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Datasheet for the decision of 20 April 2009

Case Number: T 1759/06 - 3.4.02

Application Number: 93902684.5

Publication Number: 0617791

IPC: G01N 35/02

Language of the proceedings: EN

Title of invention:
Automated analysis equipment and assay method for detecting cell surface protein and/or cytoplasmic receptor function using same

Patentee:
Merck & Co., Inc.

Opponent:
Bayer Schering Pharma Aktiengesellschaft

Headword:
-

Relevant legal provisions:
-

Relevant legal provisions (EPC 1973):
EPC Art. 83, 84, 56

Keyword:
"Sufficiency - clarity - inventive step: independent claims (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1759/06 **-** 3.4.02

D E C I S I O N
of the Technical Board of Appeal 3.4.02
of 20 April 2009

Appellant: (Opponent)	Bayer Schering Pharma Aktiengesellschaft Kaiser-Wilhelm-Allee D-51373 Leverkusen (DE)
Representative:	Linhart, Angela Bayer Schering Pharma AG Law and Patents - Patents and Licensing D-51368 Lerverkusen (DE)
Respondent: (Patent Proprietor)	Merck & Co., Inc. 1 Merck Drive P.O. Box 100 White House Station New Jersey 08889 (US)
Representative:	Horgan, James Michael Frederic Merck & Co., Inc. Hertford Road Hoddesdon Hertfordshire EN11 9BU (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 13 September 2006 concerning maintenance of European patent No. 0617791 in amended form.**

Composition of the Board:

Chairman: A. G. Klein
Members: M. Rayner
B. Müller

Summary of Facts and Submissions

I. The opponent has appealed against the interlocutory decision of the opposition division that, taking account of the amendments made by the patent proprietor according to auxiliary request 1 in the opposition proceedings, European patent 0 617 791 (application no. 93 902 684.5) meets the requirements of the Convention. The patent concerns automated analysis equipment and assay method. Reference has been made in the opposition and/or appeal procedure to documents including the following:

E2 ML 1000 Microplate Luminometer Model 2.4 and Model 2.3
E3 EP-A-0 025 350
E6 WO-A-87 06 008
E10 DE-A-39 15 421
E15 Fluoroskan II Operating Instructions

II. The decision under appeal of the opposition division is based on reasons which can be summarised as follows.

(a) Article 84 EPC 1973

Inconsistent wording in the claims relating to wells, compartments, reagent addition means and delivery means could give rise to objection only under Article 84 EPC 1973. However, the wording concerned is found in the claims as granted and thus does not have to be considered in opposition proceedings as Article 84 is not a ground for opposition.

(b) Article 83 EPC 1973

(i) With respect to the number of wells measured or illuminated, expressing "...measure...in each sample simultaneously" cannot be construed as meaning all samples in a multi-well plate at the same time. Referring to the addition of "either or both" of a known compound or a test compound to a well cannot be construed as referring to only the addition of a known compound.

(ii) With reference to step (c) of claim 51 ("within a predetermined time period..."), whether the purpose of a method is fulfilled by the technical features in a claim does not have to be considered under Article 83 EPC 1973.

(c) Article 123(2) EPC 1973

(i) Measuring each sample in a multi-well plate refers not to all but only to predetermined wells so that claims 1 and 51 do not contain added subject matter.

(ii) Recording of fluorescence change until maximum is a preferred embodiment implying that measurement before maximum is also encompassed in the teaching of the application as filed.

(d) Article 56 EPC 1973

Document E3 represents the closest prior art, a difference contained in the subject matter claimed

in claims 1 and 62 of the patent residing in the attribute which is measured to monitor a cellular reaction being fluorescence. The objective problem is thus providing a fully automated apparatus for measuring a different type of reaction to that of document E3. The modular structure of document E6 provides no clear hint to modify the teaching of document E3 to include fluorescence detection means. The teaching of document E10 appears, in view of the capillary used, inherently unsuitable for extension to a multi-well plate system.

The division therefore concluded that the requirements of the Convention were met.

III. The appellant (=opponent) requests that the decision under appeal be set aside and the patent be revoked. Oral proceedings were originally requested on an auxiliary basis.

The case of the appellant in relation to the decision under appeal can be summarised as follows.

(a) Article 84 EPC 1973

The feature "means for optically irradiating the sample in the predetermined well" introduced into amended claims 1 and 62 renders the claims unclear in view of other differing wording referring to one or more predetermined wells in the claims.

