be derivable from said application.

2. All parties and the Board agree that the invention as now claimed is not disclosed *expressis verbis* in the application as filed. The Appellants cited a number of passages as evidence that the claimed process is nevertheless directly and unambiguously derivable from said application, in particular, the passage on page 6, lines 17 to 23:

*"...auxotrophic mutants are obtained by employing a virulent strain...and creating at least one non-reverting mutation in one or more gene(s), so as to produce a complete block in biosynthesis of one or more essential metabolite(s) which are not normally available..."*.

3. This generic disclosure concerning the number of genes to be mutated **in relation to** the number of pathways to be blocked covers many possibilities. In particular, if **one is willing** to simultaneously interpret the expressions:

- "at least one non reverting mutation" as " **a** non-reverting mutation",
- "in one or more genes" as "**at least two** independent genes"
- "in biosynthesis of one or more essential metabolites as "in **a** biosynthetic pathway",

it covers the possibility of having "a non reverting

mutation in at least two independent genes in one biosynthetic pathway". Following the findings in decision T 187/81 (supra) on the interpretation to be given to the term "implicitly but unambiguously disclosed", this possibility can be considered so disclosed if the skilled person would **seriously contemplate** carrying out the claimed process by using the claimed specific combination of the number of mutations, genes and pathways.

4. The Appellants argued that it was indeed the case. They put forward that the many references to "at least one pathway" or to "one or more pathway" throughout the application would lead the skilled person to choose the option of one pathway. Having made that choice and being also taught that mutations in two unrelated genes were preferable, he/she would, in their opinion, have necessarily understood that two mutations in two unrelated genes can be in one pathway.
  
5. The Board is not convinced by this argument. The skilled person will make the choice of the number of pathways to be blocked on the basis of the general technical teaching in the application as filed rather than on the basis of an arbitrary combination of words scattered throughout the disclosure without a technical link. In the passage bridging page 7 and 8, it is taught that for any given pathway, opportunities exist for reversions re-establishing functionality. In lines 9 to 11, it is advised that, for this reason, live microorganism vaccines should be developed with two separate and **unrelated** pathway blocks. Thus, the skilled person would not seriously contemplate the specific choice which is claimed, ie. blocking only one metabolic pathway by mutations in two independent

genes.

6. In addition, the Board agrees to the position of the Respondents that the skilled person in 1984 was aware of the basic common knowledge on the screening of mutants that isolating a strain with two genes altered in one pathway is more difficult than isolating a strain with two genes altered in two different pathways, because in the earlier case, a special screening method needs to be developed to ensure that both genes have been altered. There is no disclosure of such a special screening method in the application as filed. This fact supports the Board's view that the disclosure of the application as filed was not directed towards the subject-matter as claimed.
7. For these reasons, the Board's conclusion is that the claimed invention can only be derived from the passage on page 6, lines 17 to 23 by using hindsight knowledge of said invention.
8. Other passages were cited as providing evidence that the claimed subject-matter was disclosed in the application as filed. The references to page 7, lines 29 to 32, to page 9, lines 23 to 26 and page 11, lines 9 to 13, to the passage bridging page 10, line 34 to page 11, line 3, as well as to page 15, lines 22 to 26 are of no relevance, as it is the quality of the mutations to be created (non-reverting) or their effect at the biological level (pleiotropic) which is discussed therein rather than the number of mutated genes relative to the number of biosynthetic pathways, which is the issue to be decided.
9. The passage on page 5, lines 28 to 32, the passage

bridging page 10, line 34 to page 11, line 3 and that on page 15, lines 22 to 26 specify the number of pathways to be altered. The passages on page 8, lines 31 to 33 and page 15, lines 3 to 7, line 15 to 17 specify the number of genes which may be mutated. As the earlier are silent on the number of genes to be mutated and the latter are silent on the number of pathways to be affected, it was argued that none of them eliminated the possibility that more than one gene be mutated in one pathway. In the Board's judgment, however, an **absence of disclosure** does not amount to an implicit disclosure unless the remainder of the available information directly and unambiguously leads the skilled person to interpret the absence of disclosure in such a way. In the present case, the entire thrust of the application as filed is to a process where the mutations are carried out in at least two different pathways as shown by the originally filed claims, by the examples which are directed to the isolation of strains carrying one mutation in the pathway comprising the *aro* gene and one mutation in the pathway comprising the *pur* gene, as well as by the many references to a plurality of pathways being blocked as the preferred embodiment (page 7, line 1, page 8 line 9 to 15, page 11, line 2, page 15, lines 11 to 14). The passages mentioned thus, do not amount to an implicit but direct and unambiguous disclosure of the claimed subject-matter.

10. As the application as filed provides neither an explicit disclosure nor an implicit but unambiguous disclosure of the claimed subject-matter, it is concluded that the requirements of Article 123(2) EPC are not fulfilled. The main request is rejected for failing to fulfill the requirements of Article 123(2)

EPC.

*Auxiliary request*

11. Claim 1 of the auxiliary request differs from claim 1 of the main request in that the expression "at least two independent genes" was replaced by the expression "in more than one independent genes". This latter expression is not different from the earlier in its technical teaching and content and, therefore, the reasoning in points 1 to 9 above which led the Board to the conclusion that the requirements of Article 123(2) EPC are not fulfilled applies here equally. The auxiliary request, is, thus, also rejected.

*Request for referral of questions to the Enlarged Board of Appeal*

12. Pursuant to Article 112(1) EPC, it is within the discretion of the boards of appeal to refer a question to the Enlarged Board of Appeal if this appears necessary for ensuring uniform application of the law or if an important point of law arises.
13. The essence of the questions proposed by the Appellants, which evidently fall within the second case listed in Article 112 EPC, is to decide whether the application of Article 123(2) EPC in post-grant proceedings entails for the opponents a particular onus to show that the pre-grant decision was wrong.
14. Indeed, in every opposition procedure, the onus to show that the decision to grant the patent was wrong is with the opponents, and the law makes no difference in terms of on which Article of the EPC the opposition is based,

ie whether it is Article 54, 56, 83 or 123 EPC. The amount or the contents of such an onus does not change if the grant was decided by the Examining Division or by a decision of a technical Board of Appeal setting aside the negative decision of the Examining Division. The contrary opinion expressed by the Appellants does not take into consideration the different nature of the pre-grant phase and the post-grant phase, the first one being an ex-parte proceedings where (contrary to the post-grant phase) no third party is allowed to comment or take position to defend its specific interests. (In this respect, the right of any person to present observations pursuant to Article 115 EPC is of no relevance, since "that person shall not be a party to the proceedings"). Accordingly, if during the pre-grant procedure a Board of Appeal has considered an amendment made by the applicants as meeting the requirements of Article 123(2) EPC, the burden of the opponents to demonstrate that this finding was wrong does not change. Indeed in any case, ie both when the patent was granted by the Examining Division directly or following a decision of the Board of Appeal, the opponents have to satisfy the opposition division that this finding is wrong and they can achieve this result not only by showing (as the Appellants maintain) that "a significant fact" has been overlooked in the pre-grant phase but in every other suitable way, such as, for example, by giving a more convincing interpretation of the content of the application as filed.

15. In this context, the Appellants' assumption that a particular standard (ie the standard of "beyond all reasonable doubts") has to be applied by the Opposition Division to determining whether an amendment meets the requirements provided for in Article 123(2) EPC cannot



be shared. Indeed in neither of the above quoted cases (ie when the grant of a patent has been decided by the Examining Division or following a decision of a technical Board of Appeal), this standard is to be considered as pertinent for the decision to be taken by the opposition division (as well as for the decision of the Board of Appeal in case of an appeal filed against the decision thereof) since the principle of free evaluation of the evidence applies.

16. In the Board's view, no important point of law arises from the Appellants' questions since they are based on an incorrect construction of the relevant provisions of the EPC, a construction which is moreover contrary to the general principles of procedural law. The request for remittal is therefore rejected.

## **Order**

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

The appeal is dismissed.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey