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D E C I S I O N
of 21 May 1999

Case Number: T0727/95 - 3.3.4

Application Number: 86308092.5

Publication Number: 0228779

IPC: C12P 19/04

Language of the proceedings: EN

Title of invention:
Reticulated cellulose product, sheets formed therefrom, methods and microorganisms for their production

Patentee:
WEYERSHAEUSER COMPANY

Opponent:
Ajinomoto Co., Inc.

Headword:
Cellulose/WEYERSHAEUSER

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure - no"

Decisions cited:
T 0435/91, T 0409/91, T 0612/92

Catchword:
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Case Number: T 0727/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 May 1999

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 3 July 1995 concerning maintenance of European patent No. 0 228 779 in amended form.**

Composition of the Board:

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

Summary of facts and submissions

I. European patent No. 0 228 779 with the title "Reticulated cellulose product, sheets formed therefrom, methods and microorganisms for their production" was granted with 8 claims, on the basis of European application No. 86 308 092.5.

Claim 5 read as follows:

"5. A method of producing a reticulated cellulose as defined in claim 1 comprising:

a) culturing, under agitated culture conditions, a microorganism designated Acetobacter having the ability of microorganisms obtainable from ATCC 53264, ATCC 53263 and ATCC 53524 to produce a cellulose product under agitated culture conditions, in a liquid medium suitable for cellulose production at an average volumetric productivity of at least 0.1 g/l/hr over a period of time exceeding 70 hours, said micro-organism having a frequency of change in agitated culture conditions from cellulose producing forms to cellulose non-producing forms of less than 0.5% over the course of 42-45 generations, as determined by the appearance of cellulose non-producing colonies on solid medium, and

b) removing the reticulated cellulose product obtained."

Claim 1 related to a microbiologically produced reticulated cellulose. Dependent claims 2 to 4 specified further features of the cellulose of claim 1. Claims 6 to 8 related to microorganisms suitable for the production of said cellulose.

II. A notice of opposition was filed requesting the revocation of the patent in suit under Article 100(a) EPC (lack of novelty and inventive step) and under Article 100(b) EPC (lack of sufficient disclosure).

III. The Opposition Division maintained the patent in amended form.

IV. The Appellants (Opponents) filed an appeal, paid the appeal fee and submitted a written statement setting out the grounds of their appeal together with experimental data.

V. The Respondents (Patentees) submitted an answer to the grounds of appeal also accompanied by experimental data.

VI. This submission was answered by the Appellants.

VII. A communication was sent according to Article 11(2) of the Rules of Procedure of the Boards of Appeal, setting out the Board's provisional, non-binding opinion.

VIII. The Board's communication was answered by both parties who filed further declarations and experimental evidence.

IX. Oral proceedings took place on 23 March 1999. The Respondents submitted a new main request and one auxiliary request.

Claims 1 and 3 of the main request read as follows:

"1. A method of producing a reticulated cellulose having frequently thickened strands that interconnect to form a grid-like pattern extending in three

dimensions and demonstrating resistance to densification when formed into sheets by sheet forming-means, which method comprises:

a) culturing under agitated conditions, a microorganism designated Acetobacter having the ability of microorganisms ATCC 53264, ATCC 53263 and ATCC 53524 to produce a cellulose product under agitated culture conditions, which microorganism, when cultured in accordance with Example XII, has the capability both of producing cellulose at an average volumetric productivity of at least 0.1 g/l/hr over a period of time exceeding 70 hours; and exhibiting a frequency of change in agitated culture conditions from cellulose producing forms to cellulose non-producing forms of less than 0.5% over the course of 42-45 generations, as determined by the appearance of cellulose non-producing colonies on solid medium, and

b) removing the reticulated cellulose product obtained."

"3. A microorganism designated Acetobacter and having the ability of microorganisms ATCC 53264, ATCC 53263 and ATCC 53524 to produce a cellulose product under agitated culture conditions and having a frequency of change from cellulose producing forms to cellulose non-producing forms under agitated culture conditions, as determined by the appearance of cellulose non-producing colonies on solid medium, of less than 0.5% over the course of 42-45 generations; which also has, when cultured in accordance with Example XII, the ability to produce cellulose under agitated culture conditions at an average volumetric productivity of at least 0.1 g/l/hr over a period of time exceeding 70 hours."

Claim 3 of the auxiliary request differed from claim 3 of the main request insofar as the cellulose product was further defined.