(b) Article 83 EPC 1973

Inconsistency between functionality of measuring means and the method to be carried out leads to insufficiency in relation to claim 1 and 62. The reasoning of the first instance in relation to claims 1 and 62 is not convincing because of lack of differentiation between the "wells" and the "samples", of which the number need not be the same. Examples in the description may pertain to claim 51 not claim 1. The teaching of claim 1 is also insufficient for lack of including optical irradiation of several wells. Claim 27 includes three alternatives, of which one runs counter to the method purpose and what is attained by the method. In particular, the method of claim 27 is insufficient in relation to the test compound notwithstanding the argument of the first instance that the test compound must be considered a reference, this not being derived from the wording of claim 27. According to claim 51 "detecting and measuring... for a predetermined amount of time" is "within a predetermined period of time that is less than the time for the change in the intensity of the optical attribute to reach a maximum", i.e. the former is completely before the maximum. The teaching in the claim is therefore insufficient because the characteristic part of the curve is not detected. The reasoning of the first instance is not convincing because the description does not repair a gap in the teaching of the claim but contradicts it.

(c) Article 123(2) EPC 1973

Should the board not share the view of the first instance, that measurement exclusively before reaching intensity maximum is implicitly disclosed, an objection against claim 51 is made.

(d) Article 56 EPC 1973

The opposition division finally bases its inventive step decision on measurement of transient reactions in multi-well plates. However, the subject matter of claim 27 is only insignificantly different from the disclosure of document E10. Claim 27 envisages an embodiment using only one compartment, so that the difference from the teaching of document E10 is only that the compartment is one of a number. There is no invention in using a subdivided compartment compared to an undivided compartment. Moreover programming a measurement apparatus to use a subdivided compartment with sequential sampling of the sub compartments would have been obvious to the skilled person. A corresponding argument applies to claim 51. The arrangement known from document E10 with a multi-well plate, which is as such known, was also obvious so that the subject matter of claim 1 was also obvious. So far as documents E2 and E3 are concerned, the problem to be solved to reach the subject matter of claim 1 was rearranging the apparatus to use fluorescence measurement. The solution is provided by the Fluoroskan II device, already known at the priority date and mentioned in the patent in dispute. Operation of the device is described, for example in the operating instructions (document E15), dated March 1993, but containing older pages as can be proved by declaration of the manufacturer, if doubted by the patent proprietor. The subject matter of claim 1 cannot therefore be considered to involve an inventive step. The same arguments apply analogously to the subject matter of claim 62.

IV. The respondent (=patent proprietor) requests that the patent be maintained with the claims as filed with the response to the appeal (claim 62 amended). Oral proceedings are requested on an auxiliary basis.

The case of the respondent can be summarised as follows.

The invention relates to an apparatus and methods for observing the fluorescence, or other optical attribute, of a transient event occurring when cells are contracted with a reagent or test compound. Transient events are those which lead to a temporary change in the properties of the cell. They may last only a short time and typically involve the rise and fall of a parameter (see paragraph 75 of the patent in dispute). Automated measurement of such a change is clearly of interest in drug screening. Measurement is clearly a challenge since the change is time dependent and has to be monitored rapidly and carefully so that a peak response can be observed. The rate of change over time of the measured attribute may also be of interest, and accurate measurement of this is also valuable.

The following comments can be made about the objections raised by the appellant.

(a) Article 84 EPC 1973

Clarity objections do not arise for the amendments made at the end of claims 1 and 62 because the wording introduced derives from granted claim 89 which had already been examined for clarity. Claim 62 now refers to fluorescence.

(b) Article 83 EPC 1973

The issues raised by the appellant amount to mere allegations without providing proof as to insufficiency. In fact the objections raised are not insufficiency but disguised clarity objections as is indicated by an approach directed to inconsistencies.

Concerning claims 1 and 62, an interpretation requiring a measurement means that is for measuring each well individually or all wells simultaneously is only achieved by failing to read the whole claim. Moreover, the objection that only one well is optically excited is based on a misunderstanding of the English language. Referring to claim 27, since the method can be carried out one well at a time and a reference is mentioned, it follows that the skilled person would immediately appreciate the need to measure at least two wells. Concerning claim 51, the skilled person understands measurement commences within a predetermined period which is less than the time for the change in intensity to reach a maximum and occurs for a predetermined time. It is clear that the claim as a whole relates to detection or measurement of a cell event. Consequently, part (c) must include measuring the intensity maximum.

