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D E C I S I O N
of 7 May 2002

Case Number: T 0232/99 - 3.3.4

Application Number: 87302156.2

Publication Number: 0239292

IPC: C12N 1/38

Language of the proceedings: EN

Title of invention:
Production of proteins by cell culture

Patentee:
Alusuisse Holdings A.G.

Opponent:
Boehringer Ingelheim GmbH

Headword:
Protein production /ALUSUISSE HOLDINGS A.G.

Relevant legal provisions:
EPC Art. 123(2)
EPC R. 57a

Keyword:
"Added subject-matter - main and auxiliary requests (yes)"

Decisions cited:
T 0127/85, T 0187/91, T 0367/92

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0232/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 7 May 2002

Appellant: (Proprietor of the patent)
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Respondent: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 21 December 1998 revoking European patent No. 0 239 292 pursuant to Article 102(1) EPC.**

Composition of the Board:

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

Summary of facts and submissions

I. The appeal lies from the decision of the Opposition Division dated 21 December 1998 to revoke the patent No. 0 239 292 with the title "Production of proteins by cell culture" which had been granted with 18 claims for all Designated Contracting States.

Claim 1 of the main request refused by the Opposition Division read as follows:

"1. A process for obtaining a protein by cell culture which comprises the steps of (1) culturing genetically manipulated cells which constitutively produce said protein **in the continuous presence** of an alkanoic acid or a salt thereof, wherein the alkanoic acid or a salt thereof is present at a concentration of between 0.1mM and 200mM at which production of said protein is enhanced but at which cell growth rate is not substantially decreased (2) continuing said culture until said protein accumulates and optionally (3) isolating said protein." (emphasis added by the Board).

Independent claims 8 and 9 were directed to further methods for obtaining a protein from genetically manipulated cells which also involved the concentration of the alkanoic acid or salt thereof being between 0.1mM and 200mM. Independent claims 13, 23 and 24 corresponded to claims 1, 8 and 9 respectively, the cells involved in the claimed processes being hybridoma cells.

Dependent claims 2 to 7, 14 to 22 related to further features of the processes according to claim 1 and 13

respectively, dependent claims 10 to 12, 25 to 27 related to the use of either a growth medium containing an alkanoic acid or a salt thereof, or alkanoic acid or a salt thereof, or butyric acid or a salt thereof, in processes according to claims 1 to 9 and 13 to 24, respectively.

II. Oppositions were filed by Respondents I (Opponents 1) and Opponents 2. Opponents 2 later withdrew their opposition.

III. The Opposition Division came to the conclusion that the objection raised by Respondents I under Article 123(2) EPC that the term "in the continuous presence of" in claim 1 was neither explicitly nor implicitly disclosed in the application as filed was not valid. They refused the main request on the ground that sufficiency of disclosure was not fulfilled in relation to the subject-matter of, in particular, claim 1.

IV. An appeal was lodged. With their latest submissions, the Appellants (Patentees) filed four auxiliary requests for consideration by the Board, together with the main request refused by the Opposition Division as their main request. The term "in the continuous presence of" was present in claim 1 of all the auxiliary requests.

V. The submissions in writing and during oral proceedings by the Respondents insofar as they are relevant to the present decision may be summarized as follows:

Rule 57a EPC

The granted claims related to processes for protein

production to be carried out either with genetically manipulated cells or with hybridoma cells. During opposition proceedings before the first instance, each claim was redrafted into two claims, one of them relating to genetically manipulated cells, the other relating to hybridoma cells. The number of claims, thus, increased from 18 to 27. In accordance with the case law of the Boards of Appeal (T 127/85, OJ EPO 1989, 271), it was an abuse of opposition proceedings if the patent proprietor was allowed merely to tidy up and improve his disclosure by amendments not specifically necessitated by the grounds advanced for the opposition as required by Rule 57a EPC. As this was the case here, the main request was not allowable.

Article 123(2) EPC; claim 1

- There was no basis in the application as filed for a process for protein production with the feature of:

*"... culturing genetically manipulated cells which constitutively produce said protein **in the continuous presence** of an alkanoic acid or a salt thereof, wherein the alkanoic acid or a salt thereof is present at a concentration of between 0.1mM and 200 mM ..."*
(emphasis added by the Board)

This feature implied that the culture medium should always contain an alkanoic acid or a salt thereof at a concentration falling **within the mentioned range**. The sole passage in the application as filed describing ways to ensure the presence of the enhancing agent in the culture medium was on page 8, lines 13 to 21 (A version of the patent application): it disclosed that

the concentration beyond which cell growth rate would be affected was not to be exceeded at any time during culturing, but failed to mention which minimum concentration should be maintained, if any.

As the genetically manipulated cells consumed the alkanoic acid, one would expect when starting the culture at the minimal concentration of 0.1mM that this concentration would very quickly fall. Thus, it could be assumed that the enhancing agent would not be continuously present in the culture medium within the claimed range. The patent in suit failed to give any instructions how to remedy this situation.

The passage on page 8 of the application as filed was not a clear and unambiguous disclosure of the process according to claim 1.

- Alternatively, it was suggested that the claim could be read as implying that the genetically manipulated cells used in the claimed process possessed the property of constitutively producing the protein when in the continuous presence of an alkanoic acid or a salt thereof. This interpretation, however, did not change any conclusion relative to Article 123(2) EPC as such genetically manipulated cells were not mentioned in the application as filed.

- The requirements of Article 123(2) EPC were not fulfilled by claim 1 of the main request. As claim 1 of the four auxiliary requests also contained the offending feature, these requests were equally unallowable.

VI. The submissions in writing and during oral proceedings

by the Appellants insofar as they are relevant to the present decision may be summarized as follows:

Rule 57a EPC

During opposition proceedings before the first instance, the claims of the main request were reorganized in accordance with the kind of cells used in the claimed process, to arrive at the main request now for consideration by the Board. This amendment was carried out to facilitate assessment of novelty and inventive step, the prior art concerning genetically manipulated cells being different from that concerning hybridoma cells. Hence, it was occasioned by grounds of opposition and, thus, the main request now on file was allowable under Rule 57a EPC.

Article 123(2) EPC; claim 1

- Support for **the continuous presence** of alkanoic acid or a salt thereof in the culture medium could be found on page 8, lines 13 to 21 of the application as filed where it was stated that the addition of alkanoic acid could be done at any time during culturing and had to be closely controlled and monitored, which steps could have been carried out easily by the skilled person at the priority date.

It was also disclosed on page 9 (second full paragraph) that the cells had to be maintained in the presence of alkanoic acid and in originally filed claim 7 that the culturing had to be continued in the presence of the enhancing agent until protein accumulated. The skilled person would have unambiguously derived therefrom that the alkanoic acid had to be continuously present.

The smallest concentration in the claimed concentration range was well above the amount of alkanoic acid which could be consumed by the cells and alkanoic acid was not otherwise degraded. Thus, even if the culturing were to be started at the minimal concentration of alkanoic acid, the alkanoic acid would be continuously present in the culture medium.

- As for the alleged possible alternative interpretation of claim 1, that it was a property of cells that they constitutively produced the protein in the continuous presence of an alkanoic acid or a salt thereof, it would not be an interpretation adopted by the skilled person albeit the fact that the claim could literally be read in that way. Accordingly, there was no need to assess whether or not the requirements of Article 123(2) EPC were fulfilled under this interpretation.

- For these reasons, 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 on the basis of the main request as filed on 10 December 1997 at oral proceedings before the Opposition Division or one of the auxiliary requests I, II, III or IV filed on 8 April 2002.

The Respondents requested that the appeal be dismissed.

Reasons for the decision

Main request

Rule 57a EPC

1. In their submission during opposition proceedings before the first instance (letter received on 29 June 1995), the Appellants justified the redrafting of the granted claims in accordance with which kind of cells are used in the claimed processes as a mean to facilitate the assessment of novelty and inventive step, the prior art concerning the use of genetically manipulated cells being quite different from that concerning hybridoma cells. The Board, thus, accepts that the redrafting was occasioned by grounds of opposition and considers as allowable under Rule 57a EPC the request resulting therefrom, which is now the main request under consideration.

Article 123(2) EPC; claim 1

2. The objection under Article 123(2) EPC by the Respondents is that the feature of

> *"... culturing genetically manipulated cells which constitutively produce said protein* ***in the continuous presence*** *of an alkanoic acid or a salt thereof, wherein the alkanoic acid or a salt thereof is present at a concentration of between 0.1mM and 200 mM..." (emphasis added by the Board)*

> is not disclosed in the application as filed. Indeed, the **continuous** presence of alkanoic acid in the culture medium within a given concentration range is not mentioned *expressis verbis* in said application.

