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D E C I S I O N
of 21 April 1998

Case Number: T 0510/94 - 3.3.4

Application Number: 80303272.1

Publication Number: 0025722

IPC: C12P 1/00

Language of the proceedings: EN

Title of invention:
Monoclonal antibody to human cytotoxic and suppressor T cells, and method of preparing it

Patentee:
Ortho Pharmaceutical Corporation

Opponent:
Behringwerke Aktiengesellschaft
Novartis AG Patent- und Markenabteilung
Becton, Dickinson and Company
Boehringer Mannheim GmbH Patentabteilung
Biotest-Serum-Institut GmbH

Headword:
Monoclonal Antibody (OKT5)/ORTHO PHARMACEUTICAL

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Sufficiency of disclosure (yes)"
"Inventive step (yes)"

Decisions cited:
T 0418/89, T 0495/89, T 0606/89, T 0036/90

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0510/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 April 1998

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted 13 April 1994 concerning maintenance of European patent No. 0 025 722 in amended form.

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 0 025 722 with the title "Monoclonal antibody to human cytotoxic and suppressor T cells, and method of preparing it" was granted with 20 claims based on European patent application No. 80 303 272.1.

II. Notices of opposition were filed by five parties. Revocation of the patent was requested on the grounds of Article 100(a) (lack of novelty, lack of inventive step) and 100(b) EPC (insufficiency of disclosure).

III. By a decision within the meaning of Article 106(3)EPC dated 13 April 1994, the Opposition Division maintained the patent in amended form according to Article 102(3) EPC on the basis of the set of claims filed with letter of 25 June 1990.

Claims 1, 8 and 10 were as granted except that the terms "normal" and "peripheral" were added in claim 1(i) and read as follows:

"1. Mouse monoclonal antibody which

(i) reacts with greater than 90% of cytotoxic and suppressor TH_2^+ normal human peripheral T cells (being about 20-30% of all normal human peripheral cells), but

(ii) does not react with any of the normal human peripheral cells in the group comprising helper T cells, B cells, null cells and macrophages."

"8. A monoclonal antibody produced from hybridoma ATCC CRL 8013 or 8016 (OKT5)."

"10. Hybridoma ATCC CRL 8013 or 8016 (OKT5)."

IV. With regard to sufficiency of disclosure (Article 83 EPC), the Opposition Division determined that neither the growing of the deposited hybridoma nor the production of the equine anti-TH_2^+ antiserum necessary for carrying out the screening step described in the patent specification amounted to undue burden of experimentation.

The Patentee and the Opponent had submitted experimental reports on the properties of the specifically claimed OKT5 monoclonal antibody (MAb). Their results were contradictory without any apparent reasons for the discrepancies. The benefit of the doubt thus went in favour of the Patentee. The fact that the Patentee did not perform the experiments on a sample of the hybridoma maintained by the ATCC culture collection but rather on an equivalent sample which had been kept in his laboratory did not negate the results as it could be believed that both samples were identical.

Novelty (Article 54 EPC) was acknowledged in the absence of any prior art document disclosing a monoclonal antibody with the claimed characteristics.

With regard to inventive step (Article 56 EPC), it was decided that the teachings of document (86) as the closest prior art disclosing a polyclonal antibody preparation to TH_2^+ cells did not affect the non-obviousness of the claimed subject-matter, even if combined with the then existing knowledge about isolating monoclonal antibodies.

V. The Appellants (Opponent 4) lodged an appeal against the decision of the Opposition Division paid the fee and filed the statement of grounds of appeal.

VI. The Respondents (Patentee) answered the Appellants submission.

VII. A communication was sent by the Board according to Article 11(2) EPC of the Rules of Procedure of the Boards of Appeal setting out the Board's provisional position.

VIII. Further submissions were sent by both parties.

IX. Amongst the more than 200 documents on file, the following documents are mentioned in the present decision:

(3) Barnstable, C.J. et al., Cell, Vol. 14, 1978, pages 9 to 20,

(6) Michael, A.J. et al., Eur.J.Immun., Vol. 9, 1979, pages 205 to 210,

(37) Köhler, G. and Milstein, C., Nature, Vol. 256, 1975, pages 495 to 497,

(61) Bibliography of articles describing work done with Becton-Dickinson Monoclonal antibodies, submitted with the Respondent's letter dated 29 June 1987.

