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Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : Method for the determination of antigens with the aid of two or more monoclonal antibodies.

Klassifikation / Classification / Classement : G01N 33/54

ENTSCHEIDUNG / DECISION

vom / of / du 14 February 1990

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent / Titulaire du brevet : Akzo N.V.

Einsprechender / Opponent / Opposant :
01 Unilever PLC
02 F.Hoffmann-La Roche & Co., AG
03 Diagnostics Pasteur Société Anonyme
04 Boehringer Mannheim GmbH
05 Hybritech Inc.

Stichwort / Headword / Référence : Determination of antigens/AKZO

EPÜ / EPC / CBE Article 54(3)

Schlagwort / Keyword / Mot clé : "Novelty (yes) after amendments - disclaimer"

Leitsatz / Headnote / Sommaire

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Case Number : T 3/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 14 February 1990

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Decision under appeal :	**Decision of Opposition Division of the European Patent Office dated** 7 November 1988 **revoking European patent No.** 0 045 103 **pursuant to Article** 102(1) EPC.

Composition of the Board :

Chairman : P. Lançon

Members : U. Kinkeldey

J. Stephens-Ofner

Summary of Facts and Submissions

I. The mention of the grant of European patent No. 0 045 103 in respect of European patent application No. 81 200 768.0, filed on 6 July 1981 and claiming priority of 28 July 1980 from a prior application filed in the Netherlands, was announced on 3 February 1982 (cf. Bulletin 82/05). Claims 1, 6 and 7 as granted read as follows:

"1. Method for determining antigens by means of an immunochemical reaction, whereby the antigen must enter into a bond with at least two antibody molecules, characterised in that hereby two or more different sorts of monoclonal antibodies are used directed against the same antigen.

6. Test kit, consisting of:
(a) one monoclonal antibody of some different sorts of monoclonal antibodies, directed against the same antigen and marked with a certain label,
(b) one monoclonal antibody different from that of (a), or some different sorts of monoclonal antibodies directed against the same antigen and either rendered insoluble or marked with a certain label,
(c) other suitable reagents.

7. Test kit, consisting of:
(a) a batch of particles, each coated with different monoclonal antibodies directed against the different antigens to be determined in the sample,
(b) a batch of particles, each coated with monoclonal antibodies directed against the same antigens, whereby these antigens are of a different kind than those mentioned under (a),
(c) other suitable reagents."

II. Notices of opposition were filed against the European patent by five parties in the period from 10 September 1985 to 19 September 1985. Revocation of the patent was requested on the grounds of Article 100(a) and (b) EPC. During the procedure before the Opposition Division the following document was, inter alia, cited:

(1) EP-A-0 042 755.

III. The Opposition Division revoked the patent in a decision of 7 November 1988. The ground was lack of novelty under Article 54(3) EPC of the subject-matter of Claims 6 and 7, in view of document (1).

Claims 1 to 5 were held to be novel and to involve an inventive step.

Document (1) was filed with the European Patent Office only after the filing date of the patent in suit but claimed two priorities of earlier filed priority applications in Great Britain, filed on 20 June 1980 and 16 July 1980 respectively, i.e. before the priority date of the patent in suit. Document (1) had, therefore, to be considered as state of the art in the sense of Article 54(3) EPC. This meant that the disclosure of document (1) was only relevant with respect to the question of novelty (Article 56, second sentence, EPC).

In the Opposition Division's opinion the subject-matter of document (1) was properly supported by its first priority application No. 8 020 160, e.g. in the passage from page 5, lines 19 to 34 and page 6, lines 11 to 22. Although in the cited passages the word "different" defined the specificity rather than the monoclonal antibodies themselves, it was implicit that such

antibodies had to be different from each other, if the express condition were to be fulfilled. In the light of this it was clear that different monoclonal and other antibodies of different specificity were the ones recommended in the cited passage. The mentioned passages in document (1) also found support in the second priority document No. 8 023 151, e.g. page 3, line 6 and the following lines which described a method of determining the amount of a particular protein in a sample, "which comprises reacting the sample with a combination of two monoclonal antibody preparations which are respectively specific to two distinct antigenic sides (determinants) on the macromolecule of the protein under investigation, and determining from the resulting antigen/antibody complexes formed a measure of the original antigen concentration".

