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D E C I S I O N
of 27 March 1996

Case Number: T 0441/93 - 3.3.4

Application Number: 83200714.0

Publication Number: 0096430

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Cloning system for Kluyveromyces species

Patentee:
GIST-BROCADES N.V.

Opponent:
RHONE-POULENC SANTE

Headword:
Cloning in Kluyveromyces/GIST BROCADES

Relevant legal provisions:
EPC Art. 87, 88, 89, 54, 56 114(2)
EPC R. 71(a)

Keyword:
"Priority (no)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
G 0003/93, T 0500/91, T 0455/91, T 0060/89, T 0223/92

Catchword:
If the Board concludes that a person skilled in the art would expect to have to perform scientific research rather than routine work in order to transfer a technology previously set up in one field of research to a neighbouring field, then inventive step may be acknowledged.

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Case Number: T 0441/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 March 1996

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 18 March 1993 rejecting the opposition filed against European patent No. 0 096 430 pursuant to Article 102(2) EPC.**

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. 0 096 430 (application No. 83 200 714.0) relating to "Cloning system for Kluyveromyces species" was granted with thirty claims. The priority of the earlier application NL 8 202 091 (19 May 1982) was claimed.

II. Claims 1, 16 and 23 of the patent as granted for all designated states except Austria read:

"1. A process for preparing a strain of the yeast *Kluyveromyces*, which comprises:

(1) transforming *Kluyveromyces* yeast cells with a vector comprising:
in the 5'-3' direction of transcription:

(a) a promoter regulation region functional in *Kluyveromyces;*
(b) a DNA sequence encoding a polypeptide under the regulation of said promoter regulation region;
(c) a transcription terminator; and joined thereto
(d) a selection marker; and
(e) an origin of replication functional in *Kluyveromyces;* and

(2) propagating the resultant transformed cells in a growth sustaining medium.

16. Use of *Kluyveromyces* as a host for the transformation and expression of foreign genes.

23. A *Kluyveromyces* expression vector comprising in the 5'-3' direction of transcription:

(a) a promoter regulation region functional in *Kluyveromyces*;
(b) a DNA sequence encoding a polypeptide under the regulation of said promoter regulation region;
(c) a transcription terminator; and joined thereto
(d) a selection marker; and
(e) an origin of replication functional in *Kluyveromyces*.

Claims 2 and 3 further specify that the yeast cells of claim 1 may be protoplasts or whole cells, respectively. Claims 4 to 14 relate to particular embodiments of the claimed process. Claim 15 is a process claim for preparing a polypeptide starting from *Kluyveromyces* obtained according to the process of claims 1 to 14. Claims 17 to 22 are addressed to specific, transformed *Kluyveromyces* cells, claims 24 to 30 to *Kluyveromyces* expression vectors, being specific embodiments of claim 23.

The claims for Austria correspond to the claims for the other Contracting States.

III. A notice of opposition was filed against the European patent, requesting revocation of the patent on the grounds of Article 100(a) and 100(b) EPC.

During the procedure before the Opposition Division, twenty-one documents were relied upon by the parties. Of these documents, the following are referred to in the present decision:

(2): Declaration of J.A. Van den Berg submitted to the EPO with Applicant's letter of 21 March 1986 during the examination proceedings.

(5): Beach D. and P. Nurse, Nature, vol. 290, pages 140 to 142, 1981

(6): Das S. and C. Hollenberg, Current Genetics, vol. 6, pages 123 to 128, 1982

(12): Gunge, N. et al., J. Bacteriol., vol. 145, no.1, pages 382 to 390, 1981

(17): Ito, H. et al., J. Bacteriol., vol. 153, no.1, pages 163 to 168, 1983

(21): Dickson R.C., Gene, vol. 10, pages 347 to 356, 1980

IV. By a decision dated 18 March 1993, the Opposition Division maintained the patent as granted.

It was decided that the specification of the European patent application contained enough examples backed up with the timely deposits of the relevant micro-organisms to ensure sufficiency of disclosure (Article 83 EPC).

It was also found that none of the cited documents disclosed the subject-matter of any of the claims on file, which were, thus, novel (Article 54 EPC).

The closest prior art was identified as being document (6). It was decided that said document (whether alone or in combination with other documents) did not make obvious how to isolate a recipient host or an origin of replication functional in *Kluyveromyces*. Thus, inventive step was acknowledged (Article 56 EPC).

V. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division, paying the appeal fee at the same time. A statement of grounds of appeal was submitted.

VI. The Board issued a summons to oral proceedings on the 27 March 1996, accompanied by a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal setting out the Board's preliminary position.

VII. An affidavit was filed by the Respondent with a letter dated 20 March 1996. By letter of 25 March 1996, the Appellant requested that this affidavit should not be admitted into the proceedings, as not filed in due time.

VIII. Oral proceedings took place on 27 March 1996. At the beginning of the oral proceedings, an interim main request was filed together with four auxiliary requests. The interim main request was later replaced by a "final main request".

Claims 1 to 22 of the "final main request" remained as granted, claim 23 was amended by the addition of the sentence " wherein said origin of replication is a KARS sequence" at the end of the claim, claims 24 to 29 were deleted, and claim 30 was renumbered claim 24.

IX. The arguments submitted by the Appellant in writing and maintained during oral proceedings can be summarized as follows.

- Claims 23 to 25 as granted lacked novelty over document (21) which disclosed a vector with the same structural features as disclosed in said claims.

- The priority application of the patent in suit did not disclose a process for transforming *Kluyveromyces* cells starting from whole cells. Claim 1 which was concerned with the

transformation of *Kluyveromyces* yeast cells in general and, thus, comprised transformation of whole cells enjoyed priority rights as from the filing date of the patent in suit.

- Setting up a cloning system for *Kluyveromyces* was an obvious project to try as shown by document (2).

- The closest prior art relative to the claims for a process involving the transformation of *Kluyveromyces* protoplasts was document (21). Said document disclosed the transformation of *Saccharomyces* protoplasts. It was obvious to reproduce the teachings of document (21) with *Kluyveromyces*, all the more so because the vector used in document (21) could also serve for the integrative transformation of the latter yeast. There could be reasonable expectation of success in view of document (5) which disclosed the successful transformation of *Schizosaccharomyces pombe* by the same method, whereas this yeast was much further from *Saccharomyces* in evolutionary terms than *Kluyveromyces* was.

- The closest prior art relative to the claims for a process involving the transformation of *Kluyveromyces* whole cells was document (6). Said document disclosed vectors which could be maintained in said yeast (KARS vectors) and their successful use in the transformation of *Kluyveromyces* protoplasts. Document (17) disclosed a process for the transformation of *Saccharomyces cerevisiae* whole cells. It was obvious to combine

the teachings of both documents to obtain the claimed process. Success could reasonably be expected in view of the close taxonomic relationship between *Kluyveromyces* and *Saccharomyces*.

- An objection raised initially, but not maintained at the oral proceedings, was that claims relating to a process for expressing chymosin were not entitled to the priority date.

X. The Respondent's submissions can be summarized as follows:

- A process for the transformation of whole cells was not mentioned in the application from which priority was claimed. Thus, claims specifically directed to such a process could only enjoy priority from the date of filing of the European patent application. As for the claims relating to a process for expressing chymosin, they enjoyed priority from the date of filing of the priority application, because, at the priority date, it required only routine work to isolate the chymosin DNA.

- Claim 1 was a generic claim based on the example of the transformation of protoplasts given in both the patent in suit and its priority application. Its right to an early priority date could not be denied as it concerned the same invention (transformed *Kluyveromyces*) as was disclosed in the priority document.

- In 1984, there was no incentive to transform *Kluyveromyces* yeasts, as *Saccharomyces* already provided an efficient host system for genetic engineering in lower eucaryotes.

- It could not be deduced from the fact that *Saccharomyces* and *Schizosaccharomyces* protoplasts were transformable by the same method (documents (21) and (5)) that *Kluyveromyces* protoplasts would also be transformed by that method because not all yeasts behaved in the same manner. A system was lacking with which to select the *Kluyveromyces* transformants. No evidence was available that KARS plasmids could be isolated. The frequency of transformation to be obtained with integrative plasmids was so low as to be about meaningless.

- Document (6) did not enable the isolation of stable, auxotrophic mutants of *Kluyveromyces*. Document (17) showed that some plasmids only transformed *Saccharomyces* cells with poor efficiency, which did not allow any extrapolation on whether any plasmid, even if capable of replication in *Kluyveromyces*, could be transformed into said cells. The taxonomic similarity between *Saccharomyces* and *Kluyveromyces* had been established by comparing their metabolic properties. It did not in any way imply that the technology of making cell walls permeable to DNA, which had been developed with *Saccharomyces* (document (17)) would apply to *Kluyveromyces*. Accordingly, there was no reasonable expectation of success that *Kluyveromyces* whole cells could be transformed.

XI. The Appellant requested that the decision under appeal be set aside and the patent No. 0096430 be revoked.

XII. The Respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the final main request or one of the first, second, third or fourth auxiliary requests submitted at the oral proceedings on 27 March 1996.

Reasons for the Decision

1. The appeal is admissible.

Late submitted facts and evidence (Article 114(2) and Rule 71a(1) EPC).

2. Only a few days before the oral proceedings, the Respondent introduced new evidence in the form of an affidavit from Prof. R.C. Dickson. The reason invoked for the belatedness of the filing was the impossibility of contacting Prof. R.C Dickson at an earlier time.

3. The summons to oral proceedings was sent to the parties three and a half months before the oral proceedings. The communication accompanying the summons clearly indicated that any further written submissions would only be accepted under the terms of Rule 71a(1) EPC and, more particularly, that the final date for making such submissions was one month before the date of the oral proceedings.

4. Thus, the Respondent was given two and a half months in which to contact Prof. Dickson and file the affidavit. The Board finds it difficult to accept that Prof. Dickson could not have been reached in this interval of

time, but, in any case, Prof. Dickson's affidavit refers to some documents (i.e. Genetics 95: 877-890 (1980) and Genetics 98: 729-745 (1980)) which are not on file and yet would have been essential for the proper assessment of the affidavit's content. For this reason, the Board regards the affidavit as not being submitted in due time, and pursuant to Article 114(2) does not allow it into the proceedings.

Allowability of requests

5. At the beginning of the oral proceedings, the main request on file was replaced by an interim main request (see section VIII above) which differed from the earlier one in that the expression "said expression vector being present in a transformed *Kluyveromyces* strain." was added at the end of claim 23. No reason was given why this new main request had not been filed within the time limit pursuant to Rule 71a(1) EPC stated in the communication accompanying the summons.

6. The Board believes that the introduction of new requests at such a late stage is detrimental to the smooth progression of the entire procedure. Such requests, if not prompted by the fact that the subject-matter of the proceedings has changed, are only acceptable if it is immediately apparent that they fulfil the formal requirements of Article 123(2), (3) EPC as well as those of Article 84 EPC.

7. In the present case, the limitation introduced in claim 23 creates doubt as to whether the subject-matter of the claim is an expression vector or a transformed host strain, and thus the amended claim is unclear contrary to the requirements of Article 84 EPC. Consequently, the Board refused to allow this newly filed request into the proceedings.

8. A final main request was, then substituted for the granted set of claims (see section VIII above). Although the Board is once more convinced that such request should have been filed at the latest by the time limit set in the communication accompanying the summons to oral proceedings, it is, nonetheless, prepared to accept the request into the proceedings because it is immediately apparent that none of the introduced changes leads to claims which would offend the requirements of Articles 123(2), (3) and 84 EPC (see points 9 and 10 below), the changes are made to remove objections previously raised in the proceedings, and are of a nature which the appellants can be expected to deal with after a few minutes consideration.

Main request

Formal requirements, clarity (Articles 123(2), (3) and 84 EPC)

9. The amendments with respect to the application as filed introduced into the set of claims of the main request allowed in the proceedings on 27 March 1996 consist in the deletion of granted claims 24 to 29 and in the addition of an expression at the end of granted claim 23, for which support may be found on page 7 and in Example 2 of the original description. The scope of claim 23 is restricted compared to that of the granted claim 23 in that the expression vectors which are claimed are specific in their replication origin. The requirements of Article 123(2), (3) are fulfilled.

10. Claim 23 is clear because the added expression does not introduce any ambiguity as to the nature of the claimed expression vector. The requirements of Article 84 EPC are, thus, also fulfilled.

Priority (Articles 87 to 89 EPC)

11. At oral proceedings, it was agreed by both parties that claims specifically directed to a process for the transformation of **whole cells** only enjoyed rights from the date of filing of the European patent application. It was also agreed that it was within the capacity of the skilled person to isolate and express the chymosin gene, so that no objections based on lack of enablement regarding the cloning and/or expression of the chymosin gene were maintained.

12. The question at issue is whether the whole of the subject-matter of claim 1 and dependent claims thereof is included in the Dutch application whose priority is claimed and, therefore, whether a priority right may be derived for said claims from said application in accordance with Article 88 EPC.

13. According to the Respondent, the invention which has been developed is "*Kluyveromyces* cells as hosts for transformation". Thus, it is irrelevant for determining priority rights, which process has been used to isolate *Kluyveromyces* host cells. The priority document which discloses the isolation of *Kluyveromyces* host cells by transformation of *Kluyveromyces* **protoplasts** constitutes a sound basis on which to acknowledge priority rights to the generic claim 1. The fact that claim 1 also covers the further embodiment of transforming **whole cells** does not change the nature of the invention i.e. *Kluyveromyces* as a host for transformation. Thus, in accordance with the case law of the European patent office that priority should be acknowledged if the invention of both the patent application and the priority document is the same, claim 1 should enjoy priority rights from the first filing.

14. The invention disclosed in the priority document is therein claimed as:

> A process for the preparation of new strains of the yeast Kluyveromyces, characterized in that
> - protoplasts of yeast cells belonging to the genus Kluyveromyces are mixed with and transformed by vector molecules which contain at least one gene for a selectable property and which can be cloned and expressed within the host cells,
> - the protoplasts are allowed to regenerate to complete cells with a cell wall,
> - the yeast cells are allowed to grow on a selection medium where the cells transformed by the vector can be distinguished by means of the selectable property from the other cells and are separated therefrom.

15. That these references to protoplasts are a critically important feature becomes evident when reading page 3, lines 26 to 32 of the translation of the priority document, where it is stated:

> "...yeast cells possess a cell wall impermeable for plasmids. Therefore, a usual preparatory step of yeast transformation is the removal of the cell wall yielding protoplasts which can be entered by plasmids."

16. No mention is ever in the priority document of any possibility of transforming whole cells. On the evidence put before the Board, the skilled man would not have been able to carry out such a process on the basis of the information in the priority document and the knowledge in the art at the priority date.

17. Since claim 1 is directed to a **process** for transforming *Kluyveromyces*, the Board cannot agree with the Respondent that it is irrelevant for determining the priority date to which claim 1 is entitled, what process has been disclosed in the application from which they seek to claim priority, but rather considers this of critical importance.

18. Even the Respondent accepts that claim 3, which is dependent on claim 1 and is directed specifically to a process of transforming whole cells of *Kluyveromyces*, is entitled only to the date of filing the European application, and the Board agrees with this view. For the Board it follows that insofar as Claim 1 covers whole cell transformation, it too can only be entitled to the filing date of the European application. It may be the case that all transformed *Kluyveromyces* cells which can be made using a whole cell transformation process can also be made using the protoplast transformation process of the priority document. But even this would not mean that Claim 1 is entitled to the priority date for process aspects neither disclosed nor enabled by the priority document.

19. Accordingly, the Board holds that claim 1 is entitled to the filing date of the priority application only insofar as it relates to the transformation of *Kluyveromyces* protoplasts.

20. The claims can, thus, be divided into two groups with regard to priority:

Group A enjoying priority rights from 19 May 1982 and comprising claim 1, insofar as directed to a process for the transformation of *Kluyveromyces* protoplasts, claim 2, claims 4 to 14 when dependent on claim 1 as just defined, and claims 15 to 24; and

Group B enjoying priority rights from 19 May 1983, and comprising claim 1, insofar as not directed to a process for the transformation of *Kluyveromyces* protoplasts, claim 3, and claims 4 to 14 when dependent on this latter aspect of claim 1.

Novelty (Article 54 EPC)

21. Lack of novelty over document (21) has been argued against granted claim 23 and its dependent claims 24 and 25. Claim 23 of the "final main request" differs from the granted claim 23 in that it has been limited to expression vectors with a KARS (*Kluyveromyces* **a**utonomously **r**eplicating **s**equence) sequence as origin of replication. This limitation endows the claim (and its dependent claims) with novelty over the teachings of document (21) which discloses an expression vector with an origin of replication which comes from the 2-micron yeast plasmid.

22. No other document on file jeopardizes the novelty of any of the claims. Novelty can, thus, be acknowledged.

Inventive step (Article 56 EPC)

Group A of claims:

23. None of the documents which were published before the date of filing of the priority application relate to the genetic engineering of *Kluyveromyces*. The closest prior art is, thus, document (21) which describes the transformation of auxotrophic mutants of *Saccharomyces cerevisiae* with three kinds of recombinant vectors differing in their ability to replicate: integrative, ars and 2 micron-type vectors. The experiment requires in particular, that, after regeneration of the protoplasts, the transformants be selected on a medium where the auxotrophic parental cells would not grow.

24. Starting from this prior art, the problem to be solved can be considered as the provision of another yeast as a host for the transformation and expression of foreign genes, and a process and plasmid for achieving this.

25. The solution provided by the patent in suit is the claimed Kluveromyces protoplast transformation process, and the claimed plasmid, which for the Board plausibly solve this problem.

26. At the given priority date, *Kluyveromyces* was one of the few yeast genera used commercially beside the genus *Saccharomyces*. It was considered as particularly efficient in enzyme production, as it consumed less energy and was better suited than *Saccharomyces* for the extraction and recovery of the enzymes. Thus, one may assume that it was obvious in theory to try and set up a transformation system for this yeast as had been done with *Saccharomyces*.

27. The relevant question with regard to inventive step is, however, whether the skilled person in practice would have chosen to try and develop transformation technology for *Kluyveromyces* because he or she had a reasonable expectation of success. Document (5), which

relates to the transfer of the cloning technology from *Saccharomyces* to the fission yeast *Schizosaccharomyces pombe* should be taken into account in this context.

28. Document (5) discloses that the transformation of *Schizosaccharomyces pombe* can be achieved with some but not all 2 micron-type plasmids, without any apparent reasons for this difference. The frequency of transformation with integrative plasmids is quite low. *Schizosaccharomyces* autonomously replicating sequences endow the plasmids which carry them with the ability to replicate in *Schizosaccharomyces*, albeit unstably. The selection of the transformants is only feasible if a *Saccharomyces* marker is available which is capable of complementing the specific auxotrophic defect carried by the *Schizosaccharomyces pombe* host strain.

29. Thus, at the priority date, there existed experimental evidence that the replication of the cloning vector and the selection of transformants were two potential areas where difficulties could occur when transferring transformation technology from *Saccharomyces* to another yeast. More specifically, these difficulties would have been expected to occur while attempting to transform *Kluyveromyces*, as no *Kluveromyces* autonomously replicating sequence had ever been isolated and no *Kluyveromyces* mutants had ever been characterized in terms of their specific genotypes i.e. it was not possible to foresee which *Saccharomyces* marker, if any, should be used as a selective marker.

30. Additionally, both parties agree that, at the priority date, the regeneration of *Kluyveromyces* protoplasts was considered as notoriously difficult to achieve.

31. The Board, thus, believes that, in view of the multiplicity and the complexity of problems to be solved, achieving the transformation of *Kluyveromyces* required a substantial amount of work which was not of a routine nature but rather required scientific research, the outcome of which remained uncertain.

32. A number of decisions in the field of biotechnology have already provided a definition of the notional skilled person (see T 0060/89, OJ EPO 1992, 268, point 2.2.4 of the Reasons, T 0500/91, dated 21 October 1992, point 2.2 of the Reasons, T 0455/91, OJ EPO 1995, 684, point 5.1.3.3 of the Reasons, T 0223/92, dated 20 July 1993).

According to T 0500/91 (supra), the development of the art normally expected by the skilled person does not include solving technical problems by performing scientific research in areas not yet explored.

In T 0455/91 (supra), it has furthermore been established that the notional skilled person will perform a transfer of technology from a neighbouring field to his/her specific field of interest, if this transfer involves routine experimental work comprising only routine trials.

33. Taking simultaneously into account the previous findings (point 31, supra), and this definition of the notional person skilled in the art, the Board comes to the conclusion that this person would not derive from the prior art any assurance that he or she could develop a process for the transformation of *Kluyveromyces* protoplasts with a reasonable expectation of success, because he or she would see that the transfer of existing technology set up for a neighbouring field of research would require scientific

research rather than routine work. Therefore, inventive step may be recognized to the process claims of Group A. It follows from this conclusion that the use of *Kluyveromyces* as a host for the transformation and expression of the cloned foreign genes (claim 16) as well as the vector necessary to carry out the process (claim 23) are also considered inventive.

Group B of claims:

34. Taking into account the answer to the question of law involving the treatment of documents published during the priority interval given in the opinion G 0003/93 (OJ EPO 1995, 18) of the Enlarged Board, document (6) must be treated as prior art for those claims which do not enjoy a right to priority. This document is a publication by the inventors of the patent in suit themselves, corresponding substantially to the contents of the priority document, which publication was published between the date of filing of the Dutch priority application and date of filing of the European patent application. Document (6) describes a process for obtaining transformed *Kluyveromyces* cells which involves isolating **protoplasts**, introducing plasmid DNA into them, regenerating them into whole cells and selecting those cells which have been transformed. One type of plasmids which may, thus, successfully be transferred to and expressed in *Kluyveromyces* contains a *Kluyveromyces* autonomously replicating sequence as origin of replication. For the Group B of claims document (6) is thus the closest prior art.

35. Poor regeneration of the protoplasts is singled out by the authors as one of the reasons why the transformation process is inefficient. The measure taken to enhance the number of regenerated

transformants is to add KCl to the medium. It results in an increase of the transformation frequency by a factor of three. This frequency, nonetheless, remains three fold lower than that obtained under the same conditions with *Saccharomyces cerevisiae*.

36. Starting from this prior art, the problem to be solved is considered to be the setting up of an alternative method for *Kluyveromyces* transformation which avoids the problem posed by the regeneration of protoplasts.

37. The solution which is provided by the patent in suit is a method to transform *Kluyveromyces* whole cells.

38. The method is already known from Document (17) for the transformation of *Saccharomyces cerevisiae* whole cells. It involves the permeabilisation of these cells by a $LiCl_2$-heat treatment and the introduction into the permeabilized cells of autonomously replicating plasmids which are stably maintained and expressed. The frequency of transformation is the same as that obtained with protoplasts.

41. In the Board's opinion, the satisfactory results obtained with *Saccharomyces cerevisiae* could probably encourage the person skilled in the art to try the method with *Kluyveromyces*.

42. The relevant question with regard to inventive step is, however, whether this person would have felt reasonably confident of success while assuming that the transfer of technology would routinely work without any unexpected problems to be overcome.

43. Document (6) shows that KARS plasmids are stably replicated and expressed, once introduced into *Kluyveromyces*.

Thus, the key point which remains to be considered is whether the permeabilisation of *Kluyveromyces* cell walls would have been thought achievable by the same means as with *Saccharomyces*.

44. The Appellant argues that it certainly would in view of the very close relationship between both genera.

45. The Board, however, notices that this relationship has been established on taxonomic criteria. It, thus, essentially implies that the yeasts are compared for their metabolic properties such as substrate assimilation and resistance to metals. A similarity established on these phenotypic criteria does not necessarily mean that both yeasts are similar in terms of the genetic pathways leading to the observed metabolic properties. It is **a fortiori** uninformative as to the similarity of the barriers caused by their respective cell walls.

46. Further, it was common general knowledge that both yeasts differed in a number of respects at the genetical level: they do not cross with each other and respectively grow as haploid and polyploid. Furthermore, *Kluyveromyces* has linear plasmids (document (12)) .

47. It is the Board's opinion that, in the absence of any suggestion from the prior art that the cell walls of both yeasts might behave in a similar fashion, the skilled person would not have reasonably expected to transfer the technology developed for permeablizing *Saccharomyces* cell walls to *Kluyveromyces*, by simple routine experimentation but might rather have expected that scientific research would be necessary to succeed.

Accordingly, the same reasoning with regard to inventive step as in points 27 and 33, **supra** also prevails with regard to the Group B of claims and inventive step is acknowledged.

48. In view of what precedes, the Board decides that the final main request introduced into the proceedings on 27 March 1996 fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the final main request submitted at the oral proceedings on 27 March 1996.

The Registrar: The Chairwoman:

L. McGarry U. M. Kinkeldey