X. The following documents on file are mentioned in this decision:

(45): Declaration by Dr. Shoda dated 31 October 1995,
(53): Declaration by Prof. Streeck dated 31 October 1995.

XI. The submissions in writing and during oral proceedings by Appellants relating to the requirements of Articles 83 and 123 EPC can be summarized as follows:

Article 123(2)(3) EPC

In the application as filed, the ability of the microorganisms Acetobacter (claim 1 a)) to produce cellulose was not defined in direct relation to the deposited strains.

In the same manner, the culture medium of Example XII was not originally disclosed in connection with Acetobacter strains in general but in connection with the specific strain 1603-11. Furthermore, it was not used as a medium in which to produce cellulose but as a growth medium to be used prior to cellulose production.

Example XII did not specify whether the growth medium should be liquid or solid, whereas granted claim 1 required that the growth medium be liquid. Thus, the replacement of the feature "liquid medium" by the feature "cultured in accordance with Example XII" amounted to a broadening of the scope of protection.

Article 83 EPC

Claims 1 to 4 were not restricted to a method to be carried out with the deposited microorganisms (claim 1 or 2) nor to deposited microorganisms (claim 3 or 4). The question was, thus, whether other microorganisms having the claimed productivity and stability could be isolated without undue burden.

It had been argued that the skilled person would consider conventional mutagenesis as a means to obtain them. Yet, the skilled person would not know which Acetobacter strain should be mutagenised. Furthermore, the essential step, namely the selection of a strain fulfilling the productivity and stability conditions, was not disclosed in an enabling manner.

The frequency of cellulose high-producers in a mutagenised population would be around 1 in 50, 000. The optical appearance of the mutagenized colonies was not an indication of their ability to overproduce cellulose (document (45)). Selecting the fast-growers in shake flasks would lead to cellulose non-producers being retained as these grew quicker than cellulose producers. It was undue burden to check the stability and productivity of each mutant in 14 liter fermentors because it could even take one or two years to isolate one of interest.

The case was not comparable to cases in the field of biotechnology where the knowledge of an appropriate DNA sequence gave the skilled person the possibility to rework the invention even in the scope of a broader claim to variants. This was impossible in the case of an invention directed to a random mutant where it was only by chance that another mutant having the required property would be created and where it was not possible

without undue burden to select such a mutant in the case where the selection step involved fermentation over 70 hours on a technical scale.

XII. The Respondents answered essentially as follows:

Article 123(2)(3) EPC

The application as filed disclosed that microorganisms which were functionally equivalent to the deposited strains for producing cellulose were within the scope of the invention.

The culture medium of Example XII was originally disclosed not only in connection with strain 1603-11 but also in connection with strain 1603-21 in Example XIII. In both examples, cellulose was produced from strains grown in this medium.

It was implicit from the wording of Example XII that the medium defined therein was a liquid medium.

Article 83 EPC

In biotechnology cases, the policy decision was that it was permissible to extrapolate from a cloned sequence to any sequences hybridizing to it. Thus, a very large number of molecules could be claimed although only one such molecule had been isolated and obtaining others may involve much work. As a legal matter, it was unfair and inappropriate to refuse a similar type of protection for a different technology involving the same kind of broad claims.

Given the starting point of the strains of the invention, it was not necessary for a process of mutation to be considered at all in relation to the provision of the relevant characteristics of the

invention. Yet, if mutants having further characteristics were required, they could be obtained without undue burden by classical mutagenesis of the deposited strains.

Stable cellulose high-producers could also be obtained without undue burden, performing classical mutagenesis on any Acetobacter strains. It would be possible to obtain 5000 mutants from one such mutagenesis. The first step in screening the mutants would then be to observe the morphology of the survivors to the mutagenesis: 400 to 500 survivors would be retained on this criterion. Their growth would then be tested in shake flasks and the slow-growers would be thrown out as it was advantageous for the purpose of industrial fermentation that the microorganisms grew well. This way to proceed narrowed down the number of mutants in the final screening. Thus, twenty to thirty fast-growers would be tested in 14 liter fermentors, which was quite feasible.

It would be unfair to require the Respondents to put an upper limit on the volumetric productivity as they were the first to disclose a productivity as high as the lowest claimed productivity.

XIII. The Appellants requested that the decision under appeal be set aside and that the European patent No. 0 228 779 be revoked and by way of auxiliary request the opportunity to file further experimental evidence.

The Respondents requested that the Appellants' auxiliary request be refused and that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request filed at the oral proceedings on 23 March 1999.

XIV. At the end of the oral proceedings after deliberation by the Board, the Chairwoman gave the following decision: "The decision of the Board will be notified in writing. No further submissions will be accepted unless the Board should decide that proceedings are to be continued and set a timetable for further submissions."

Reasons for the decision

1. The appeal is admissible.

Main request

Article 123(2)(3) EPC

2. On page 40, in the application as filed, it is stated that "any microorganism strains which are functionally equivalent to those deposited are considered to be within the scope of this invention." The objection that microrganisms were not originally defined in direct relationship to the deposited strains thus fails.

3. Example XII as filed discloses the production of cellulose by the strain 1603-11 in a medium called CSL medium, the composition of which is given on page 14. This medium is also used (albeit at a slightly lower concentration) in Example II to test the cellulose productivity of other Acetobacter strains (ATCC 31174, ATCC 2376A or B). The medium of Example XII was, thus, originally disclosed as a medium in which cellulose would be produced by Acetobacter strains in general.

4. The medium of Example XII is used in a fermentor under agitated conditions and, therefore, must be a liquid medium. There has been no extension of the scope of the claim by replacing the term "liquid medium" by the term "medium of example XII".

5. The requirements of Article 123(2)(3) EPC are fulfilled.

Article 83 EPC; sufficiency of disclosure

Main and Auxiliary requests, claims 3

6. These claims relate to Acetobacter microorganisms **having the ability** of the deposited microorganisms ATCC 53264, ATCC 53263 and ATCC 53254 in terms of cellulose production and frequency of change from cellulose producing forms to cellulose non-producing forms. By the wording "having the ability of", the claim covers not only Acetobacter microorganisms derived from the deposited strains, but also Acetobacter microorganisms which have the stated characteristics in common with the deposited strains.

7. Article 83 EPC requires that the European patent application disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In accordance with the case law of the Boards of Appeal, this provision has to be interpreted as meaning that the whole subject-matter which is defined in the claim should be enabled without undue burden by the teaching of the patent specification (see for example, T 409/91, OJ EPO 1994, 653; T 435/91, OJ EPO 1995, 188; T 612/92 of 28 February 1996). This requires, in the present case, that the patent specification gave sufficient information not only for the isolation of further

mutants of the deposited microorganisms but also for the isolation of stable, cellulose high-producing Acetobacter from a different genetic background.

8. On page 10 lines 7 to 12, Examples II and IV of the patent specification, a process is described whereby the deposited microorganism ATCC 53264 (1603-3) is mutated to glcA$^-$. The conditions in which to carry out the mutagenesis are specified as well as the test for screening the glcA$^-$ mutants. Example II shows how to test the stability of the cellulose producing phenotype and Example XII shows how to test the cellulose productivity. Accordingly, the Board sees no undue burden, starting from the deposited strain, to isolate other mutants of interest which would possess a selectable phenotype and would yet keep the claimed characteristics of cellulose productivity and stability. In this respect, the patent specification is enabling.

9. However, claims 3 of both requests also cover stable cellulose high-producers which are not derived from the deposited microorganisms. To assess the feasibility of isolating such strains, it is of interest to consider how a stable, cellulose high-producer was initially obtained, as is described on page 9, lines 20 to 25 of the patent specification: "The stable Acetobacter strains according to the invention were derived from an initial isolate of an initial isolate of a A. xylinum strain obtained ...under Accession No. NRRL B42. Growth of the NRRL strain on agar plates of R20-2 medium revealed two colony morphologies, one white, the other beige. Microscopically, the beige colonies have elongated rod shape cells typical of Acetobacter strain. This strain is designated 1306-3. Unlike the parent NRRL B42 strain, 1603-3 produces no water soluble polysaccharide ...".

10. There is no other information given in the patent. In particular, it is not disclosed that beige colonies which fail to produce said polysaccharide always are stable, cellulose high-producers. In fact, in their reply to the Board's communication, the Respondents stated: "Whereas it may be possible to find other such strains *(stable, high producers)* in nature, this is very far from being the total basis for sufficiency of disclosure. The Article 83 question does not depend on such further "strokes of luck". (words in brackets added by the Board).

11. In the Board's judgment, finding other stable, cellulose high-producing Acetobacter strains in nature is indeed a chance event and relying on chance for reproducibility amounts to undue burden in the absence of evidence that such chance events occur and can be identified frequently enough to guarantee success. There must exist other reliable means for producing such strains for sufficiency of disclosure to be acknowledged.

12. It was suggested that one such mean was classical mutagenesis. The Board would accept that at the priority date, improving bacterial properties by mutagenesis was a matter of common knowledge. Thus, the skilled person might have come to the idea of mutagenizing the already existing Acetobacter strains to cellulose overproducion, although the patent specification is totally silent as to embarking on such a course of action.

13. According to the Respondents, 400 to 500 survivors of the mutagenesis would be retained on the basis of their morphological appearance and tested in shake flasks for their growth properties. Those 20 to 30 amongst them which were fast-growers would be tested for their

cellulose productivity in 14 liter fermentors according to Example XII of the patent in suit and for their stability. Few such tests would have to be carried out to find the desired mutant.

14. Yet, at the same time, it was never argued that survivors producing high amounts of cellulose had a morphology which would help distinguishing them from survivors producing expected amounts of cellulose (such as those bacterial cells in the mutagenized culture which may have escaped the mutagenesis). Even if cellulose non-producers can be morphologically distinguished from cellulose producers, this does not help in screening for the **high**-producers.

15. Nor was the ability to grow fast ever linked to a high cellulose productivity or stability. Indeed, the patent in suit discloses on page 3, lines 25 to 27 that Acetobacter which do not produce cellulose grow faster under agitated conditions than cellulose producers. This property would tend to imply that unstable cellulose producers, ie cellulose producers which revert to cellulose non-producers at a high frequency would be seen as growing better than stable producers.

16. Thus, in the Board's judgment, the steps preceeding the testing in 14 liter fermentors are not suited to distinguish fast-growing micro-organisms which produce high amounts of cellulose from fast-growing microorganisms which produce expected amounts of cellulose. Nor are they suited to the selection of mutants stable in their cellulose producing capacity.

17. The question which, thus, remains, is whether it is undue burden to test fast-growing, cellulose producing survivors of the mutagenesis, individually in 14 liter fermentors, for being stable, cellulose high-producers. In case of the mutagenesis to glcA$^-$, the patent in suit

discloses on page 10, lines 9 to 12 that two glcA$^-$ mutants were obtained from a population of 8100 survivors. According to document (53) "there are many more possibilities to inactivate (destroy) a genetic function... than there are possibilities to increase the synthesis of a gene product". Thus, mutations to cellulose overproduction should be rarer than mutations to glcA$^-$. Nonetheless, one may accept for the sake of the argument that the frequencies of mutations to glcA$^-$ and to cellulose overproduction would be about the same. In this case, about 4000 survivors would have to be tested in 14 liter fermentors to isolate a high-producer. In the Board's judgment, this amounts to undue burden and it is not even sure that a suitable mutant will be obtained by testing such a high number of survivors.

18. The Board, thus, concludes that the subject-matter of claim 3 of the main request is not repeatable without undue burden over the entire breadth of the claim. Claim 3 of the auxiliary request differs from claim 3 of the main request in that the cellulose produced by the claimed microorganisms is further characterised. This feature does not change the conclusion with regard to sufficiency of disclosure.

19. The Respondents compared the present case to cases in the biotechnology field where the isolation and characterisation of a specific DNA was considered an acceptable basis to acknowledge sufficiency of disclosure in respect of a broad claim to the DNA **and** to DNAs hybridisable thereto. In their view, such claim covered an even greater number of compounds than the number of mutant strains which were covered by a claim

to Acetobacter microorganisms having the ability of deposited strains in terms of cellulose productivity and stability. And, therefore, it was only fair to acknowledge sufficiency of disclosure in respect of the broad claim in this case.

20. In drawing this comparison, the Respondents necessarily imply that there exists the same kind of relationship between the claimed microorganisms and the deposited strain as exists between the DNAs hybridizing to the claimed DNA and the claimed DNA, namely, that it is conceivable that the earlier might be derived from the latter. This would indeed be the case for the microorganisms comprised in claim 3 which, while keeping the cellulose productivity and stability of the deposited strains, are derived therefrom by the addition of further desired mutations (see point 6 above).

21. However, claim 3 is not limited to such microorganisms but also comprises Acetobacter microorganisms having the claimed cellulose productivity and stability which are not derived from the deposited strains. It is in relation to those that sufficiency of disclosure was found lacking. As the above reasoning does not apply to them, it cannot justify acknowledging sufficiency of disclosure over the full width of the claim.

Order

For these reasons, it is decided that:

1. The patent is revoked

The Registry: The Chairwoman:

U. Bultmann U. Kinkeldey