(86) Reinherz, E. and Schlossman, S., J. Immunol., Vol. 122, No. 4, 1979 (April issue mailed on 30 March 1979), pages 1335 to 1341,

99(68) Leucocyte Typing, Edited by Bernard et al., Springer-Verlag, 1984, pages 1 to 60.

99(80) Leucocyte Typing III, Edited by McMichael A.J., Oxford University Press, 1987, Chapter 5.1,

99(G) Reinherz, E. et al., J. of Immunology, Vol. 123, No. 1, 1979, pages 83 to 86,

99(I) Reinherz, E. et al., Proc.Nat.Acad.Sci. USA, Vol. 76, 1979, pages 4061 to 4065,

(148) First experimental report by the Appellants submitted with letter of 7 September 1989,

(151) Second experimental report by the Appellants submitted with letter of 10 October 1990,

(152) Third experimental report by the Appellants submitted with letter of 22 November 1991,

(153) Second declaration of P.S.Rao submitted by the Respondent with letter of 22 July 1992

(155) Fourth experimental report by the Appellants submitted with letter of 8 March 1993.

X. Oral proceedings were held on 21 April 1998.

XI. The submissions in writing and during oral proceedings by the Appellants can be summarized as follows:

Article 83 EPC; claims 8 and 10

(a) The deposition of the OKT5 producing hybridoma had not been achieved in a proper way, as a special medium was necessary in which to grow it, to be able to obtain a sufficient quantity of OKT5. This medium was not mentioned in the patent specification which led the skilled person to use another unsuitable medium.

(b) The Appellants had provided four sets of data showing that OKT5 did not possess the claimed properties.

(c) The data presented by the Respondents were not to be taken into account as they were not obtained with the deposited, OKT5 producing, hybridoma but rather with a supposedly equivalent sample kept by the Respondents. In any case, the protocol used was flawed and even under such circumstances, the results obtained confirmed the conclusion reached by the Appellants.

(d) Documents 99(68) and 99(80) presented compilations of data obtained by more than 55 laboratories on more than 15 monoclonal antibodies recognizing the same antigen (CD8) as OKT5. The reagents used were common to all groups. The cell purification was achieved in most laboratories by the same method of E-rosetting which was also the method used in the patent in suit. The data were mostly analysed by the same method. The results obtained provided ample evidence that the antibodies reacted with other cell subsets than the T suppressor cells i.e. with on average 10% of the B-cells population and 10% of the monocytes. Thus, the definition of OKT5 as not reacting with these latter cells had to be erroneous.

(e) The case was analogous to the cases T 418/89 (OJ EPO 1993, 20) and T 495/89 (of 9 January 1991) where the patents were revoked as the claimed hybridoma could either not be grown without undue burden of experimentation (T 418/89) or the properties of the claimed specific antibodies did not correspond to the written description (T 418/89 and T 495/89).

Article 83 EPC; claim 1

(f) No reproducible method was provided for the screening of an antibody with the claimed properties since the OKT4 antibody used for this screening was not publicly available at the filing date of the patent and undue burden of experimentation was associated with obtaining the anti-TH_2^+ antiserum.

(g) Isolating further hybridomas possessing the characteristics listed in claim 1 also amounted to undue burden of experimentation because the patent specification did not provide sufficiently clear information on how to test for the reactivity pattern of the claimed antibody: in particular, on the way to prepare the cells to be tested, on the amount of antibody to be used, on the necessity to block unspecific binding, on the relevance of negative controls. In fact, neither the Appellants nor the Respondents were able to show that even deposited OKT5 had the expected properties.

Article 56 EPC

(h) The closest prior art document was document (99-I) where the authors suggested that the protocol which they used for the isolation of a monoclonal antibody specific for the population of helper T cells would be generally useful in defining T cell subsets. The protocol followed in the patent in suit was indeed that of document (99-I) except for the fact that thymocytes were used as the immunogen rather than peripheral T cells.

Document (86) showed that, by using thymocytes as an immunogen, it was possible to obtain a polyclonal anti-serum (anti-TH_2 anti-serum) which recognized T suppressor cells. Therefore, by combining the teachings of both documents, one necessarily arrived at the conclusion that there existed a reasonable expectation of success that a monoclonal antibody specific for T suppressor cells could be isolated.

(i) The case law of the Boards of Appeal in relation to monoclonal antibodies (T 36/90 of 7 October 1991) made it clear that the isolation of a monoclonal antibody was not to be considered inventive when a polyclonal antibody with the same properties had already been isolated.

XII. The Respondents replied essentially as follows:

Article 83 EPC; claims 8 and 10

(j) The medium necessary to grow the OKT5 producing hybridoma was identified in the letter from ATCC accompanying the delivery of the hybridoma. The composition of this medium was part of the state of the art since 1978. Adding serum to the growth medium of hybridomas was also common practice. As for a different medium being disclosed in the patent, the skilled person would readily have recognized that the recommended medium was to be used for cell fusion, not for the culture of hybridomas. Alternatively, the hybridoma could always be grown in ascites.

(k) The protocol followed by the Appellants to test the reactivity pattern of OKT5 was flawed and, thus, no conclusion could be drawn whether the monoclonal antibody had the reactivity pattern described in the patent specification.

(l) It was perfectly justified for the Respondents not to have carried out the experiment with the deposited hybridoma, the ATCC requiring that the depositor keep a batch of the deposited organism, such as was directly used by the Respondents. The experimental reports showed that OKT5 did not react with B-cells or macrophages.

(m) Documents 99(68) and 99(80) provided information on the average reactivity pattern of antibodies recognizing the same antigen as OKT5. This average reactivity pattern was in no way indicative of the reactivity pattern of OKT5. A large number of laboratories participated in the tests. No standardized procedure was used: the cell populations tested were not always isolated by the same protocols. The compilation of the results to arrive at the average reactivity pattern did not exclude stray values.

(n) It was important to remember that a considerable number of post-publications disclosed making use of OKT5 without ever mentioning that it reacted with other cell subsets than T suppressor cells. Nor was there any mention in the post-published literature that the CD8 antigen recognized by OKT5 was ever found on other cells than T suppressor cells.

(o) The case was not at all analogous to the cases dealt with in decisions T 418/89 and T 495/89 (see supra) because there was no problem in growing the hybridoma and also because, in these latter cases, there existed post-published documents which showed that the then claimed antibodies did not have the reactivity pattern to be expected from reading the patent.

Article 83 EPC; claim 1

(p) To isolate further monoclonal antibodies with the reactivity pattern given in claim 1, there was no need to carry out the protocol originally described which made use of OKT4 and anti-TH_2 antiserum, as the deposited OKT5 antibody provided an efficient alternative tool. Thus, it was irrelevant whether at the date of filing, OKT4 and the anti-TH2 antiserum were available or reproducible without undue burden.

(q) The Appellants had not shown that it was not possible to isolate antibodies with the reactivity pattern given in claim 1. The great number of copycat antibodies which were made by different firms, once the isolation of OKT5 had been described, was a very good indication that the disclosure was sufficient in relation to claim 1.

Article 56 EPC

(r) At the filing date of the application, the technique of making monoclonal antibodies was still very much in its infancy. Document (3), for example, showed that monoclonal antibodies to human cell surface antigens could not be isolated by immunising BALB/c mice with membranes from human tonsil lymphocytes. According to

document (6), using human thymocytes as antigen led to the isolation of a monoclonal antibody specific for thymocytes and not for suppressor T cells. The teachings of one single document such as document (99-I) were not necessarily indicative of reasonable expectation of success for the isolation of the claimed monoclonal antibody. As for document (86), it only taught the isolation of a polyclonal antiserum without any guarantee that the antibodies it contained would recognize only one specific antigenic structure.

(s) A secondary indication of inventive step was to be found in document (61) which listed very many publications describing the use of OKT5 in clinical experiments.

(t) The case law of the Boards of Appeal regarding the inventive step of monoclonal antibodies when there already existed the equivalent polyclonal antibody was established on cases having much later priority dates than the present one, when much more was known on the feasibility of obtaining monoclonal antibodies and, thus, could not be taken into account.

XIII. The Appellants (Opponent 4) requested that the decision under appeal be set aside and that the European patent No. 0 025 722 be revoked.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The two issues to be decided are sufficiency of disclosure and inventive step in relation to the subject-matter of claims 1, 8 and 10.

Article 83 EPC; claims 8 and 10

Deposition of the hybridoma

2. The Appellants argued that the written description of the patent specification was not sufficient for the skilled person to be able to reproduce the invention and that thus a deposition of the OKT5 producing hybridoma with a recognized depositary institution was necessary for sufficiency of disclosure. This deposition had not been achieved in the proper way as the medium in which to grow the hybridoma was not disclosed in the patent as filed and also because IL-6 needed to be added to the growth medium in order to make the monoclonal antibody in sufficient quantities.

3. The patent as filed teaches in example 1B to multiply the hybridoma in ascites. Furthermore, when delivering the hybridoma upon request, the ATCC recommended a specific growth medium "because it had been published", supplemented with 20% fetal bovine serum (letter from the ATCC submitted by the Appellants with the grounds of appeal). Thus, there are two ways available to grow the deposited OKT5 hybridoma. In fact, in the course of opposition proceedings before the first instance, the Appellants themselves did not dispute being able to grow the hybridoma in the medium recommended by the ATCC or in ascites (letter of 22 November 1991).

4. The objection that the hybridoma could not be grown in such a way that OKT5 could be obtained in sufficient quantities leaves entirely open, which purpose the quantities of OKT5 should be sufficient for. However, it should at least be possible to make the antibody in such quantities that its properties can be tested. The Appellants tested the properties of the OKT5 in four independent experiments (documents (148), (151), (152) and (155)). In each experiment, two preparations of OKT5 were made, one from the OKT5 hybridoma grown in the presence of IL-6, and one, of much higher concentration, from this hybridoma grown from ascites. Thus, although the experiments are ambiguous as to which of these antibody preparations was tested, the impossibility of producing OKT5 "in sufficient quantities", by culturing the deposited hybridoma has not been shown in a convincing manner.

5. The Appellants submitted that because the patent taught the RPMI 1640 medium was the medium suitable for cell fusion, the skilled person would have assumed that it was a proper growth medium as well, whereas, in fact, the hybridoma did not satisfactorily grow in RPMI 1640. This argument is not convincing since the depositary ATCC had given advice in which medium to grow said hybridoma.

6. Thus, the situation is different from the one dealt with in T 418/89 (see supra) where there was evidence on file that the then claimed hybridoma could only be grown after repeated requests by many recipients had been made and by applying techniques considerably more sophisticated than those recommended by the depositary institution.

7. For all of these reasons, the Board sees no evidence that the hybridoma has not been properly deposited.

Experimental reports from the Appellants

8. The Appellants submitted experimental reports on the reactivity pattern of OKT3. Its ability to bind to the subpopulations of lymphocytes or to macrophages was tested using double staining, flow cytometry technique. The problems associated with, and limitations of this technique were extensively discussed by both parties. It appears that double staining involves no less than five hybridisation steps with the cell population to be tested and, in sequence, an unspecific MAb, OKT5, a marker antibody for OKT5, an additional unspecific antiserum and a cell population marker antibody. The hybridisation conditions, in particular the antibodies concentration, their origin and subclass are of critical importance. In the same manner, many different and apparently essential parameters seem to have to be taken into account when setting up the flow cytometer because of their impact on the interpretation of the data. The overall impression which the Board gets from the submissions on file is that the double staining, flow cytometry technique is a highly sophisticated technique, the results of which should be interpreted with the greatest caution.

9. The data from the Appellants relative to the reactivity pattern of OKT5 with B cells or macrophages are presented in documents (148), (151), (152) and (155). The Board was able to identify in the protocols used many departures from a "satisfactory protocol" as suggested by the submissions from both parties, from qualitatively incomplete binding (document (148)) to insufficient presentation of the data (documents (151) and (152)) and to unclarity as to the concentration of OKT5 used (all documents).