Thus, document (1) validly claimed both priorities, and so the subject-matter of the claims of the patent in suit was held to be anticipated by document (1) because its disclosure extended clearly beyond the use of two monoclonal antibodies in the particular apparatus.

IV. The Appellants (the proprietors of the patent) filed an appeal against the decision on 21 December 1988 with the payment of the fee, and submitted a statement of grounds on 3 March 1989, together with several new sets of claims. Respondents 1, 3 and 5 filed various observations in the period from 4 August 1989 to 27 September 1989.

V. During oral proceedings on 14 February 1989 two new sets of claims were filed as a main request and subsidiary requests respectively. Claims 1, 5, 6 and 7 of the main request read as follows:

"1. Method for determining antigens by means of an immunological reaction, whereby the antigen must enter

into a bond with at least two antibody molecules at least one of which is labelled, characterized in that hereby two or more different sorts of monoclonal antibodies are used directed against the same antigen; with the exception of the use of two monoclonal antibodies one of which is bound to a solid surface and rendered insoluble and the other of which is labelled, in sandwich assays.

5. Method for determining antigens by means of an immunochemical reaction, whereby the antigen must enter into a bond with at least two antibody molecules at least one of which is labelled with red blood cells (haemagglutination), polystyrene latex spheres (latex agglutination), finely-suspended dyestuff particles or metal sol particles, characterized in that hereby two or more different sorts of monoclonal antibodies are used directed against the same antigen.

6. Test kit, comprising:
(a) one monoclonal antibody or some different sorts of monoclonal antibodies, directed against the same antigen and marked with a certain label,
(b) one monoclonal antibody different from that of (a), or some different sorts of monoclonal antibodies directed against the same antigen and either rendered insoluble or marked with a certain label,
with the exception of a test kit for sandwich assays which comprises two monoclonal antibodies one of which is bound to a solid surface and rendered insoluble and the other of which is labelled.

7. Test kit for the determination of antigens by means of an immunological agglutination reaction, comprising:
(a) a batch of particles, each coated with different monoclonal antibodies directed against the different antigens to be determined in the sample,

(b) a batch of particles, each coated with monoclonal antibodies directed against the same antigens, whereby these antigens are of a different kind than those mentioned under (a)."

The claims according to the subsidiary request differ from those of the main request only insofar as Claim 5 was made dependent on Claim 1.

In the proceedings, the Appellants argued substantially as follows:

(a) In comparison with the disclosure of document (1) the new main claim was rendered novel by the disclaimer "...with the exception of the use of two monoclonal antibodies one of which is bound to a solid surface and rendered insoluble and the other of which is labelled, in sandwich assays." The disclaimer was sufficient to distinguish the claims according to the main and subsidiary requests from the disclosure of document (1), since this document only referred to test configurations, where all reaction ingredients were mixed in a single step for reaction in a single reaction liquid, and more specifically to "sandwich" test configurations using only three specific markers for labelling at least one monoclonal antibody. Other reaction conditions and other markers were not disclosed in document (1), and thus did not have to be taken into consideration in a disclaimer.

(b) The Guidelines for Examination in the European Patent Office, C-IV, 7.2, stated that "when considering novelty, it is not correct to interpret the teaching of a document as embracing well-known equivalents which are not disclosed in the document; this is a matter of obviousness."

This was particularly true in respect of Claim 5 of the main request which is an independent claim, mentioning four different ways of labelling at least one of the monoclonal antibodies which were not mentioned expressly as labels in document (1). In particular the decision T 12/81, (Diastereomers/-BAYER, OJ EPO 1982, 296), should not be considered relevant. Rather, there were various decisions of different Boards of Appeal which clearly took the position that equivalents are not included in the judgment of novelty. Thus, according to the main request, Claim 5 was kept as an independent claim. In the set of claims according to the subsidiary requests, Claim 5 was made dependent of Claim 1, to avoid a revocation of the patent solely for the reason that the Board might decide differently from the consistent case law, dealing with equivalents and novelty.

