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D E C I S I O N
of 9 March 2006

Case Number: T 1336/04 - 3.3.08

Application Number: 91908986.2

Publication Number: 0531315

IPC: C12N 9/42

Language of the proceedings: EN

Title of invention:
An enzyme capable of degrading cellulose or hemicellulose

Patentee:
Novozymes A/S

Opponent:
GENENCOR INTERNATIONAL INC.

Headword:
Cellulase/NOVOZYME

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Keyword:
"Main request, first and second auxiliary requests - added subject-matter (no)"
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
T 0153/93, T 0386/94, T 0767/95, T 0345/01, T 0090/03, T 1329/04

Catchword:
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Case Number: T 1336/04 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 9 March 2006

Appellant: (Proprietor of the patent)
Novozymes A/S
Krogshoejvej 36
DK-2880 Bagsvaerd (DK)

Representative:
Bassett, Richard Simon
Eric Potter Clarkson LLP
Park View House
58 The Ropewalk
Nottingham NG1 5DD (GB)

Respondent: (Opponent)
GENENCOR INTERNATIONAL INC.
925 Page Mill Rd.
Palo Alto
CA 94304-1013 (US)

Representative:
Kremer, Simon Mark
Mewburn Ellis LLP
York House
23 Kingsway
London WC2B 6HP (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 20 August 2004 revoking European patent No. 0531315 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: F. Davison-Brunel
Members: P. Julià
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 0 531 315 with the title "An enzyme capable of degrading cellulose or hemicellulose" was granted on the basis of European patent application No. 91 908 986.2 with 18 claims for all designated Contracting States except Spain (ES) and with 10 claims for ES. The patent was opposed on the grounds of Articles 100(a), (b) and (c) EPC. On 29 January 2001, the opposition division revoked the patent because the granted claims were considered to contravene Article 123(2) EPC.

II. The patentee lodged an appeal against the interlocutory decision of the opposition division. In the course of appeal proceedings, the appellant maintained the claims as granted as main request and filed auxiliary requests 1 and 2 (AR1, AR2). The then competent board decided that the main request and AR1 did not fulfil the requirements of Article 123(2) EPC. These requirements were found to be fulfilled by AR2 and, pursuant to Article 111 EPC, the board remitted the case to the opposition division for further prosecution on the basis of this auxiliary request (cf. T 345/01 of 14 February 2003).

III. In its interlocutory decision of 20 August 2004, the opposition division decided that the main request, which corresponded to the AR2 underlying decision T 345/01 (*supra*) and auxiliary requests 1 to 3 filed on 30 January 2004 did not fulfil the requirements of Article 56 EPC. Furthermore, the main request and the auxiliary requests 1 and 2 were found not to fulfil the requirements of Article 83 EPC.

IV. An appeal was lodged by the patentee (appellant), who filed the statement of grounds of appeal on 21 December 2004 and requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request and the auxiliary requests 1 to 3 that had been considered by the opposition division in the decision under appeal. On 13 May 2005, the opponent (respondent) replied to the grounds of appeal.

V. Summons to oral proceedings were sent on 20 October 2005. In a communication annexed thereto (Article 11(1) of the Rules of Procedure of the Boards of Appeal, OJ EPO 2003, 89), the parties were informed of the board's preliminary opinion.

VI. On 9 February 2006, both appellant and respondent filed further observations in reply to the board's communication.

VII. Oral proceedings took place on 9 March 2006. During oral proceedings the appellant withdrew all auxiliary requests and filed new auxiliary requests 1 and 2.

VIII. Claim 1 of the **main request** for all designated Contracting States except ES read as follows:

"A cellulose- or hemicellulose-degrading enzyme which is derivable from a fungus other than *Trichoderma* or *Phanerochaete*, and which comprises a carbohydrate binding domain homologous to a terminal A region of *Trichoderma reesei* cellulases, wherein the carbohydrate

binding domain comprises the following amino acid sequence

Trp Gly Gln Cys Gly Gly Gln Gly Trp Asn Gly Pro Thr Cys Cys Glu Ala Gly Thr Thr Cys Arg Gln Gln Asn Gln Trp Tyr Ser Gln Cys Leu;

Trp Gly Gln Cys Gly Gly Ile Gly Trp Asn Gly Pro Thr Thr Cys Val Ser Gly Ala Thr Cys Thr Lys Ile Asn Asp Trp Tyr His Gln Cys Leu;

Trp Gly Gln Cys Gly Gly Ile Gly Phe Asn Gly Pro Thr Cys Cys Gln Ser Gly Ser Thr Cys Val Lys Gln Asn Asp Trp Tyr Ser Gln Cys Leu;

Trp Gly Gln Cys Gly Gly Asn Gly Tyr Ser Gly Pro Thr Thr Cys Ala Glu Gly - Thr Cys Lys Lys Gln Asn Asp Trp Tyr Ser Gln Cys Thr Pro;

Trp Gly Gln Cys Gly Gly Gln Gly Trp Gln Gly Pro Thr Cys Cys Ser Gln Gly - Thr Cys Arg Ala Gln Asn Gln Trp Tyr Ser Gln Cys Leu Asn;

Trp Gly Gln Cys Gly Gly Gln Gly Tyr Ser Gly Cys Thr Asn Cys Glu Ala Gly Ser Thr Cys Arg Gln Gln Asn Ala Tyr Tyr Ser Gln Cys Ile;

Trp Gly Gln Cys Gly Gly Gln Gly Tyr Ser Gly Cys Arg Asn Cys Glu Ser Gly Ser Thr Cys Arg Ala Gln Asn Asp Trp Tyr Ser Gln Cys Leu;

Trp Ala Gln Cys Gly Gly Asn Gly Trp Ser Gly Cys Thr Thr Cys Val Ala Gly Ser Thr Cys Thr Lys Ile Asn Asp Trp Tyr His Gln Cys Leu;

Trp Gly Gln Cys Gly Gly Gln Asn Tyr Ser Gly Pro Thr Thr Cys Lys Ser Pro Phe Thr Cys Lys Lys Ile Asn Asp Phe Tyr Ser Gln Cys Gln; or

Trp Gly Gln Cys Gly Gly Asn Gly Trp Thr Gly Ala Thr Thr Cys Ala Ser Gly Leu Lys Cys Glu Lys Ile Asn Asp Trp Tyr Tyr Gln Cys Val

or a subsequence thereof capable of effecting binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate."

Claims 2 to 6 were embodiments of claim 1, wherein claim 3 defined eight further amino acid sequences comprised in the linking B region that connected the carbohydrate binding domain (CBD) to the catalytically active domain of an enzyme of claims 1 or 2. Claims 7 to 10 related, respectively, to a DNA construct comprising a DNA sequence encoding an enzyme of any of claims 1 to 6, to an expression vector carrying said DNA construct, and to a cell transformed with this DNA construct or expression vector. Claim 11 was directed to a method of producing the enzyme of any of claims 1 to 6 using transformed cells. Claims 12 and 13 were concerned with an agent for degrading cellulose or hemicellulose comprising an enzyme of any of claims 1 to 6. Claims 14 and 15 were directed, respectively, to specific amino acid sequences comprised in the CBD (and subsequences thereof) and in the linking B region.

IX. **Auxiliary request 1** (AR1) for all designated Contracting States except ES read as the main request except for the deletion of claims 4, 5 (with consequent

renumbering) and of claims 14 and 15 and the limitation of claim 1 to the eighth amino acid sequence of claim 1 in the main request.

X. **Auxiliary request 2** (AR2) for all designated Contracting States except ES read as AR1 except for the deletion of references to any subsequence in claim 1.

XI. The corresponding sets of claims were filed for ES.

XII. The following documents are mentioned in the present decision:

(3): J. Knowles et al., Trends in Biotechnology, 1987, Vol. 5, pages 255 to 261;

(4): P. Sims et al., Gene, 1988, Vol. 74, pages 411 to 422;

(11): WO-A-89/09259 (publication date: 5 October 1989);

(15): M. de O. Azevedo and A. Radford, Nucleic Acid Res., February 1990, Vol. 18(3), page 668;

(16): "Description of PASC assay", filed with patentee's letter dated 30 January 2004;

(17): A report from the patent proprietor filed with submissions dated 21 December 2004 and entitled: "In silico hybridization of three DNA sequences to the *Humicola insolens* Endoglucanase V cDNA sequence", pages 1 to 17;

(19): "Chambers Twentieth Century Dictionary", Ed. by A.M. Macdonald BA(Oxon), edition 1972, pages 20 and 412.

XIII. Appellant's arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Main request
Article 123(2) EPC

According to the established case law, the same binding effect applied to a subsequent appeal in respect of an earlier decision of a board of appeal as it applied to the department of first instance. Insofar as the facts were the same, the board was, thus, bound by the *ratio decidendi* of the earlier decision T 345/01 (*supra*). Since the main request did not differ from the AR2 found to fulfil the requirements of Article 123(2) EPC by the then competent board of appeal, the issue of conformity with this article was *res judicata* and may not be investigated anymore.

Article 54 EPC; Claim 1 relating to enzymes with a CBD comprising a subsequence capable of effecting binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate.

Document (19) showed that the term "affect" meant "to act upon or to influence" in contrast to the term "effect" which meant "to produce; to accomplish; to bring about or to cause". Hence, the CBD subsequence referred to in the claim had to be capable of **accomplishing** the binding to cellulose. The

respondent's argument that a subsequence capable of **influencing** (affecting) the binding was comprised within the claim implied that said subsequence could be as short as a single amino acid since individual amino acids were expected to contribute to the binding and thus, it was not technically sensible. The CBD subsequences identified by the respondent as being in documents (4) and (15) as well as in the CBD sequences of the claims had not been shown to **effect** the binding to cellulose and, therefore, could not be detrimental to novelty.

Article 56 EPC; Claim 1

The closest prior art document (3) gave the skilled person an incentive to look for new cellulases and genes encoding them. However, document (3) gave no guidance as to how to isolate them. The document described the presence of homologous terminal domains within four cellulases from *Trichoderma reesei* but there was no indication that similar domains were to be found in other cellulases. In fact, these homologous terminal domains from *Trichoderma* were described as being different from the domains found in two cellulases from *Cellulomonas*. Document (3) referred to the great variety in the structure of different cellulases and to their very dissimilar primary structure even when comparison was made among cellulases derived from a single organism. The comparison of carbohydrate binding proteins with known three dimensional structures showed that there was a surprising amount of diversity in their tertiary structures and, therefore, in their CBDs as well.

Since the activity of the cellulose-degrading enzymes was defined by their catalytic domains, which were of much larger size than the CBDs, the skilled person would have obviously used the full-length sequence of the known cellulase genes or oligonucleotide probes derived from these catalytic domains for screening cDNA libraries. There was no hint in the prior art inciting the skilled person to use an oligonucleotide probe derived only from the CBD.

Document (4) reported the cloning of cellobiohydrolase I (CBHI) gene from *Phanerochaete chrysosporium* using as a probe a genomic fragment from *T. reesei* which encompassed half of the coding region of the CBHI gene (Figure 1). However, there was no evidence on file showing that this probe comprised a sequence encoding the CBD. Although document (4) referred to the homology between the C-termini of the CBHI enzymes from *P. chrysosporium* and *T. reesei*, the comparison of their complete amino acid sequences showed other regions with homology, in particular in their catalytic domain (Figure 9). There was no suggestion that homologous terminal CBDs were to be found in all cellulases nor an indication that probes derived therefrom could be of any particular relevance. In fact, the presence of homologous CBDs in other fungi could not be directly predicted from document (4), since their presence in both the phylogenetically unrelated *P. chrysosporium* and *T. reesei* could be due to a recent horizontal genetic exchange between these fungi.

Document (15) disclosed the cloning of the CBHI gene from *Humicola grisea* var. *thermoidea* using as a probe essentially the entire coding region of the CBHI gene

from *P. chrysosporium*. Although the putative amino acid sequence encoded by the CBHI gene was disclosed, there was no reference to the domains of the enzyme nor to the presence of any homology with other CBHI enzymes or domains thereof.

Thus, the selection of an oligonucleotide probe derived from the CBD could not be plainly inferred from this prior art and the cloning strategy of the patent in suit was not obvious to the skilled person. A contrario, there was evidence on file showing that a probe derived from the CBD was essential for obtaining the enzymes of the patent.

Document (17) (cited as expert opinion) showed that probes directly derived from the prior art, i.e. CBHI genes from *T. reesei*, *H. grisea* or *P. chrysosporium*, did not hybridize to a cDNA sequence encoding the endoglucanase V (EGV) from *H. insolens* which comprised the eighth amino acid sequence of claim 1. Since all sequences of claim 1 were closely related, the results obtained for EGV could be reasonably extrapolated to the other sequences of claim 1. None of these sequences could thus be isolated using the probes directly available from the prior art.

As for document (16), it showed that the EGV from *H. insolens* was unexpectedly more active (145%) than other known cellulases, such as the EGI from *T. reesei*. Since all sequences of claim 1 were closely related, the surprising results obtained for the EGV could be reasonably extrapolated to all other sequences. Although filed in 2004, this evidence could be taken into account in the assessment of inventive step

because it supplemented the technical contribution disclosed in the patent. The present situation was thus different from the one underlying decision T 1329/04 of 28 June 2005, in which inventive step was denied because it was solely on the basis of post-published evidence that the then claimed subject-matter could be identified as a bona fide solution to the problem to be solved.

In summary, the patent in suit disclosed an inventive cloning strategy using a non-obvious probe and also provided advantageous cellulases that were themselves inventive. Claims concerned with specific CBDs or linker sequences were also inventive, since they were directly derived from this cloning strategy and they were only "part" of the complete (inventive) cellulases.

Auxiliary requests 1 and 2
Article 56 EPC; Claim 1

The subject-matter of claim 1 of both these requests was limited to a cellulose- or hemicellulose-degrading enzyme comprising a CBD comprising the eight amino acid sequence shown in claim 1 of the main request (with or without subsequences derived therefrom, respectively, AR1 or AR2). Evidence was on file showing that an endoglucanase comprising this specific CBD had an advantageous higher activity. It was plausible that this specific CBD also improved the performance of other cellulases, since lower cellulose-degrading activity was found with other CBDs. The unexpected effect disclosed in document (16) could reasonably be extrapolated to all cellulases that comprised this specific CBD. There was no evidence on file showing

that such extrapolation was wrong or not reasonable. Thus, inventive step was to be acknowledged on the basis of this advantageous effect.

XIV. Respondent's arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Main request
Article 123(2) EPC

Article 100(c) EPC was a ground for opposition from the beginning of the proceedings. It was always within the discretion of the board to decide whether an argument was so relevant as to need to be considered. This was the case for the argument under Article 123(2) EPC which was presented in the course of this appeal.

Article 54 EPC; Claim 1 relating to enzymes with a CBD comprising a subsequence capable of effecting binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate.

The binding of cellulose to a CBD was a quantitative effect. However, there was no indication in the claims nor in the description, of the degree of binding required for the CBD subsequences referred to in the claims to be considered as being able to bind to cellulose. In the absence of any indication, the only technically sensible interpretation of the term "capable of effecting binding" was that these CBD subsequences only had "to contribute" or "to play a role" in the binding to cellulose.

Document (15) disclosed the CBHI gene of *H. grisea* var. *thermoidea* encoding a cellobiohydrolase. The CBD at the C-terminus of the amino acid sequence comprised several subsequences which were also found in the CBD sequences of claim 1. Since these subsequences were conserved in all known CBD, it was reasonable to assume that they played an important role in effecting the binding to cellulose in the same manner as the CBDs disclosed in the patent in suit were assumed "to effect" the binding of the enzyme to cellulose on the basis of sequence homology with known CBD sequences. The teaching of document (15) was thus detrimental to the novelty of claim 1.

Article 56 EPC; Claim 1

The closest prior art document (3) referred to four cellulases from *T. reesei* having homologous terminal domains and the same basic architecture as other known cellulases (catalytic domain and CBD joined by a linking B region). Although there was no reference to the presence of these homologous domains in cellulases from other organisms, the attention of the reader was nevertheless drawn to a document (document (4) on file) disclosing that a gene had been isolated from *P. chrysosporium* which was similar but not identical to the *T. reesei* CBHI gene. In fact, the person skilled in the field of cellulose-degrading enzymes was well aware of documents (4) and (15) which disclosed cellulases with homologous terminal CBDs.

Starting from the closest prior art, the problem to be solved was the provision of alternative cellulases comprising a CBD homologous to the ones from *T. reesei*

but different therefrom. Claim 1 purportedly provided cellulases comprising those homologous CBD sequences. The problem was not, however, credibly solved since the activity of the alleged cellulases was not shown in the patent and it could not be directly derived from the disclosed CBDs, which were not the catalytic domain of these enzymes.

Homologous terminal CBDs were known to be present in the cellulases disclosed in documents (3), (4) and (15). The selection of probes based on these homologous CBDs was almost a "one-way-street" situation associated with a reasonable expectation of success. Nothing inventive could be seen in the use of these probes for which sequences and function were already described in the prior art.

Document (17) showed that a cDNA encoding the EGV from *Humicola* did not hybridize (using a very particular set of stringency conditions, which were not representative of the ones used in the prior art) to cDNAs encoding the CBHI from different organisms. This evidence was irrelevant since it was obvious to the skilled person that probes based on the known homologous terminal CBDs were a better choice than a sequence encoding the full-length CBHI enzyme or the catalytic domain thereof.

Document (16) was also not suited to prove that the claimed enzymes had unexpectedly advantageous properties since deficiencies could be identified in the protocol used to obtain the results described. In particular, only a single, very specific type of substrate was used, there was no indication of the kinetics of the reaction and the enzymes compared

therein were of different types, namely the endoglucanase I (EGI) from *T. reesei* and the EGV from *H. insolens*. These enzymes had different specificities, optimal conditions of activity, storage requirements, etc. Moreover, the alleged results obtained with the EGV from *H. insolens* could not be extrapolated to the other enzymes of claim 1, which comprised hemicellulose-degrading enzymes of a very different nature from that of the EGV (specificity, activity, etc.). In any case, the cloning strategy disclosed in the patent was obvious to the skilled person and thus, the claimed sequences were also obvious to achieve. If a surprising effect was associated to those sequences, then it was only a bonus that could not make them less obvious.

In line with the established case law (T 1329/04, *supra*), post-published evidence could not serve as the sole basis to establish that a patent solved the problem that it purported to solve. In the present case, the patent did not disclose any activity for the enzymes of claim 1, their structure was incompletely characterised (partial amino acid sequence of only one of their domains, namely the CBD), and no further structural or functional features were described. Since the technical problem addressed by the patent was not credibly solved in the patent per se, document (16) which aimed at demonstrating the advantages of the alleged solution should not be taken into account.

Auxiliary requests 1 and 2
Article 56 EPC; Claim 1

Claim 1 was not restricted to the specific EGV from *H. insolens* - i.e. comprising a defined catalytic domain, linker B region and CBD sequence - used in document (16). There was no reason nor any evidence on file that allowed an extrapolation of the results obtained with EGV (alleged high activity) to other enzymes that shared only a common CBD sequence. Thus, even if the results obtained in document (16) in relation to EGV were considered surprising – which they should not be – they could not serve as a basis to acknowledge inventive step to the other enzymes.

XV. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request as filed with the grounds of appeal, alternatively on the basis of the first or second auxiliary request as filed during oral proceedings.

XVI. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Main request
Article 123(2) EPC

1. The respondent's submissions dated 9 February 2006 contained an argument under Article 123(2) EPC against claim 1 of the main request. In accordance with the

established case law, the same binding effect applies to a subsequent appeal in respect of an earlier decision of a Board of Appeal as it applies to the department of first instance (cf. "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, VII.D.10.1 and *inter alia* T 153/93 of 21 February 1994, point 2 of the Reasons). In the present case, the main request is identical to the second auxiliary request considered in the earlier decision T 345/01 (*supra*). The present board is, consequently, bound by the *ratio decidendi* of this earlier decision (Article 111(2) EPC), which found the second auxiliary request to fulfil the requirements of Article 123(2) EPC (cf. T 345/01, *supra*, point 9 of the Reasons). Otherwise stated, the allowability of the main request under Article 123(2) EPC is a matter which has already been settled and may not be given any further consideration.

Article 54 EPC;
Claim 1 relating to enzymes with a carbohydrate binding domain comprising a defined, specific amino acid sequence.

2. In accordance with the case law (cf. *inter alia* T 767/95 of 5 September 2000, point 6 of the Reasons and T 90/03 of 17 March 2005, points 13 to 15 of the Reasons), the preparation of an enzyme sufficiently pure to allow sequencing is novel over a preparation which is not in such a state of purity. In the present case, there is no prior art disclosing a cellulase from *H. insolens* strain DSM 1800 - the strain used in the patent - in the degree of purity required to obtain its amino acid sequence, as document (11) only discloses partially purified cellulases (endoglucanase and cellobiohydrolases) from *H. insolens* strain DSM 1800.

None of the specific CBD and linking B sequences referred to in the claims has been disclosed in the prior art. Thus, these specific CBD and linking B sequences as well as the cellulose- and hemicellulose-degrading enzymes comprising them are novel (Article 54 EPC).

Article 54 EPC;
Claim 1 relating to enzymes with a CBD comprising a subsequence capable of effecting binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate.

3. The question which arises in relation to claim 1 is whether or not any of the enzymes known from the prior art comprises a subsequence "*capable of* ***effecting*** *binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate*" (cf. point VIII *supra,* emphasis added by the board). According to document (19), a dictionary, the term "*effecting*" is to be read as "capable to bring about, to produce or to accomplish", a meaning different from that of "*affecting*" which is to be read as "capable to act upon or to influence". Thus, to be novelty destroying, a document of the state of the art would have to disclose a cellulose or hemicellulose-degrading enzyme comprising a subsequence of the listed CBD sequences of claim 1 capable of bringing about the actual binding of the enzyme to the insoluble substrate rather than being capable of playing a role in this binding.

4. Document (15) provides the DNA sequence of the gene encoding the CBHI enzyme of *Humicola grisea* var. *thermoidea* as well as the amino acid sequence of the enzyme predicted from the DNA sequence on the basis of

the genetic code. The C-terminal end of the protein "looks like" a putative CBD in view of its homology to other known CBDs. In particular, it contains an heptapeptide "Gln Cys Gly Gly Ile Gly Phe" and an octapeptide "Asn Asp Trp Tyr Ser Gln Cys Leu" which are also present in, for example, the third CBD sequence identified in claim 1. As for the first four amino acids in the heptapeptide, i.e. "Gln Cys Gly Gly", they are conserved in all known CBDs. One may, thus, assume that this specific sequence at least may be involved in the binding of the enzyme to cellulose. No evidence has however been produced showing that it is per se capable of bringing about said binding, whether it be weak or strong.

5. Document (4) discloses a gene which shows strong homology to the exocellobiohydrolase I of *Trichoderma reesei* and also the predicted amino acid sequence of the enzyme which comprises the "Gln Cys Gly Gly" tetrapeptide at the C-terminal end. Yet again, no evidence has been produced that this subsequence is, per se, capable of bringing about the binding of the enzyme to cellulose.

6. According to the established case law, for an invention to lack novelty its subject-matter must be clearly and directly derivable from the prior art and it is not justifiable to decide whether a document is prejudicial to novelty on the basis of probability (cf. "Case Law", supra, I.C.2.1). In the board's judgement, although the conserved sequences described in document (15) or (4) may bring about binding, it might also be the case that they are only necessary for stabilizing, facilitating or enhancing the binding involving the entire of the

CBD. The teachings of the enzymes sequenced in document (15) or (4), thus, do not amount to a disclosure of any specific subsequence within the CBD being capable of effecting the binding of the enzyme to cellulose and, therefore, these documents are not detrimental to the novelty to claim 1 relating to a cellulose- or hemicellulose-degrading enzyme comprising a CBD, wherein the CBD comprises a subsequence of the listed CBD capable of **effecting** the binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate.

7. In summary, the subject-matter of claim 1 in its various embodiments and of dependent claims thereof fulfil the requirements of Article 54 EPC.

Article 56 EPC

8. Document (3), which represents the closest prior art, is a review article on cellulase families and their genes from bacteria and fungi. Cellulolytic enzymes or cellulases are divided into three classes, namely endoglucanases, exoglucanases or cellobiohydrolases and β-glucosidases (cf. page 256, left-hand column, first paragraph). Reference is made to biochemical and genetical studies of fungal cellulolytic enzyme systems, which generally comprise at least two cellobiohydrolases and an ill-defined number of endoglucanases (cf. page 260, left-hand column, lines 7 to 12). In order to "*improve current industrial processes using lignocellulose raw materials and permit the development of new areas*", document (3) suggests to improve the enzymes available, "*either by finding new enzymes and genes from nature or even by ... protein*

engineering" (cf. page 260, middle column, first and second full paragraphs).

9. Starting from this closest prior art, the technical problem underlying the patent in suit is the provision of alternative fungal cellulases and their genes. The subject-matter of claim 1 indeed relates to novel cellulose- or hemicellulose-degrading enzymes as characterized by the homology of their CBDs to that of known cellulases. The endoglucanase activity of one of these enzymes is also shown in document (16). On this basis, the board accepts that the above mentioned problem was satisfactorily solved. In this context, it is worth noticing that the present situation is different from that underlying the decision T 1329/04 (*supra*) as to the quality of evidence provided in the patent in suit relating to the claimed invention being a bona fide solution to the problem to be solved. In this earlier case, it was not accepted that the then claimed polypeptide SEQ ID No.3 was a member of the TGF-β family because it had not been shown to have any function, its structure did not conform to that expected from members of the family and the expected sequence homology to previous members of the family was not present.

10. At the priority date of the patent (9 May 1990), it was a matter of common general knowledge - as shown in document (3) itself - that using the powerful tools of modern molecular technology, it was possible to explore in details the complexity of lignocellulose biodegradation (cf. page 255, paragraph bridging columns). Thus, the approach followed in the patent which consisted in identifying further cellulase genes

by cloning and sequencing said genes was obvious to try. The appellant argued however that, in doing so, the choice of the probe to be used for screening the recombinant clones would not have been obvious to the skilled person (cf. point XIII *supra*).

Selection of a probe for screening

11. Notwithstanding the great variety in the structure of different cellulases and the dissimilarities in their primary sequences, document (3) refers to some common features in their architecture such as the presence of three different domains, namely a catalytic domain with the active site, a terminal domain with a role in substrate binding or solubilisation (required for hydrolysis of crystalline cellulose but not for other soluble substrates), and a glycosylated hinge that links the other two domains (cf. page 257, paragraph bridging left-hand and middle columns, page 258, Figure 1). Whereas the comparison of different cellulases has not revealed any conserved sequences in the active site regions (cf. page 258, right-hand column, last paragraph), the terminal domain (associated with cellulose-binding function) is conserved in the four cellulases produced by *T. reesei* irrespective of whether they are celloobiohydrolases or endoglucanases (cf. page 257, middle column, page 258, left-hand and middle columns). In fact, these enzymes, such as CBHI and EGI, have a close evolutionary relationship arisen by gene duplication. In addition, document (3) refers to genes similar to the *T. reesei* CBHI and EGIII genes having been isolated, respectively, from *P. chrysosporium* and *S. commune* (cf. page 260, left-hand column, last full paragraph).

12. The former reference corresponds to document (4) which was published before the priority date of the patent (9 May 1990) and thus was available to the person skilled in the field of cellulolytic enzymes. This document explicitly confirms the presence of the conserved homologous terminal CBDs in the *T. reesei* CBHI and the *P. chrysosporium* enzyme (cf. page 417, right-hand column, last full paragraph and page 420, figure 9). Moreover, although not explicitly identified in document (15), this conserved homologous terminal CBD is also easily recognisable at the C-terminus of the CBHI sequence from *H. grisea*. Thus, at the priority date of the patent, the person skilled in the art was aware that the presence of this homologous terminal CBD was not restricted solely to cellulases from *T. reesei* but that it was also found in cellulases from other fungi, such as *Phanaerochaete* and *Humicola*.

13. In the board's judgment, the skilled person aware of this knowledge would have found it obvious to use a probe derived from a domain common to many classes of cellulases when wanting to identify, isolate and clone as many cellulases as possible, independently of their class or type – the actual problem to be solved (cf. point 9 *supra*), just as a probe comprising the full-length sequence of a very particular class of cellulases - such as CBHI or EGI - was used to screen fungi libraries for the presence of corresponding genes encoding this very particular class of cellulases (which is the approach followed in documents (4) and (15) for cloning CBHI genes). Thus, no inventive contribution is seen in the selection of the particular screening probe.

14. It is worth to note here that the ("in silico") evidence provided in document (17) to sustain the argument that the choice of the probe was inventive is, in fact, irrelevant. This document shows that, under the conditions referred thereto, three full-length cDNA sequences encoding the CBHI enzymes from *T. reesei*, *H. grisea* and *P. chrysosporium* do not hybridize to a full-length cDNA sequence encoding a completely different class of cellulase, namely the EGV from *H. insolens* - having a CBD comprising the eighth amino acid sequence of claim 1. This may well be true but it does not affect the above reasoning on inventive step which does not rely on "full-length" probes. Nor do the data shown in document (17) demonstrate that the skilled person would have encountered difficulties in using as a probe DNA derived from the conserved homologous terminal CBDs of those cellulases.

Cloning strategy

15. Once an appropriate screening probe is available to the skilled person, the selection of a cellulolytic fungus (known to produce cellulose-degrading enzymes) as starting material for the cloning is also obvious to the skilled person as many fungal cellulolytic organisms were already known. In fact, document (11) discloses the presence of several cellulose-degrading enzymes in the very same organisms as the ones used in the patent in suit: *H. insolens* strain DSM 1800 (example 1) as well as *Fusarium oxysporum* strain J 79 (DSM 2672) (example 2) and *Myceliophthora thermophila* strain CBS 11765 (example 3). Reference is also made in this document to the potential production of these

enzymes by standard, well-known recombinant methods (cf. pages 8 and 9).

16. Thus, the skilled person - using the screening probe as defined above - would obtain in a direct and straightforward manner the genes encoding cellulose- and hemicellulose-degrading enzymes comprising the claimed CBD and linking B sequences and, consequently, the claimed enzymes. No technical difficulties were expected by the skilled person nor has it been argued that they were encountered (cf. T 386/94, OJ EPO, 1996, 658). Thus, the cloning strategy disclosed in the patent does not involve an inventive step.

Alleged unexpected effect

17. Inventive step was also argued on the basis of an alleged unexpected effect shown in document (16), namely a high activity of the EGV enzyme from *H. insolens* which has a CBD comprising the eighth amino acid sequence of claim 1. In view of the highly conserved CBD sequences disclosed in the patent, the appellant further argued that this advantageous effect might reasonably be expected to be present in all disclosed cellulases (cf. point XIII *supra*).

18. Document (16) describes a protocol for measuring the specific activity of endoglucanases on phosphoric acid-swollen cellulose (PASC). There is, however, no disclosure of experimental data (kinetic curves, tables, etc.) or results obtained with any of the claimed enzymes. It is only in appellant's letter of 30 January 2004 that it is stated that "*(i)n this assay, the prior*

art Trichoderma reesei endoglucanase EGI had a specific activity defined as 100%, whereas the Humicola insolens endoglucanase EGV, which has the partial sequence that appears eighth in the list in Claim 1, had an activity of 145%". In the board's judgement, if inventive step is to be acknowledged on the basis of comparative data, then these data should be available for critical scrutiny. In their absence, no conclusion may be reached as to the suitability of the results mentioned for proving the point which they are intended to prove.

19. Furthermore, the alleged unexpected effect is demonstrated only for a single cellulase, namely the EGV of *H. insolens* which comprises a CBD with the eighth amino acid sequence of claim 1. And there is no evidence on file that allows to extrapolate this effect to all the other cellulases referred to in claim 1. In particular, the board cannot accept appellant's argument that the presence of a strong homology within the disclosed CBD sequences implies a similar high level of cellulase activity. Indeed, it has not been demonstrated that the level of activity of a given cellulase would solely be linked to the conformation of its CBD independently from, for example, the conformation of its active site.

20. It is established case law that if the inventive step of a claimed invention is based on a given (unexpected) technical effect, this effect must be achievable over the whole area claimed, i.e. for all products claimed (cf. "Case Law", *supra*, I.D.6.9.2). This requirement is not met in the present case where the alleged technical effect has only been demonstrated for a single product, namely the EGV of *H. insolens*, and thus, this effect

may not serve as a basis for acknowledging inventive step to the subject-matter of claim 1 as a whole.

21. Thus, from all the above considerations, it follows that the main request is refused since the subject-matter of claim 1 fails to fulfil the requirements of Article 56 EPC.

First and second auxiliary requests
Articles 123(2) and 54 EPC

22. No objections under these articles other than the ones raised against the main request have been put forward by the respondent. Nor does the board see any other. Thus, the conclusions that the claims of the main request do not comprise added subject-matter and that the subject-matter of the claims are novel equally apply to these auxiliary requests (cf. points 1 to 7 *supra*).

Article 56 EPC; Claim 1 of both requests

23. By applying the "problem-solution approach" in the same way as for claim 1 of the main request (cf. points 8 to 16 *supra*), the same conclusion is reached that inventive step may not be acknowledged on the basis of an inventive merit in cloning the genes encoding the claimed enzymes.

24. Furthermore, as claim 1 of both requests comprises many more enzymes than the specific enzyme for which an advantageous specific activity was seemingly observed (cf. point 19 *supra*), the reasoning which led to the conclusion that inventive step could also not be

acknowledged on the basis of this effect (cf. points 19 and 20 *supra*) remains valid.

25. Consequently, these auxiliary requests must be refused, since the subject-matter of claim 1 does not fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski F. Davison-Brunel