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# D E C I S I O N
## of 15 December 1999

**Case Number:** T 0071/95 - 3.3.4

**Application Number:** 89300062.0

**Publication Number:** 0324540

**IPC:** G01N 33/78

**Language of the proceedings:** EN

**Title of invention:**
A method for measuring the free fraction of ligands in biological fluids

**Patentee:**
AMERSHAM INTERNATIONAL plc

**Opponent:**
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B.R.A.H.M.S. Diagnostica GmbH

**Headword:**
Immunoassay/AMERSHAM INTERNATIONAL plc

**Relevant legal provisions:**
EPC Art. 54(3)

**Keyword:**
"Main request: novelty of a sub-range - (yes)"

**Decisions cited:**
T 0666/89

**Catchword:**

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0071/95 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 15 December 1999**

**Appellant:** (Opponent)
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**Decision under appeal:** **Interlocutory decision of the Opposition Division of the European Patent Office posted 14 November 1994 concerning maintenance of European patent**

**No. 0 324 540 in amended form.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
C. Holtz

## Summary of Facts and Submissions

I. European Patent No. 0 324 540 (application No. 89 300 062.0) was granted on the basis of 10 claims. The patent relates to a method for measuring the free fraction of ligands in biological fluids.

II. This appeal concerns the novelty of the claimed subject-matter under Article 54(3) EPC, in view of document (1),

EP-A-0 303 284.

III. Claim 1 of the main request on appeal (claim 1 as maintained by the Opposition Division) read as follows:

"1. A method of assaying the free portion of a ligand in a biological fluid sample which also contains a portion of the ligand bound to one or more natural binders, by the use of a signal reagent which is an antibody for the ligand and of a differential-binding ligand analogue which competes with the ligand for binding to the antibody, which method comprises incubating the sample with the analogue and the antibody, and observing the extent of binding of the antibody to the analogue, the antibody being a monoclonal antibody to the ligand, and the analogue is being chosen to have a lower affinity than the ligand for binding with the antibody, characterized in that the binding affinity of the analogue with the antibody is from 0.01% to 10% of the binding affinity of the free ligand with the antibody, the portion of said range from 8% to 10% being disclaimed."

IV. The submissions provided in writing and during the oral proceedings by the appellant can be summarised as follows:

- The disclaimer in claim 1 "the portion of said range from 8% to 10% being disclaimed" was not sufficient to establish the novelty under Article 54(3) EPC of claim 1 of the patent in suit over the immunoassay disclosed by document (1) also involving a ligand analogue having a cross-reactivity below 50% of that of the ligand for binding with the antibody.

- Document (1) taught the skilled person to use ligands analogues with cross-reactivities below 50% as a general teaching, without any indication to avoid the range below 8%.

- It could be deduced from Figure 1 of document (1) representing the percentage of $B/B_0$ versus the concentration of free thyroxine ($FT_4$) that ligand analogues with cross-reactivities of less than 8% would not have been discarded by the skilled person. This was because if one wished to obtain a curve whose 50%-intercept fell within the lower part of the physiological range of Figure 1, ligand analogues with a cross-reactivity of less than 8% had of necessity to be used .

V. The submissions provided in writing and during the oral proceedings by the respondent can be summarized as follows:

- Document (1) did not teach the skilled person to

use ligands analogues with cross-reactivities **anywhere** below 50%.

- An assay for a given free ligand could be optimised not only by choosing a ligand analogue having a rather low cross-reactivity, but also by adjusting the ratio analogue/labelled antibody. Therefore, the skilled person would not necessarily use ligand analogues with a cross-reactivity of less than 8% in order to obtain a 50% intercept falling within the lower part of the physiological range of Figure 1 of document (1).

- By plotting the figures of the two last r-h columns of the table on page 9 of document (1), no meaningful extrapolation could be made to lower $FT_4$ concentrations and/or cross-reactivities.

VI. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 324 540 be revoked.

The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following (main request):

**Claims:** 1 to 9 as maintained by the first instance

**Description:** Pages 1 to 4, 7 to 9 and 11 to 21 as granted, pages 5 and 5a as submitted in the oral proceedings before the first instance and pages 6 and 10 as submitted

in the oral proceedings before the Board of Appeal.

**Figures:** Figures 1 to 3 as granted;

alternatively on the basis of Alternate Claims A submitted on 1 July 1999 (auxiliary request).