3. In accordance with the case law of the Boards of Appeal

(T 187/91, OJ EPO 1994, 572, T 367/92 of 22 August 1996), the decisive question under Article 123(2) EPC is whether an added feature can be directly and unambiguously derived from the application as filed. In the present case, this implies that there should be a clear, albeit implicit basis in said application for the process feature that it is always present in the culture medium **within the claimed concentration range**.

4. The Appellants pointed to two passages as the basis for this feature: on page 8, lines 13 to 21, on page 9, second full paragraph, as well as to originally filed claim 7.

5. The passage on page 8 reads as follows:

"In the process according to the invention, the enhancing agent may be added to the culture medium at, before or after addition of the cells to the culture medium. If desired more than one addition of enhancing agent may be employed. Thus, for example, it may be desirable to add the enhancing agent at the beginning of the culture and then to add more enhancing agent as the culture proceeds, providing of course that the addition is closely controlled such that the concentration of enhancing agent does not go beyond that which is likely to reduce cell growth rate."

This passage tells the skilled person that it is important that the enhancing agent be present in the culture medium at all times but that care should be taken that it should not be present in such a high amount as would be deleterious to the cells. Yet, any direct or indirect reference to the necessity of

keeping **a defined minimal** amount of alkanoic acid in the culture medium is missing ie the continuous presence of alkanoic acid above a specific **minimal concentration** is not disclosed even implicitly.

6. The Appellants pointed out that the claimed minimal concentration (0.1mM) was well in excess of that corresponding to the amount of alkanoic acid likely to be consumed by the cells. This may well be true but it remains nonetheless that they will consume some of it and, therefore, if culturing is started at the claimed minimal concentration, then, at some point in time, the concentration of alkanoic acid in the culture medium will necessarily fall below this claimed minimal concentration. In contrast, when and how much alkanoic acid is to be added to the culture medium are not issues which are considered in the passage on page 8 (except for the highest concentration). Thus, as already mentioned in point 5, the skilled person could not derive from this passage, the necessity to retain a defined minimal amount of alkanoic acid.

7. The passage on claim 9 reads as follows:

"Thus, in another aspect the invention provides a process for the production of a protein which comprises ***maintaining*** *genetically manipulated or hybridoma cells which constitutively produce said protein in culture* ***in the presence of an agent*** *which enhances protein production wherein the agent is present at a concentration at which production of said protein is enhanced but which does not significantly reduce cell viability (e.g.) is substantially non-toxic to the cells."* (emphasis added by the Board).

This passage thus teaches that the enhancing agent must be present. Like the passage on page 8, it warns against it being in such a high amount as to damage the cells. It is, however, silent on any defined minimal concentration having to be maintained.

8. The same observation is all the more true for originally filed claim 7 which does not define any specific range for the concentration in alkanoic acid.

9. For these reasons, the Board concludes that the above cited passages and claim may be taken as a disclosure that the enhancing agent should be present throughout the culturing, yet, it is not possible to consider them as a clear and unambiguous teaching that the enhancing agent must be continuously present within the claimed specific concentration range.

10. When claim 1 is read in a literal manner, it can be interpreted as meaning that it is a property of the cells that "they constitutively produce the protein in the continuous presence of alkanoic acid or a salt thereof". Such cells which presumably would not constitutively produce the protein in the absence of alkanoic acid are not described in the application as filed. Indeed, cells which are constitutive producers are defined on page 5, lines 22 to 24 as those cells "*which do not need to be induced to produce the protein*" without any reference as to the growth conditions. Thus, under this interpretation of claim 1, there is also added subject-matter in the form of an hitherto undisclosed kind of cells.

11. For these reasons, the main request is refused for failing to fulfill the requirements of Article 123(2)

EPC.

Auxiliary requests I to IV

Article 123(2) EPC

12. Claim 1 of each of auxiliary requests I to IV contains the feature of culturing genetically manipulated cells **in the continuous presence** of an alkanoic acid or a salt thereof, wherein the alkanoic acid or a salt thereof is present at a defined concentration range. Thus, the same reasoning regarding Article 123(2) EPC applies as for claim 1 of the main request. Accordingly, it is concluded that the auxiliary requests are not allowable under Article 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey