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**D E C I S I O N**  
**of 2 December 2005**

**Case Number:** T 0544/03 - 3.3.04  
**Application Number:** 86117432.4  
**Publication Number:** 0231495  
**IPC:** C12Q 1/68, C07H 19/04  
**Language of the proceedings:** EN

**Title of invention:**

One-step method and polynucleotide compounds for hybridizing to target polynucleotides

**Patentee:**

ENZO BIOCHEM, INC.

**Opponent:**

Roche Diagnostics GmbH

**Headword:**

One-step polynucleotide probes/ENZO

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Main, first and second auxiliary request - inventive step (no) "

**Decisions cited:**

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**Catchword:**

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Case Number: T 0544/03 - 3.3.04

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.04  
of 2 December 2005

**Appellant:** ENZO BIOCHEM, INC.  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 24 February 2003  
revoking European patent No. 0231495 pursuant  
to Article 102(1) EPC.

**Composition of the Board:**

**Chairman:** R. Gramaglia  
**Members:** G. Alt  
R. Moufang

## Summary of Facts and Submissions

- I. The appeal was lodged by the patent proprietor (appellant) against the decision of the Opposition Division to revoke the European Patent No. 0 231 495 pursuant to Article 102(1) EPC. The patent having the title "One-step method and polynucleotide compounds for hybridizing to target polynucleotides" had been granted on the basis of claims 1 to 25. It had been opposed in its entirety under Article 100(a) EPC for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) EPC and Article 100(c) EPC. The Opposition Division found that the subject-matter of (amended) claim 1 of the main request lacked novelty and that the subject-matter of claim 1 of the auxiliary request lacked inventive step.
- II. With the statement setting out the grounds of appeal a new main request and two new auxiliary requests were filed.
- III. The respondent (opponent) replied to this submission.
- IV. Both parties requested oral proceedings to which they were summoned. Together with the summons for oral proceedings the board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) setting out a preliminary view on some of the issues.
- V. Both parties replied to the communication. The appellant submitted a new main request and two new auxiliary requests.

Claim 1 of the main request read:

"1. A polynucleotide probe comprising:  
(i) at least twelve bases;  
(ii) at least two entities; and  
(iii) a linker arm having at least 3 carbon atoms and a double bond at an alpha position relative to the base moiety,  
wherein each entity being covalently or non-covalently attached to the base moiety via the linker arm,  
wherein each entity is separated from each other by a stretch of about ten other nucleotides, and  
wherein the entities upon hybridization to a complementary polynucleotide are capable of generating a change in property in said hybrid, detectable in a homogeneous reaction."

Claim 1 of auxiliary request I read:

"1. A polynucleotide probe comprising:  
(i) at least twelve bases;  
(ii) at least two entities; and  
(iii) a linker arm having at least 3 carbon atoms and a double bond at an alpha position relative to the base moiety,  
wherein each entity being covalently or non-covalently attached to the base moiety via the linker arm,  
wherein each entity is separated from each other by a stretch of about ten other nucleotides, and  
wherein the entities upon hybridization to a complementary polynucleotide are capable of generating a change in property in said hybrid, detectable in a homogeneous reaction;

and wherein said entities comprise an aromatic dye selected from the group consisting of phenanthridines, acridines and anthracyclines."

Claim 1 of auxiliary request II read:

"1. A polynucleotide probe comprising:

(i) at least twelve bases;

(ii) at least two entities; and

(iii) a linker arm having at least 3 carbon atoms and a double bond at an alpha position relative to the base moiety,

wherein each entity being covalently or non-covalently attached to the base moiety via the linker arm,

wherein each entity is separated from each other by a stretch of about ten other nucleotides, and

wherein the entities upon hybridization to a complementary polynucleotide are capable of generating a change in property in said hybrid, detectable in a homogeneous reaction;

and wherein said linker arm or said linker arms are selected from the group consisting of

-CH=CH-CH<sub>2</sub>-NH-,

-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-S-,

-CH=CH-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-NH-."

All requests contained further dependent claims.

VI. In a further letter the appellant informed the board of its intention not to attend the oral proceedings.

VII. The oral proceedings were cancelled.

VIII. The following documents are mentioned in this decision:

D2: Frumgarts, L.A. et al, Molekulyarnaya biologia, vol. 19, 1985, pages 1394-1399 and the English translation of the article in: Molecular Biology (USSR), vol. 19, pages 1142-1147

D8: EP-A-0 144 914

D21: WO-A-84/3285

D27: EP-A-0 063 879

D28: EP-A-0 117 777

D37: EP-A-0 070 685

IX. The appellant's arguments as far as they are relevant for the present decision may be summarised as follows:

Document D21 involved chemical synthesis of modified nucleosides while document D2 taught introducing a fluorescent probe in an already synthesized RNA/DNA molecule. It was readily recognizable that many of the linkers disclosed in document D21 were too bulky and therefore, if introduced in the molecule disclosed in document D2, they were expected to interfere with hybridization. Consequently, a combination of documents D21 and D2 would not solve the technical problem of formulating an alternative probe that had an improved linker molecule.

As to a combination of document D2 and document D27, document D27 differed from document D2 in the following aspects: It taught away from using a chromophore; it disclosed a different linkage site for the signalling moiety at the purine base residue and also taught away from attachment to purine; it disclosed a different synthesis process for the modified polynucleotides; the labelling density of the modified polynucleotides could not be regulated similar to that in document D2; it did not disclose entities that could generate a change in property of the formed hybrid upon hybridization; it did not provide any motivation or suggestion to change the density of labels. Hence a skilled person would not have combined the teachings of the two documents.

- X. The respondent's arguments as far as they are relevant for the present decision may be summarised as follows:

Document D21 disclosed all the features of the claimed polynucleotide probe except for the feature that the entities were separated from each other by a stretch of about 10 other nucleotides. The problem to be solved was the provision of an alternative polynucleotide probe. Document D2 disclosed polynucleotides labelled at a degree corresponding to a spacing of about 10 nucleotides between the labels.

Starting from document D2 as the closest prior art, it disclosed all the features of claim 1 except a linker arm having a double bond at the alpha position, which was however disclosed in document D27, relating to the same field as document D2, i.e. labelled probes for the detection of complementary nucleic acids, or in document D21. In contrast to the appellant's assertions

purine labelling was taught in document D27 and also, as far as the attachment to the position in purine was concerned, documents D2 and D27 were in agreement.

Document D8 disclosed a homogeneous assay in which the detectable signal was exhibited by a labelling pair. The only feature not explicitly disclosed was a linker arm of at least three carbons and a double bond at the alpha position. Such a linker was however disclosed in documents D21 or D27.

#### XI. Requests

The appellant requests (letter dated 1 June 2005) to set aside the decision under appeal and to maintain the patent on either the main request or auxiliary request I or II filed with the submission dated 6 May 2005.

The respondent requests (letter dated 4 May 2005) to dismiss the appeal.

### **Reasons for the Decision**

1. Objections under Articles 123(2) and (3), 84, 54 and 56 EPC were raised against the claims of the main and auxiliary requests. Since, as set out below, the patent must be revoked for lack of inventive step, the board considers it expedient to deal with this issue only and to leave aside the other objections without discussion of their merits.



*Main Request*

2. Whether claimed subject-matter involves an inventive step is normally assessed by applying the problem-and-solution approach. It consists essentially in (a) identifying the "closest prior art", (b) assessing the technical effects achieved by the claimed invention when compared with the closest prior art, (c) defining the technical problem to be solved as the object of the invention to achieve these effects and (d) examining whether or not a skilled person having regard to the state of the art would have suggested the claimed technical features for obtaining the results achieved by the claimed invention. As to the first step, certain criteria were developed by the boards of appeal of the European Patent Office for identifying the closest prior art document. Normally, it is a document disclosing subject-matter conceived for the same purpose as the claimed invention.
  
3. Claim 1 relates to polynucleotide probes which are used to detect the presence of a target polynucleotide by virtue of the signalling entities being "capable of generating a change in property of said hybrid, detectable in a homogeneous reaction". The term "homogeneous reaction" is known and used for denoting assays in which the detection and identification of target nucleotides by the polynucleotide probe is made in solution without the need of carrying out washing procedures before detection (for example D37, page 4).
  
4. The actual detection of the hybrid between the polynucleotide probe and the target polynucleotide is enabled by the signalling moiety or, in the terminology

of the patent in suit, the "entity" attached to the nucleic acid portion of the probe.

5. In accordance with the definition of "homogeneous reaction" used in the art and with the role of the "entity" as the signalling moiety, it is stated in the patent in suit at the bottom of page 4: "This invention permits the polynucleotide compound to be used as a polynucleotide probe to detect the presence of a target polynucleotide in a homogeneous or one-step assay. [...] Thus, the entities permit the detection of a target polynucleotide in one-step; an additional step of removing unbound polynucleotide probes from the sample, before verification of the presence of the target polynucleotide can be achieved, is not required."
  
6. Hence, in view of point 2 above, for a document to qualify as the closest prior art, it should disclose nucleic acid hybridization probes serving the purpose of being used in a homogeneous reaction.
  
7. Document D21 is, in the board's view, not such a document for the following reasons. Firstly, the usefulness of the polynucleotide probes disclosed in document D21 for a homogeneous reaction is not explicitly mentioned in this document. Secondly, regarding an implicit disclosure, the document alludes to the entities (called "reporter groups" in document D21) as being chemical groups having a physical or chemical characteristic which can be "readily measured or detected by appropriate physical or chemical detector systems or procedures." (page 11, lines 12-16), like "colorimetric, spectrophotometric, fluorometric or radioactive detection, as well as those which are

capable of participating in the formation of specific ligand-ligand complexes which contain groups detectable by such conventional detection procedures." (page 11, lines 27-31). Specific examples include reporter groups which are known to be detectable only in more than one step, like the biotin-avidin system relying on the labelling of the probe with biotin with subsequent verification of the hybridized probe by avidin, radioactive moieties which are used for detecting hybridization in multiple step blotting procedures or the dinitrophenyl-antidinitrophenyl antibody system involving detection of the probe by an antibody to dinitrophenyl (for example page 16), but included are also acridine (for example page 16, line 17), which is an intercalating agent and one of the entities contemplated by the patent in suit and therefore suitable for use in a homogeneous assay. However, intercalating dyes may not only be used in homogeneous reactions, but also in "more-than-one-step" detection systems, as for example disclosed in document D8 where a probe is biotinylated and further modified by ethidium residues (ethidium is an intercalating agent), but where hybridization of the probe is not monitored following a change of property of the hybrid due to intercalation, but by an fluorescein-labeled antibody to the ethidium-DNA intercalation complex. Therefore, in the absence of any further description, the mere mentioning of acridines is ambiguous as to the type of assay in which they are used. Consequently, the purpose of being used in a homogeneous assay is not clearly demonstrated through the disclosure of document D21.

8. Document D28 was cited by the respondent and regarded as rendering certain claimed subject-matter obvious in combination with the closest prior art document identified by the respondent. The document discloses oligonucleotide hybridisation probes having intercalating dyes as signalling moieties. In the context of a description of the means by which hybridisation of a target polynucleotide with the probes of document D28 is detected, the mechanism underlying the signalling by intercalating dyes is explained in the first two paragraphs at the top of page 19: "Des modifications spectrales importantes sont observées dans les bandes d'absorption de l'intercalant (hypochromisme important pouvant atteindre 50%, déplacement du spectre vers les grandes longueurs d'ondes. Lorsque l'oligonucléotide contient une séquence de thymine (T4, T8, T12), ces modifications spectrales ne s'observent que par fixation sur la séquence complémentaire (poly A). Aucune interaction n'est observée avec polyU et polyC." In the board's view, the skilled reader would recognize that this statement is the description of a homogeneous detection reaction, namely that the changed absorption characteristics are a property of the hybrid and not of the probe alone, thus allowing a distinction between the hybrid and the probe on this basis even if they are coexistent in the same solution. Hence, even if an explicit reference is absent, document D28 - in contrast to document D21 - albeit implicitly, unambiguously discloses polynucleotide probes useful in homogeneous reaction assays.
9. A further criterion developed by the boards of appeal for identifying the closest prior art is, that if there

- are several documents disclosing subject-matter serving the same purpose as the claimed subject-matter, the document with the minimum of structural differences is given precedence.
10. Document D8 explicitly deals with homogeneous hybridization assays. However, the detection system disclosed therein is structurally more remote with regard to the claimed subject-matter than that of document D28 as it relies on the use of interacting labelled pairs (page 5, lines 13-15) and not on the activity of a single kind of labelling moiety.
  11. Therefore, the closest prior art document is document D28.
    - 11.1 In its examples it discloses the preparation of a multiplicity of oligonucleotide probes. The exemplified compounds have the following features in common: Their signalling moiety - acridine or psoralene (page 22, Z' and Z'')- is covalently coupled by an alkylic linker group, for example  $-(CH_2)_5-$  or  $-(CH_2)_3-$  to the sugar group at either the 3' or 5' end or to the sugar group at both the 3' and 5' end or to interphosphate groups of the nucleic acid portion.
    - 11.2 All the specifically disclosed compounds of document D28 are distinguished from the compounds of claim 1 by more than one feature and moreover, these are different, depending on which compound is looked at. Thus, since none of the compounds is especially predestined, the board will consider the compound prepared in example LIV (page 55; hereinafter: "compound LIV") as the closest prior art compound for the purposes of the

problem-solution-approach because the length of its nucleotide portion comes within that contemplated by claim 1 and because its hybridization data are reported in document D28 (pages 20 and 21).

11.3 The compound LIV has the structure  $T_{12}-(CH_2)_5-Z''$ , wherein  $Z''$  is acridine (page 22) and  $T_{12}$  is a thymidine dodecamer.

12. A comparison of the features of this nucleotide probe with those characterizing the probes of claim 1 reveals the following:

- (a) The nucleic acid portion as claimed has "at least twelve bases" and may thus have the same size as that of compound LIV of document D28, but may also be longer.
- (b) Compound LIV has one entity, whereas the claimed compounds have "at least two entities".
- (c) The entities of the closest prior art compound are covalently attached via a linker arm to the sugar group of the nucleotide whereas, according to claim 1, attachment occurs via a linker arm to the base moiety.
- (d) The linker group of the compound LIV has five carbon atoms without a double bond at the alpha position. The linker group as claimed has "at least 3 carbon atoms and a double bond at an alpha position relative to the base moiety".

- (e) The distance between two entities is "about 10" unmodified nucleotides according to claim 1 whereas the question of distance does not arise in relation to the compound LIV because there is only one signalling moiety.
- (f) The signalling moiety of compound LIV is acridine, belonging to the group of intercalating dyes, which are, as concluded above in point 8, "capable of generating a change in property in said hybrid, detectable in a homogeneous reaction". In contrast, the detection moieties in claim 1 are functionally defined as being "capable of generating a change in property in said hybrid, detectable in a homogeneous reaction".

13. There is no evidence before the board that the claimed compounds have a technical effect beyond that disclosed for the compound LIV of document D28 (page 19, lines 1 to 10 and lines 19 to 28; page 20, line 2; page 21, line 2)), namely that the nucleotide probes are capable of binding to a target nucleotide and of detecting its presence in a homogeneous reaction. Accordingly, the problem to be solved by the patent in suit can only be formulated as the provision of further labelled polynucleotide probes suitable to detect complementary polynucleotides in a sample in a homogeneous reaction. The two last examples of the patent in suit demonstrate that a polynucleotide probe falling under the terms of the claim solves this problem.

14. It can be taken from the comparison in point 12 above that the closest prior art compound LIV and the claimed compounds are distinguished by more than one feature.

According to the case law of the boards of appeal inventive step is judged differently in this situation depending on whether or not the features are functionally linked ("Case law of the Boards of Appeal of the European Patent Office", 4th edition 2001; I.D.6., 6.4).

- 14.1 If the differing features are functionally interrelated in the sense that the intended effect is achieved only by the sum of features, their common presence in a claim is viewed as a true combination requiring for the assessment of inventive step an answer to the question whether the skilled person would have or would not have made the specific combination in order to achieve the effect.

However, in the present case it has never been argued that the invention presented in the patent in suit is such a combination invention.

- 14.2 The second situation is present if the differing features are a simple aggregation with no mutual influence on each other for achieving a technical effect. In that case the obviousness of each of the features has to be examined individually with the possible consequences, for example, that the features may be solutions to more than one problem ("partial problems") or that different combinations of documents may have to be taken into consideration.

An inventive step is acknowledged if one of the features is not derivable in an obvious way from the prior art as a solution to the problem ("Case law of



the Boards of Appeal of the European Patent Office", 4th edition 2001; I.D.6., 6.4.2, second paragraph).

15. On the evidence before the board, the different features in claim 1 have to be considered as such an aggregation. Hence the evaluation of inventive step requires assessing separately for each of them, whether it contributes in an obvious or non-obvious way to the solution of the problem as defined in point 13 above, i.e. the provision of further labelled polynucleotide probes suitable to detect complementary polynucleotides in a sample in a homogeneous reaction.
- Nucleotide probes with more than 12 nucleotides are disclosed in document D28 (page 2, lines 22-24: between 1 and 50, preferably 1 to 25). Likewise, document D21 contemplates probes having "a length of fewer than 200 base units" (page 1, lines 7 and 8).
  - On page 1 in lines 8 and 9 document D21 refers to nucleotide probes having more than one detection group which is attached via a linker arm to the base moiety of a nucleotide.
  - This document also discloses linker arms having a double bond at an alpha position and at least three carbon atoms (page 16, first compound in line 3 and both compounds of line 4).
  - As to the spacing of entities, document D2, dealing with the hybridization behaviour of nucleotide probes, discloses that an alkylating amine, i.e. the linker to which the entity is attached, is added to a polynucleotide at a final concentration of 0.03 mM

to 0.6 mM (page 1143, under "Alkylation of polynucleotides") yielding polynucleotides with degrees of modification (expressed as the number of alkylating amine per 100 nucleotide; page 1144, under "Degree of modification") between 0.3 to 16.7% (page 1144, last line). Since a labelling density according to document D2 of 9% corresponds to a stretch of 10 unlabelled nucleotides between the entities, a stretch of about 10 unlabelled nucleotides between the entities as required by claim 1 falls within the range which the skilled person would not exclude from consideration.

- Finally, document D28 discloses that intercalating dyes in general fulfil the function required by the signalling moieties of probes of the patent in suit, namely that they are "capable of generating a change in property in said hybrid, detectable in a homogeneous reaction" (page 19, lines 1 to 10).

Thus, it is concluded that the structural features by which the claimed compounds differ from the closest prior art compound are either known (document D21 and D28) or would have been envisaged by the skilled person (document D2).

16. The board has no evidence that the skilled person had reasons to disregard any of these features as alternative features when looking for further labelled polynucleotide probes suitable to detect complementary polynucleotides in a sample in a homogeneous reaction. In this respect it is noted that the argument that the linkers disclosed in document D21 may be too bulky and therefore interfere with hybridization is not

convincing because in the exemplified compounds of document D21 (for example, page 36), the entities attached to the linkers are separated by only two, one or even no nucleotide at all, implying that there is no sterical hindrance. As regards the way in which the labels are incorporated, it is not considered to be of relevance whether this is achieved by statistical incorporation of the entity in an already-synthesized nucleic acid molecule as in document D2 or by chemical synthesis with modified nucleosides as in document D21, because the subject-matter of claim 1 relates to a compound and there is thus no restriction as to the process by which it is produced.

17. Hence, the modification of the compound LIV of document D28 by the features identified in point 12 above is, in the board's judgment, an obvious measure that the skilled person would adopt in the light of the problem to be solved.
18. Claim 1 thus does not meet the requirement of Article 56 EPC and the main request is rejected.

*Auxiliary requests I and II*

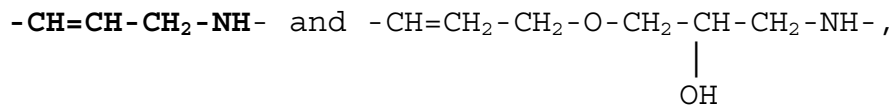
19. The nucleotide probes of claim 1 of auxiliary request I are defined as in claim 1 of the main request with the exception that the entities are specifically denoted:

"wherein said entities comprise an aromatic dye selected from the group consisting of phenanthridines, acridines and anthracyclines".

- In claim 1 of auxiliary request II the linker is no longer generally defined, but reference is made to three specific ones.
20. The closest prior art is, as for the subject-matter of the main request, considered to be compound LIV of document D28.
  21. There is no evidence before the board about an unexpected effect caused by the nucleotide probes claimed in the auxiliary requests. Hence, the underlying problem is, as for the main request, the provision of further labelled polynucleotide probes suitable to detect complementary polynucleotides in a sample in a homogeneous assay.
  22. Given that there is no indication for a combination invention, the features of claim 1 of auxiliary request I and II must be regarded as functionally unrelated so that the question for the assessment of inventive step is the same as for the main request, namely whether a skilled person would derive them in an obvious or non-obvious way from the prior art.
  23. With the exception of the definition of the entities, the compounds of claim 1 of auxiliary request I are the same as those of the main request. Therefore, in respect of the identical features, the reasoning leading the board to the finding of their obviousness applies here as well.
  24. Of the three entities specifically recited in claim 1, acridine is the signalling entity of compound LIV. Compounds of the group of phenantridines or

anthracyclines are well-known intercalating agents making their suitability for generating a change in property in a hybrid, detectable in a homogeneous reaction, evident in view of document D28 (for example page 2, lines 25 to 28).

25. To those features of claim 1 of auxiliary request II which are the same as those of the main request, the judgement of the main request also applies.
26. Concerning the specific linker arms, document D27, dealing with the preparation of nucleotide probes, is of relevance. It discloses on page 14, lines 20 to 27 that "examples of preferred linkages derived from allylamine and allyl-(3-amino-2-hydroxy-1-propyl)ether groups have the formulae



respectively" (emphasis added).

Thus, document D27 describes the linker first mentioned in claim 1 of auxiliary request II (in bold above).

27. The remaining two linkers are not specifically recited in document D27, but are structurally very close to the disclosed ones. The second linker of claim 1 differs from the first one disclosed in document D27 (in bold above) in that it bears an additional alkyl group and a thiol group instead of an amine group. The third linker in the claim is identical with the allyl-(3-amino-2-hydroxy-1-propyl)ether group of document D27 (formula not in bold above) with the exception only that the 2-hydroxy group is absent.

It is stated in document D27 on page 14, lines 1 to 15 that "the linkage or group joining moiety A to base B may include any of the well known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds, or carbon-oxygen single bonds. However, it is generally preferred that the chemical linkage include an olefinic bond at the  $\alpha$ -position relative to B. The presence of such an  $\alpha$ -olefinic bond serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix configuration. This permits interaction with polypeptide to occur more readily, thereby facilitating complex formation. Moreover, single bonds with greater rotational freedom may not always hold the moiety sufficiently apart from the helix to permit recognition by and complex formation with polypeptide."

Given, in view of the statement above, that the disclosure of document D27 emphasizes as the most important part of the linker the olefinic bond at the alpha position relative to the base; given moreover that the problem to be solved is the provision of further polynucleotide probes and given the absence of evidence for an unexpected effect generated by the linker, the board considers the modifications carried out with respect to the linkers known from document D27 as arbitrary. Therefore, the presence of either of the two linkers in the polynucleotide probes is not suited to impart an inventive step on them.

28. In summary, the features new to claim 1 of auxiliary requests I and II and also the remaining features have

either been disclosed in the prior art (documents D21 and D28) or are obvious alternatives in view of disclosed features (document D27) or would have been envisaged by the skilled person (document D2).

29. In view of this situation, the modification of the compound LIV of document D28 by these features is, in the light of the problem to be solved, in the board's judgement, an obvious measure that the skilled person would consider.

30. Consequently, auxiliary requests I and II have to be rejected as well, so that the appeal is to be dismissed.

## **Order**

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

The appeal is dismissed.

Registrar:

Chair:

P. Cremona

R. Gramaglia