## Reasons for the Decision

1. The appeal is admissible

*Main request*

2. The appellant neither objected under Article 100(c) with regard to the claims of the main request, nor objected at the opposition or appeal stage that the claims of this request lacked an inventive step. The board also sees no valid reasons to question the conclusions arrived at by the opposition division as regards these claims insofar as Article 123(2)(3) and 56 EPC are concerned, so that the only issue left at the appeal stage, regarding the main request, is whether or not the claims thereof are novel under Article 54(3) EPC.

*Novelty (Article 54(3) EPC)*

3. Document (1) is state of the art by virtue of the provisions of Article 54(3) EPC. It discloses an immunoassay for assaying the free portion of a ligand in a biological fluid sample which also contains a

portion of the ligand bound to natural binders, said immunoassay involving a differential binding ligand analogue, ie an analogue that binds much less strongly to the labelled antibody than does the ligand itself. Claim 1 of document (1) states that the cross-reactivity of the labelled antibody with the analogue (hereafter: the cross-reactivity) should be **less than 50%**.

4. Claim 1 under consideration relates to the same immunoassay as document (1), however, it is stated therein that the cross-reactivity should be "**... from 0.01% to 10%, the portion of said range from 8% to 10% being disclaimed.**" (see Section II supra). Thus, by virtue of the disclaimer, the stated range of cross-reactivity reduces oneself to **from 0.01% to less than 8%** (the latter boundary value being excluded).

5. Document (1) discloses *expressis verbis* preferred ranges of cross-reactivity (from 8 to 25%: see claim 2 and page 4, line 9 and less than 30% (9.5 to 28%): see page 9, line 41). A table on page 9 comprises further explicit disclosure of cross-reactivity values (310%, 36%, 28%, 13.5% and 9.9%). In conclusion, document (1) does not **explicitly** disclose any cross-reactivity value falling within the range of 0.01 to less than 8% stated in claim 1 of the patent in suit. However, there is numerical overlap between the said range (0.01 to less than 8%) and the one taught by document (1) (less than 50%). In case of overlap of numerical ranges of a parameter between a claim and a prior art document, it has to be established whether or not the skilled person would seriously contemplate applying the technical

teaching of the prior art document in the range of overlap (see decision T 0666/89, OJ EPO 1993, 495) in the present case, in the range of cross-reactivity below 8%.

6. There is a table on page 9 of document (1), whose two last r-h columns correlate five different cross-reactivities (310%, 36%, 28%, 13.5% and 9.9%) with five corresponding 50%-intercept values expressed in pg/ml (70, 40, 17, 16 and 15). The latter five values can also be deduced from Figure 1 of this document, where the thick horizontal line (the line of 50%-intercept) cuts the five curves labelled "1 to 5" and relating each to one of the five cross-reactivities listed in the table on page 9. Each curve shows the variation of the relative signal (% $B/B_0$) versus the concentration of $FT_4$ expressed in pg/ml. It is stated under the table of page 9 that any curve% $B/B_0$ versus pg/ml $FT_4$ has to cross the line of 50%-intercept within the dark vertical stripe of Figure 1, namely within the normal physiological range of $FT_4$ of 8 to 20 pg/ml, where the slope is maximum (point of inflection) and hence the sensitivity of the assay, too.

7. The appellant maintains that the skilled person wishing to obtain a curve whose 50%-intercept falls within the lower part of the physiological range of Figure 1, has of necessity to make $T_4$ analogues with a cross-reactivity of less than 8%. This is because it is possible to extrapolate and arrive at cross-reactivities below 8% by drawing a straight line through the five points derived from the last r-h columns of the table on page 9 of document (1) (P1 = (70, 310%), P2= (40, 36%); P3 = (17, 28%); P4 = (16,

13.5%) and P5 = (15, 9.9%)) plotted on a graph 50%-intercept vs. cross-reactivity.

8. However, the board observes that if one plots the five points P1 to P5 above on a graph, they are not co-linear. A straight line, which would possibly allow an extrapolation according to the appellant's submission, can be drawn there only if one or more of the points P1 to P5 are discarded. By doing that, one obtains rather a bundle of straight lines instead of a single line of extrapolation. Considering one of these lines to be more plausible than the others, is mere guesswork. Given this situation of uncertainty, one cannot draw the conclusion that document (1) directly and unambiguously discloses the claimed subject-matter.

9. This shows that the skilled person would not seriously contemplate to work in the range of cross-reactivity below 8%, and thus it must be concluded that the subject-matter of claim 1 and dependent claims 2 to 9 of the main request also fulfil the requirements of novelty (Article 54(3) EPC). In view of this, no need arises for the board to consider the auxiliary request.

## Order

## For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent in accordance with the

respondent's main request.

The Registrar: The Chairwoman:

A. Townend U. Kinkeldey