10. The results with regard to macrophages are that OKT5 isolated from ATCC CRL 8016 reacts with 75% (document (148)) or 25.6% (document (151)) of a population of such cells, whereas OKT5 isolated from ATCC CRL 8013 binds to 98.5% (document (152)) or more than 50% (document (155)) of that same population. In document (155), the percentage of macrophages able to bind OKT5 was also tested by simple staining and the values obtained were then of 45.6% and 25.6% in two independent experiments. Although these results are widely scattered, the Appellants find them meaningful of the point they wanted to make: i.e of the fact that OKT5 did not have the claimed reactivity pattern.

11. Taking into account the findings of paragraphs 8 to 10 and the fact that the survey of the scientific literature presented in document (61) shows that OKT5 was made use of in sixty-three scientific publications within the next two years of it being available, without its reactivity pattern seemingly ever being challenged, the Board is not prepared to attribute decisive significance to the experimental reports presented.

12. In summary, the Appellants have not provided the necessary evidence that OKT5 did not possess the claimed properties. To the contrary, OKT5 has been much used for testing the presence of T suppressor cells in populations of lymphocytes (document (61)). The case is, thus, fundamentally different from those dealt with in T 418/89 and T 495/89 (see supra) where evidence by later published scientific papers existed that the then claimed MAbs had a different reactivity pattern from that disclosed in the patent specification.

Experimental reports from the Respondents

13. In answer to the Appellants's experimental reports, the Respondents also provided experimental reports using the double staining flow cytometry technique. In view of the above finding that the Appellants (Opponent) were not able to show that the deposited hybridoma does not fulfil the requirements of Article 83 EPC, there is no burden of proof on the Respondents (Patentee) to show that it does. The validity of the Respondents' experiments need not be discussed.

The Leukocyte workshops

14. Documents 99(68) and 99(80) disclose studies of the then existing MAbs for the characterisation of normal and malignant leukocyte populations. The purpose of these studies carried out by 55 laboratories in 14 countries is defined on page 9 of document 99(68): a joint effort was to be made "to prevent that the rapidly increasing number of MAbs being produced would result in a plethora of individual systems of nomenclature being adopted which "would create complete confusion and render impossible any coherent dialog...". Thus, the MAbs were regrouped in clusters, the clusters being defined statistically, a MAb being classified to one of the already delineated cluster if its distance to the furthest MAb in the group was the least (passage bridging pages 29 and 31). Eight clusters were, thus, identified. Both parties agree that OKT5 falls within the CD8 cluster including 16 other MAbs.

15. Document 99(68) reports the testing by 27 laboratories of these 16 MAbs (but not of OKT5) against cell populations identified as T-PBL and non-T PBL (Table T26). The medium reactivity with non-T PBL cells is in the range of 10-15% depending on the antibody

tested with the lowest percentage ranging from 0% (five antibodies) to 4% and the highest from 25% to 44%. The overall median reproducibility of the experiments is said to be of 6% to 8%. It was in particular the scattering of the results which was a serious concern of the scientific community as discussed on pages 114 to 116 together with figures TEC 1 and TEC 2.

16. The Appellants interpret these results as meaning that OKT5 reacts with B cells. Yet, as already stated, OKT5 was not part of the studies. B cells were not tested as such, as the non-T PBL population is a mixed population containing B cells. The scientists themselves while allocating each MAb to a statistically defined group did not draw any firm conclusion as to the reactivity pattern of any specific anti-CD8 antibodies. As above stated, they rather tried to understand why the results obtained for anyone MAb and for anyone cluster of MAbs could so vary from laboratory to laboratory. For these reasons, the Board is not convinced that document 99(68) can be taken as a proof that the reactivity pattern of the specific OKT5 antibody as claimed is wrong, no more than document 99(80) which is conceptually identical to document 99(68) can be taken as such proof.

17. In view of what precedes the Board decides that there is no insufficiency of disclosure with regard to the properties of the specific hybridoma and monoclonal antibody of claims 8 and 10.

Article 83 EPC, claim 1

18. In the light of the finding above, the arguments by the Appellants that OKT4 was not available at the filing date and that undue burden was attached to producing the anti-TH_2 antiserum and to testing the antibody's

properties if ever isolated, need not be discussed. The deposited hybridoma and its secreted antibody ensures reproducibility of claim 1 which thus fulfils the requirements of Article 83 EPC.

Article 56 EPC: inventive step

19. At oral proceedings, the Appellants cited documents (86) and document (99-I) in connection with inventive step. Document (86) discloses a polyclonal anti-serum: the anti-TH_2 antiserum which specifically binds to suppressor T cells. Document (99-I) describes the isolation of the OKT4: OKT4 binds to the cell subset which is not recognized by the anti-TH_2 anti-serum and is thus identified as specific for helper T cells.

20. The polyclonal antiserum of document (86) and the claimed MAb both recognize the suppressor T cells subset.

21. In accordance with the case law of the Boards of Appeal that the closest prior art is that which corresponds to a similar use requiring the minimum of structural and functional modifications (T 606/89 of 18 September 1990), the Board is of the opinion that document (86) constitutes the closest prior art.

22. Starting from this document, the objective technical problem to be solved can be defined as the provision of an alternative means for identifying the suppressor T cells subset. This problem is not directly derivable from document (86) alone as no suggestion is made therein of the possibility of recognizing the suppressor T cells subset by any other means than the

anti-TH_2 antiserum except by testing for functionality. Yet documents (86) and (99-G) point out that producing the anti-TH_2 antiserum, while feasible involves quite a cumbersome procedure. However, the state of the art on file shows that the advantages of using a monoclonal antibody rather than a polyclonal antiserum were appreciated. Thus, in the Board's view, the teachings of document (86) taken in the context of the state of the art would have led the skilled person to this problem.

23. The solution provided by claim 1 is a monoclonal antibody which reacts with greater than 90% of cytotoxic and suppressor TH_2^+ human peripheral T cells while not reacting with helper T cells, B cells, null cells and macrophages.

24. The objective technical problem is, thus, solved and the question to be answered is whether the skilled person would have had a reasonable expectation of success to isolate such a monoclonal antibody.

25. Document (99-I) shows that using human peripheral T cells as an immunogen and following the technique of Köhler and Milstein (document (37)), it is possible to produce monoclonal antibodies. The great majority of them (32 out of 34) are not specific for T lymphocytes as they react with E^- cells (page 4062). The two remaining antibodies have the same specificity in that each of them recognizes the same T cell subset: i.e. the one which comprises helper T cells. In the Board's opinion, this result is not especially encouraging that an MAb against the suppressor/cytotoxic T cells subset may be isolated.

26. Document (6) discloses the isolation of seven MAbs following the technique of document (37) and using human thymocytes as immunogen. One out of these seven antibodies is said to be interesting as it is directed against an antigen which is exclusively expressed on thymocytes.

27. Document (3), co-authored by Dr Milstein himself, discloses that using a membrane from human tonsil lymphocyte preparations, it is not possible to obtain any MAbs.

28. In the Board's opinion, the skilled person aware of documents (99-I),(5) and (6) would wonder which immunogen, if any, would be likely to help in the isolation of a MAb to suppressor T cells and, thus, would not reasonably expect success when attempting this isolation.

29. In decision T 36/90 of 7 October 1991, inventive step was denied to a claim to a monoclonal anti-cancer antibody for the reason that a polyclonal anti-cancer antibody was already known in the art, as well as the method for isolating monoclonal antibodies. Thus the situation in this earlier case seems analogous to the present situation as the method for isolating monoclonal antibodies is also known, as well as an anti-T suppressor cells polyserum: the TH_2^+ antiserum.

30. However, it is important to note that the patent on appeal in case T 36/90 (see supra) had a priority date (8 June 1981) which is later by nearly two years than that of the present patent. The very great amount of documents on file shows that extremely fast developments were taking place in the field of immunology in this time period. The conclusion reached

in T 36/90 (see supra) was thus based on a much more developed state of the art in this particular field and cannot simply be transferred to the present case, seeing that it was still a matter of conjecture how easy it would be to adapt the monoclonal antibody technique to each and every situation.

31. In view of the findings in points 22 to 30, the Board decides that the requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairwoman:

D. Spigarelli U. M. Kinkeldey