(c) Article 123(2) EPC 1973

No issues arise under this Article because the objections raised by the appellant only occur when an interpretation of the claim is taken requiring all the measurements to be taken before the intensity maximum is reached, but measurement is, in fact, as referred to

in the last sentence of the discussion relating to Article 83 above.

(d) Article 56 EPC 1973

It is considered that document E10 is not a disclosure which the skilled person would have modified to reach the invention because the skilled person could not modify the teaching without losing the advantages document E10 is purported to provide, e.g. alternating monochromatisation of a sample, rapid fluid changing with a capillary tube and measuring multiple samples by pre-programming a computer. Moreover, there is no room for an excitatory light source in the devices of documents E2 and E3. There is no reagent addition means in the Fluoroscan II device and no obvious way to add it. Just because individual features can be pulled out of various pieces of prior art, this does not mean the skilled person would have considered it obvious to put them together. Consequently, the finding of inventive step by the opposition division was correct.

V. Consequent to the auxiliary requests of the parties, the board appointed oral proceedings. In a communication attached to the summons, the board observed, inter alia, that concerning the operating manual E15, the parties had both mentioned a date in March 1993 after the priority date of the patent (20.12.1991). The respondent did not consider document E15 need be discussed further. The appellant had offered, yet not provided, proof of an earlier publication date. The board explained furthermore that the oral proceedings would offer an opportunity to elaborate on the appeal cases and requested that the

parties carefully check for omissions in a summary of the procedure given in the communication.

VI. Following the summons, the appellant withdrew its request for oral proceedings and indicated that it would not attend any such proceedings. The appellant also submitted that the subject matter of claims 27 and 51 was not new in the light of document E10 so far as an embodiment with one compartment is concerned as it makes no difference whether this method is carried out in a single or single divided compartment. For its part, the respondent observed it would attend the oral proceedings but if its submissions were accepted, the procedure could be concluded in writing. Introduction of lack of novelty as a ground should be rejected as late filed, in any case use of a divided culture vessel is completely ignored by the appellant.

VII. Following the submissions of the parties, the board cancelled the oral proceedings.

VIII. Independent claims 1, 27, 51 and 62 of the patent in dispute are worded as follows.

"1. A transient reaction automated measurement apparatus for automatically measuring transient reactions associated with ion channel activity or cell receptor activity, the apparatus comprising:
control means for coordinating the operation of the apparatus;
sample-containing means comprising a plurality of wells arranged as a plurality of columns of an equal number of wells on a multi-well plate for individual solution samples;

movement means responsive to the control means for aligning each predetermined well with a reagent-adding position or for simultaneously aligning more than one predetermined well with more than one reagent adding position;
reagent addition means responsive to the control means for adding reagent to one or more of the predetermined wells while aligned with the reagent-adding position;
measurement means responsive to the control means to:
(i) measure at least the fluorescence in each sample simultaneously or measuring at least the fluorescence in one sample at a time while aligned with a measurement position;
(ii) effect the commencement of measurement within a predetermined time period after reagent addition that is less than the time required for the transient reaction to reach its peak response; and
(iii) effect measurement of the fluorescence for a predetermined amount of time and which measurement means can effect multiple measurements for a predetermined time period, and wherein reagent addition and measurement of the fluorescence or the one or more predetermined wells is completed before reagent addition and measurement for the next one or more predetermined wells commences;
and means for optically radiating the sample in the predetermined well.

27. An automated method for identifying compounds that induce the occurrence of a cellular event that results in a change in the intensity of an optical attribute of an indicator moiety in response to the cellular event, the method comprising;

(a) introducing a divided culture vessel having an array of individual compartments into an apparatus, wherein:
(i) at least one compartment contains cells that when contacted with a compound that causes the cellular event to occur, the cells undergo the cellular event;
(ii) the cytoplasm of the cells comprises an amount of an indicator moiety sufficient to exhibit a detectable change in the intensity of the optical attribute upon occurrence of the event; and
(iii) the apparatus has delivery means to deliver reagent solution to one or more compartments of the divided culture vessel, and detecting and measuring means to detect and measure at least one attribute of the contents of the compartments;
(b) effecting alignment of a well or wells with the reagent adding means and automatically delivering to one or more predetermined compartments an aliquot solution comprising either or both of (i) an amount of a known compound that is effective to induce the cellular event; and (ii) a test compound of unknown activity; and
(c) within a predetermined time period that is less than the time for the change in the intensity of the optical attribute to reach a maximum, commencing measurement in one or more of the predetermined compartments, for a predetermined amount of time, of the level of the optical attribute emitted by the cells, wherein the detecting and measuring means and the predetermined compartments are aligned, whereby a compound that induces the occurrence of a cellular event is identified.

51. An automated method for detecting or measuring the occurrence of a cellular event that results in a change in the intensity of an optical attribute of an indicator moiety in response to the cellular event, the method comprising:
(a) introducing a divided culture vessel having an array of individual compartments in loan apparatus, wherein:
(i) at least one compartment contains cells that when contacted with a compound that causes the cellular event to occur, the cells undergo the cellular event;
(ii) the cytoplasm of the cells comprise art amount of the indicator moiety sufficient to exhibit a detectable change in the intensity of the optical attribute upon occurrence of the event; and
(iii) the apparatus has delivery means to deliver reagent solution to one or more compartments of the divided culture vessel, means for optically irradiating the compartments and detecting and measuring means to detect and measure at least the fluorescence of the contents of the compartments;
(b) effecting alignment of a well or wells with the reagent adding means and automatically delivering to one or more predetermined compartments an aliquot of a solution comprising an amount of a compound that causes the cellular event to occur, thereby allowing a detectable change in the level of the optical attribute in the compartment containing the cells to be measured, wherein the delivery means and the predetermined compartment(s) is (are) aligned; and
(c) within a predetermined time period that is less than the time for the change in the intensity of the optical attribute to reach a maximum, detecting and measuring in one or more of the predetermined

compartments, for a predetermined amount of time, the level of the optical attribute emitted by the cells, wherein the detecting and measuring means and the predetermined compartments are aligned, and whereby the occurrence of a cellular event is detected or measured.

62. An automated measurement apparatus for automatically measuring transient reactions, the apparatus comprising:
control means for coordinating the operation of the apparatus;
sample-containing means comprising a plurality of wells arranged as a plurality of columns of an equal number of wells on a multi-well plate for individual solution samples;
means responsive to the control means for aligning each predetermined well with a reagent-adding position or for simultaneously aligning more than one predetermined well with more than one reagent adding position;
means responsive to the control means for adding reagent to one or more of the predetermined wells while aligned with the reagent-adding position;
means responsive to the control means to:
(i) align each predetermined well with a measurement position or aligning more than one of the predetermined wells with more than one measurement position after addition of the reagent to the predetermined wells; and
(ii) effect the alignment of the predetermined wells with the measurement position within a timer period that is less than the time required for the transient reaction to reach its peak response;
measurement means responsive to the control means to:
(i) measure at least the fluorescence in each sample simultaneously or measuring at least the fluorescence

in one sample at a time while aligned with the measurement position;
(ii) effect the commencement of measurement within a time period such that alignment with the measurement position after reagent addition and the beginning of measurement is effected within 10 seconds or less; and
(iii) effect measurement of the attribute for a predetermined amount of time and wherein reagent addition and measurement of the fluorescence in one or more predetermined wells is completed before reagent addition and measurement for the next one or more predetermined wells commences; and means for optically irradiating the sample in the predetermined well."

Reasons for the Decision

1. The appeal is admissible.

2. The board considers the opening remarks of the respondent concerning transient reactions to be helpful in setting a backdrop for the invention. That these remarks are correct is confirmed by the opening remarks of the appellant in relation to inventive step that the opposition division based its decision on measurement of transient reactions in multi-well plates.

3. *Clarity*

The board concurs with the position of the opposition division and the respondent that the objection of lack of clarity concerns granted claims against which it is not a ground for opposition. The skilled person reading

the claims just has to make the best of the language used.

4. *Sufficiency*

4.1 In the present case, the appellant has not, in reading the patent specification in dispute, particularly the claims, demonstrated the knowledge of a skilled person, but has sought to play on verbal differences. Taking a more technical approach, the board is satisfied that an internally consistent reading of claim 1, and correspondingly claim 62, means that a skilled person understands that clauses (i) and (ii) of claim 1 refer back to "one or more" in the preceding clause. The approach of the appellant pertaining to uses of the terms "wells" and "samples" is contrived to read embodiments into the claim, which are not supported by any experimental or other evidence casting doubt on sufficiency of the disclosure, amounting in fact to an objection of lack of clarity, which, as explained in section 3 above, is not relevant. Moreover, the skilled person understands from the context of the claims that the feature deriving from granted claim 9 and concerning "means for optically radiating the sample in the predetermined well" is not in context limited to just one well. Furthermore, it is simply not feasible that a skilled person understands that implementing the invention as claimed in claim 27 and seeking to identify compounds means that only a known compound is used.

4.2 In the case of claim 51, the reference in (c) to "a predetermined time period" means a period within which the "detecting" or "measuring" commences and the

reference to "a predetermined amount of time" means the time measuring takes place. In other words, "measuring after it is all over" is not done, which the skilled person of course realises because the cellular event is detected or measured. In its submissions, the appellant reversed the order of the features concerned to make it appear that "within" implies the latter feature is contained in the former, but this is not what a skilled person understands. The board is therefore satisfied as to sufficiency.

5. *Added subject matter*

Since the board agrees with the respondent, as set out in the preceding point, about detecting the event, no issue of added subject matter arises.

6. *Clarity of amended claims*

Since feature (i) of claim 62 has been amended to refer to fluorescence, the objection made by the appellant has been met. Moreover, incorporation of the feature of granted claim 9 does not mean that just one well is irradiated (see section 3 on clarity and section 4.1 on sufficiency above), so that no clarity issue arises with respect to this amendment.

7. *Documents considered in the appeal proceedings*

7.1 Documents E2 and E3

The luminometers described in these documents measure luminescence but do not have any excitatory light source.

7.2 Document E6

The automated analytical chemistry processing centre described in this document is of a modular construction. While the appellant mentioned this document with reference to the decision under appeal, it did not use it in support of its arguments against patentability. The board has reviewed the remarks of the opposition division with reference to this document and sees no reason to depart therefrom.

7.3 Document E10

This document discloses an apparatus which measures fluorescence, the apparatus not using a multiwell plate but a measurement chamber containing a number of cells.

7.4 Document E15

In the summons attached to the summons to oral proceedings, the board drew attention to the fact that prior publication of this document had not been proven by the appellant. Since no proof has been forthcoming, the board is placed in the position of having to disregard the document as not pre-published.

8. *Patentability*

8.1 While it could be argued that the Fluoroskan II apparatus represents the closest disclosure, it is removed from consideration in this respect because prior publication of the document concerned, document E15 has not been proven.

8.2 Apart from the question of admissibility of introducing the ground of novelty in the appeal proceedings, there is no dispute that document E10 does not disclose a multiwell plate. Therefore, at least for this reason, it is necessary only to discuss inventive step in relation to patentability.

8.3 Inventive Step

8.3.1 Among the prior art documents, document E3 can be considered exemplary of a type showing an automated system using a multiwell format and document E10 of a type measuring fluorescence in cells. Since the patent in dispute is concerned with providing an automated system, the board concurs with the opposition division that document E10, which lacks a multiwell plate and has a delivery and measurement system not particularly suited to high throughput, cannot be considered to represent the closest prior art. Accordingly, document E3 constitutes the closest prior art and the novel features of the claims are those pertaining to fluorescence (claims 1, 51,62) or to the cellular event (claim 27).

8.3.2 No convincing reason has been provided by the appellant as to why it would have been obvious for the skilled person to have redesigned the device of document E3 in the light of document E6, to address transient events or in particular, for fluorescence measurement. The submissions provided in this direction relied on document E15, the prior publication of which has not been proven. These submissions are not therefore relevant. The board does not, therefore see any reason

to diverge from the positive position of the opposition division in relation to inventive step.

8.3.3 The point about using a multiwell plate is that it enables a greater throughput, which is not achieved by the apparatus according to document E10, which is focused on alternating monochromatisation of a sample, rapid fluid changing with a capillary tube and measuring multiple samples by pre-programming a computer and would therefore lead to rejection of the teaching of document E10 by the skilled person starting from document E3. Although the skilled person could have considered rebuilding the system of document E10 as urged by the appellant, this person following the teaching would not have done so because this would have lead to loss of the properties mentioned in the first sentence of this point. Accordingly, inventive step of the subject matter of the independent claims is not called into question either by the disclosure of document E10, alone or in combination with document E3, as was suggested by the appellant.

9. In view of the foregoing, the board has not been convinced that the decision of the opposition division is in error. The appeal accordingly fails.

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 the following version:

Description:

pages 2,5-18,20-26 of the patent specification
pages 3,4,19, filed during the oral proceedings before the opposition division on 26.07.06

Claims

Nos. 1-61, 63-69 filed with the letter of 23.05.06
No. 62 filed with the letter of 28.08.07

Drawings of the patent specification

The Registrar The Chairman

M. Kiehl A. G. Klein