VI. The Respondents submitted substantially the following arguments in the oral proceedings with regard to the two newly submitted sets of claims:

Decision T 12/81 (see above) was to be applied in the present case so that the markers used to label at least one monoclonal antibody (mentioned in Claim 5), were not sufficient to render the claim novel, having regard to document (1), because the mentioning of "other markers" for labelling at least one monoclonal antibody in document (1) included all markers mentioned in Claim 5, and those used in a "sandwich assay" as defined by the disclaimer in Claims 1 and 6. Respondents (5) further submitted that a disclaimer for restricting a claim with regard to a given prior art document should only be used if there was no other proper wording for the claim possible for that

purpose. Claim 5 was clearly positively worded when mentioning certain markers for labelling at least one monoclonal antibody, thereby demonstrating that it was possible to find a positive wording to distinguish the claimed subject-matter from document (1); Claims 1 and 6 however, were worded by using a disclaimer, which should not be allowable.

None of the Respondents objected to the subsidiary request submitted during oral proceedings by the Appellants.

VII. The Appellants requested that the decision of the first instance be set aside and the patent be maintained on the basis of Claims 1 to 7 according to the main request, or of Claims 1 to 7 according to the subsidiary request, both requests submitted during oral proceedings.

The Respondents requested the appeal to be dismissed.

At the conclusion of the oral hearing the Board's decision was announced in accordance with the order set out below.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. **Amendments** (Article 123(2) and (3) EPC)

2.1 Claim 1 of the main request is differently worded from Claim 1 of the granted patent in as much as the disclaimer "...with the exception of the use of two monoclonal antibodies one of which is bound to a solid surface and rendered insoluble and the other of which is labelled, in sandwich assays" is used. Besides these embodiments

literally mentioned in the specification of document (1), there may be others covered by the broader term of the claim which are not disclosed in document (1). In the present case a limitation of the claim over document (1) by specifically mentioning those embodiments in the claim which are exemplified in the description and thus avoiding a disclaimer, may therefore result in unduly depriving the patentee of fair protection. In similar cases, the Boards of Appeal have allowed disclaimers of the above kind (T 04/80, OJ EPO 1982, 149; T 43/82 of 16 April 1984, unpublished in the OJ EPO; T 289/84 of 10 November 1986, unpublished in the OJ EPO and T 80/85 of 12 March 1987, unpublished in the OJ EPO). This disclaimer represents a limitation of the claims, which neither extends beyond the content of the application as filed (Article 123(2) EPC), nor does it extend the protection conferred (Article 123(3) EPC), since it literally excludes one embodiment contained in document (1) from the claim.

2.2 Claim 5 of the main request is supported by Claim 1 as granted, and the patent specification page 3, lines 27 to 29 and page 4, lines 10 to 13, and therefore no objections with regard to Article 123(2) and (3) EPC can be raised.

2.3 Claim 6 is amended as Claim 1, i.e. by a disclaimer which excludes test kits for sandwich assays. The reasons for allowability with regard to Article 123(2) and (3) EPC given for Claim 1 thus apply to Claim 6 likewise.

3. **Novelty** (Article 54(3) EPC)

3.1 The only issue to be dealt with in this appeal is the question whether independent Claims 1, 5, 6 and 7 of the main request submitted during oral proceedings are novel over the prior art document (1).

During the proceedings the question was raised whether document (1), which is a European patent application filed before the filing date of the patent in suit but only published after that filing date, can validly rely on the priority applications filed in Great Britain before the priority application of the patent in suit. The Apellants particularly objected that labelling of one of the monoclonal antibodies used in the method for determining antigens was not mentioned in the priority applications. After comparison of the disclosures of document (1) and its priority applications, the Board cannot follow this argument, and draws attention to the priority application GB-20 160, page 6, lines 11 to 19, where it is inter alia stated that "a second antibody carrying an enzymic or other (e.g. fluorescent or radioactive) marker is specifically bound to the adsorbed antigen under tests." The disclosure of labelling at least one monoclonal antibody by a marker was thus already made before the priority date of the patent in suit. The Board, therefore, accepts the finding of the Opposition Division that these priorities are validly claimed in document (1).

3.2 Document (1) discloses a process for carrying out a specific binding assay, for example an immunoassay, in which (a) a sample under assay, possibly containing a substance being tested for, is reacted with (b) a specific binding partner for the substance being tested for, immobilised on a solid support, and (c) a specific binding partner for the substance being tested for which is conjugated to a detectable marker, thereby to form a complex by reaction between whatever quantities are present of the substance being tested for, with reagents (b) and (c), in which the marker is immobilised to the support via the substance being tested for, and is detected or assayed as an index of the quantity present in the sample (a) of any of the substance being tested for,

wherein reaction ingredients (a), (b) and (c) are all mixed in a single step for reaction in a single reaction liquid. This kind of reagent is usually called a "sandwich" test configuration, in which the antigen under test can be specifically adsorbed to a first antibody bound to a solid surface and a second antibody carrying an enzymic or other (e.g. fluorescent or radioactive) marker is specifically bound to the adsorbent antigen under test. In preferred sandwich tests, the two antibodies used have different, non-interfering specificity with respect to the same antigen under test.

3.3 Claims 1 to 4 and 6 of the main request submitted during oral proceedings relate to a method for determining antigens by the same kind of immunological reaction, but with the exception of such test configurations which form the "sandwich" assays disclosed in document (1). The formal allowability of such a disclaimer, which is bound to limit a claim over certain state of the art, and is a means for limiting a claim with respect to a claimed broader scope of which only a certain part is contained in a prior art document, has already been discussed in paragraph 2.1 above. Furthermore, in the Board's opinion, this disclaimer clearly renders Claim 1 novel over the disclosure of document (1).

3.4 Independent Claim 5 of the main request is worded differently from Claim 1 insofar as in this case no disclaimer is used, but, instead, four specific ways of labelling at least one of the monoclonal antibodies are expressly mentioned. The decisive question is whether or not the literal wording of four distinct ways of labelling at least one monoclonal antibody in the assay renders the claim novel over document (1), in which three different types of markers are disclosed, namely enzymic, fluorescent or radioactive ones, whereby the fluorescent

or radioactive markers are mentioned as examples of "other markers". The Respondents relied on decision T 12/81, (see paragraph V(c) above) according to which, in the case of one of a number of chemical substances described by its structural formula in a prior publication, that substance's particular configuration -though not explicitly mentioned - is anticipated if it proves to be the inevitable but undetected result of one of a number of processes adequately described in the prior publication, by specification of both the starting materials and the process to be used. In such cases, novelty by selection cannot be claimed, since none of the possible combinations of all the listed starter compounds and process variants introduces a new element, that would result in a true, and not just "identical" modification of the starting substances. It seems to be clear that the facts in the present case differ from those of that decision. Thus, in the present case, on the one hand generally "other markers" are mentioned exemplifying fluorescent or radioactive markers; on the other hand as one further specific example enzymic markers are explicitly disclosed in document (1). It is not the case here, that by mentioning the general term "markers" and three examples out of the indefinite number of possible markers the claimed ones are inevitably disclosed. Rather the facts in the present case resemble the situation exemplified in the Guidelines, wherein halogens in general were disclosed by exemplifying chlorine, and it then remained to be judged whether or not other halogens would be novel over this disclosure. In agreement with the Guidelines (see paragraph V(b) above), various decisions (cf. T 167/84 of 20 January 1987, unpublished in the OJ EPO; T181/82, "Spirocompounds" OJ EPO 1984, 401; T 7/86 "Xanthine", OJ EPO 1988, 381; T 296/87 "Enantiomere"/HOECHST, to be published) show that specific embodiments of a general term which are neither explicitly mentioned in a prior art

document, nor are implicitly and inevitably derivable from the general disclosure of a prior art document (as they were in the case of the decision T 12/81 (see above)), are novel over the respective general disclosure. This is the situation for Claim 5 of the main request and the Board sees no reason to deviate from this established case law.

3.5 Whether or not the four markers mentioned in Claim 5 are equivalent to those described in document (1) in their effect and function, namely to detect a certain antigen in a sample by the use of labelled monoclonal antibodies, does not play a decisive role in the present decision because the Board follows the general approach developed in the case law cited above, namely that equivalents are not to be taken into account in the examining of novelty.

3.6 Claims 1, 5 and 6 of the main request are, therefore, novel over the disclosure of document (1).

4. Claims 2 to 4 are dependent on Claim 1 which is novel and thus are also allowable with respect to the question of novelty; Claim 7 clearly relates to a test kit for the determination of antigens by means of an immunological agglutination reaction which doubtless differs from the kind of immunoassay described in document (1) and is thus also novel over this document.

5. In view of the above a decision on the subsidiary request is not necessary.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division for further prosecution on the basis of Claims 1 to 7 of the main request.

The Registrar: The Chairman: