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D E C I S I O N
of 7 April 2005

Case Number: T 0215/01 - 3.3.2

Application Number: 90909103.5

Publication Number: 0471794

IPC: A61K 31/35

Language of the proceedings: EN

Title of invention:
Antiviral therapy using thiazine and xanthene dyes

Patentee:
Oklahoma Medical Research Foundation, et al

Opponent:
Blutspendedienst der Landesverbände des DRK Niedersachsen, Sachsen-Anhalt, Thüringen, Oldenburg und Bremen gGmbH
Baxter International Inc.

Headword:
Method of inhibiting HIV replication: OKLAHOMA MEDICAL RESEARCH FOUNDATION, et al

Relevant legal provisions:
EPC Art. 56, 123(2), 111(1)

Keyword:
"Main request and auxiliary request 1 - inventive step - (no): use of methylene blue obvious"
"Auxiliary requests 2 and 3 - added matter - (yes): methods carried out independently "in vitro" and "in vivo" provide no support for a method carried out "ex vivo""
"Remittal (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0215/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 April 2005

Appellant: (Proprietor of the patent)
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Representative: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 7 December 2000 revoking European patent No. 0471794 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. H. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 471 794, based on application No. 90 909 103.5, was granted on the basis of 13 claims comprising two independent claims, namely claims 1 and 10.

Independent claims 1 and 10 read:

"1. The use of a xanthene or thiazine dye in the manufacture of a medicament for selectively inactivating HIV, in vivo, or in vitro, without significant toxicity to cells or a patient."

"10. A method of inhibiting HIV replication in cells exposed to the virus ex vivo, comprising exposing the cells to a xanthene or thiazine dye, without significant toxicity to the cells."

II. Notices of opposition were filed against the granted patent by the respondents.

The patent was opposed under Article 100(a) EPC for lack of novelty, lack of an inventive step and lack of industrial application (Article 52(4) EPC), under Article 100(c) EPC (added matter) and because the patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

The following documents, inter alia, were cited during the proceedings before the opposition division and the board of appeal:

(1) EP-A-0 196 515

(8) ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA, 1964, vol. 62, pages 461-462, H. Thormar et al. "Photoinactivation of Visna Virus"

(32) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1987, vol. 31, pages 1369-1374, K. Frank et al. "Visna Virus as an In Vitro Model for Human Immunodeficiency Virus and Inhibition by Ribavirin, Phosphonoformate, and 2',3'-dideoxynucleosides"

III. The appeal lies from a decision of the opposition division revoking the patent under Article 102(1) EPC pronounced at the oral proceedings held on 4 October 2000.

The opposition division held that neither the claims as granted of the patent in suit nor the claims of auxiliary requests 1 or 2 met the requirements of the EPC.

Thus the opposition division took the view that claim 1 of the patent as granted did not meet the requirement of inventive step and that claim 1 of auxiliary requests 1 and 2 contravened Article 123(2) EPC.

Claim 1 of the first auxiliary request was furthermore judged to lack clarity.

As to inventive step, the opposition division considered that document (1) was the closest prior art.

Concerning the in vitro aspect, it defined the technical problem to be solved as the identification of those agents among the list given in document (1) which actually showed the intended activity against HIV.

In view of document (8) and document (32), it considered that the skilled man would have expected HIV inactivation by methylene blue and toluidine blue.

As to Article 123(2) EPC, the opposition division furthermore considered that the introduction into claim 1 of auxiliary requests 1 and 2 of "wherein the dye is an intracellular or solution concentration of 0.1 to 10 μM" contravened Article 123(2) EPC.

IV. The appellant (patentee) lodged an appeal against the said decision and filed arguments.

V. With a letter of 17 March 2005, the appellant filed three auxiliary requests in replacement of the previous auxiliary requests.

Independent claims 1 and 5 of the first auxiliary request read:

"1. The use of methylene blue in the manufacture of a medicament for selectively inactivating HIV, in vivo, or in vitro, without significant toxicity to cells or a patient."

"5. A method of inhibiting HIV replication in cells exposed to the virus ex vivo, comprising exposing the

cells to methylene blue, without significant toxicity to the cells."

Independent claims 1 and 5 of the second auxiliary request read:

"1. The use of methylene blue in the manufacture of a medicament for selectively inactivating HIV, in vivo, or in vitro, without significant toxicity to cells or a patient, wherein the medicament yields an intracellular concentration between 0.1 and 10 µM."

"5. A method of inhibiting HIV replication in cells exposed to the virus ex vivo, comprising exposing the cells to methylene blue, without significant toxicity to the cells, wherein the method yields an intracellular concentration between 0.1 and 10 µM."

Independent claim 1 of the third auxiliary request is identical to claim 5 of the first auxiliary request.

VI. Oral proceedings were held before the board on 7 April 2005.

During the oral proceedings, the respondent filed four further auxiliary requests, namely auxiliary requests 2 and 5 in addition to the previous auxiliary requests 1 and 3, which were renumbered consequently, and later on auxiliary requests 4 and 5.

All the newly-filed auxiliary requests were rejected by the board as late-filed.

VII. The submissions of the appellant can be summarised as follows:

As regards the objection of added matter with respect to claim 10 as granted, the appellant was of the opinion that claim 10 of the main request was supported by claim 1 as originally filed restricted to an "ex vivo" aspect, in combination with page 8, lines 22 and 23, of the originally filed description.

The appellant further explained that a method of inhibiting HIV replication in cells ex vivo consists in extracting cells from a living organism, treating the cells in vitro and finally reintroduction of the cells into the same or another living organism.

From this definition, the appellant concluded that "ex vivo" had a restricted meaning with respect to "in vivo" and consequently a method carried out ex vivo was actually fully encompassed by a method carried out in vivo.

The appellant furthermore indicated that example 10 of the application as originally filed related to the treatment of blood in vitro while the inhibition of HIV in vivo was disclosed in example 9 on page 35, lines 8 to 11.

With respect to novelty, it argued that novelty was established by the selection within two different lists of considerable lengths.

With respect to inventive step, the appellant referred to the lack of predictability in the field of viruses

in that the inactivation of a given virus by a compound could not be extrapolated to the inactivation of another virus, more particularly the AIDS virus, by the same compound.

It thus considered that the teaching of document (1) was speculative.

It furthermore pointed out the differences in the mechanism of action to inactivate viruses in document (1) and in the patent in suit and highlighted the importance of lack of toxicity in the claimed uses.

It furthermore referred to data provided with a letter of 17 March 2005 comparing the efficacy of the inactivation by methylene blue with other thiazine dyes.

As to the request to remit the case to the first instance, the appellant held that the opposition division did not make a reasoned decision by completely ignoring the declaration of Dr Raymond Schinazi and Dr Robert Floyd who are renown international experts in AIDS research.

There had been thus a procedural irregularity justifying the remittal of the case to the opposition division.

The appellant furthermore added that new issues were put forward for the first time during the oral proceedings, i.e. substantives aspects of the first priority document (US 350 383 of 11 May 1989) and added

matter with respect to the "*ex vivo*" aspect of claim 10 as granted.

VIII. Respondent 01 contested these arguments.

In its view, claims 1 and 10 as granted contravened Article 123(2) EPC, since claim 1 also encompassed the inhibition of extracellular HIV virus and since no basis could be found for "*ex vivo*" in the original description.

It furthermore maintained that the claimed matter lacked novelty and an inventive step over document (1) alone, or in combination with other prior-art documents.

IX. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1 to 3, filed with letter dated 17 March 2005, or, as a further auxiliary request, that the case be remitted to the first instance for further prosecution.

The respondent (opponent 1) requested that the appeal be dismissed.

The respondent (opponent 2) had requested in writing that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2. *Admissibility of the auxiliary requests*

2.1 Admissibility of the auxiliary requests filed with a letter of 17 March 2005

These auxiliary requests were filed about three weeks before the oral proceedings without any new issues appearing in the file.

The board notes that the newly-filed auxiliary requests constitute a simplification of the issues to be dealt with, since they meet foreseeable objections, and that they do not amount to an abuse of the appeal proceedings since they do not require any further investigation into the assessment of their patentability.

Under these particular circumstances and as it is in its interest to have improved requests, the Board considers it appropriate to deviate from the standard admissibility requirements and exceptionally to admit these requests into the proceedings.

2.2 Admissibility of the auxiliary requests filed during the oral proceedings

2.2.1 Auxiliary requests 2 and 5 filed during the oral proceedings.

These auxiliary requests were filed in direct response to the board's observation made during the oral proceedings that it saw problems with the "*in vitro*" aspect covered by claim 1.

Claim 1 of newly-filed auxiliary requests 2 and 5 differs from claim 1 as granted only in that the in vitro alternative is deleted, i.e. is restricted to an *in vivo* use.

However, claim 1 still contains the expression "without toxicity to cells or a patient".

The Board informed the appellant that it saw a clarity problem in this claim in that the mention of the toxicity to cells seemed to relate to an "*in vitro*" aspect which, according to the wording of the claim, should no longer be claimed.

In response to the invitation of the board to correct this lack of clarity, e.g. by amending the expression "without toxicity to cells or a patient" into "without toxicity to cells of a patient", the appellant wished to maintain this expression, giving furthermore explanations which implied that claim 1 actually still covered *in vitro* aspects.

Under these circumstances, as it was not immediately apparent whether these auxiliary requests were allowable under Article 84 EPC, they were considered as late-filed and are therefore not admitted into the proceedings.

2.2.2 Auxiliary requests 4 and 5 filed at the end of the oral proceedings.

The argument submitted by the respondent for filing these requests at that stage was that it was a in response to the argument heard for the first time that claim 10 as granted (main request), claim 5 of auxiliary requests 1 and 2 and claim 1 of auxiliary request 3 infringed Article 123(2) EPC on account of the expression "ex vivo".

Claim 1 of auxiliary requests 4 and 5 differed from claim 10 as granted (main request) only in that the expression in vivo had been amended into *in vitro* and deleted respectively.

As claim 1 of these requests obviously infringed Article 123(3), these requests were not admitted into the proceedings.

3. During the oral proceedings, the appellant expressed its fear that the appeal would only be dismissed for formal reasons and not on its merits.

Accordingly, although the board saw formal problems under Article 123(2) EPC with claim 10 of the main request and claim 5 of the first auxiliary request directed to "*ex vivo*" methods (see point 5 below), in the circumstances of the case, the Board has decided to give reasons regarding inventive step of the subject-matter of claim 1 of the main and first auxiliary requests which was discussed extensively during the oral proceedings.

4.1 Main request and auxiliary request 1

Claim 1 of these requests is supported by the original disclosure, more particularly by page 8, lines 2 to 11, in combination with page 7, lines 19 to 25, of the application as originally filed.

4.2 Novelty over document (1)

Document (1) discloses a method for inactivating a virus in a therapeutic composition comprising the addition of a photosensitizer to the composition.

Among the photosensitizers cited there are inter alia porphyrins, psoralens, neutral red, methylene blue, acridines, toluidines, flavine and phenothiazine derivatives (see claim 3 of document (1)).

Document (1) also mentions that the claimed method comprises inter alia the inactivation of HTLV III which is an HIV (see page 9, lines 27 to 30, of document (1)).

In the working examples, the inactivation of HIV (called LAV in document (1)) is carried out with chlorpromazine, which is a thiazine photosensitizer.

Claim 1 of the contested patent (main request) is concerned with the inactivation of HIV with, inter alia, thiazine dyes.

The board has some doubts whether chlorpromazine, especially under exposure to unfiltered light from an 85-watt high-pressure mercury arc lamp at a distance of 10 cm, i.e. under an excited form, can be regarded as a

dye or not. However, in view of the outcome of the discussion of inventive step (see point 4.3 below), there is no need to give a final decision on the issue of novelty of the claimed subject-matter over the disclosure of document (1).

4.3 Inventive step

4.3.1 Document (1) is the closest prior art. This document discloses the inactivation of LAV with 10^{-4}M chlorpromazine in an antihemophilic factor (AHF) composition, under exposition to unfiltered light from an 85-watt high-pressure mercury arc lamp at a distance of 10 cm (see example 5, second set of data, of document (1)).

Document (1) further teaches that the inactivation of viruses in a therapeutic protein composition can be carried out with porphyrins, psoralens, dyes such as neutral red, methylene blue, acridine[s], toluidines, flavine and phenothiazine derivatives (see document (1), on page 7, lines 9-12, claim 3).

Document (1) adds that the preferred photosensitizers are compounds which are not toxic and do not present a biohazard and that these include compounds naturally occurring within the body such as protoporphyrine or compounds which have been approved for other therapeutic uses at much higher concentration, such as chlorpromazine (see claim 3 and page 7, lines 12 to 17, of document (1)).

Document (1) discloses all the technical features of claim 1 of the first auxiliary request, except the

particular combination of HIV specifically inactivated with methylene blue.

4.3.2 Accordingly, in view of this prior art the problem underlying the patent in suit can be seen in the provision of an alternative method of inactivating HIV *in vitro*.

4.3.3 The problem is solved by the choice of methylene blue.

Having regard to the data provided in examples 3 and 4 (e.g. those of tables 3 and 4 of the description) showing the HIV inhibitory activity of methylene blue and those provided with the letter of 17 March 2005, the Board is satisfied that the problem has been solved indeed.

4.3.4 The skilled person faced with the above stated problem would first consider solutions suggested in document (1) itself.

Document (1) teaches preferably choosing from the list of derivatives disclosed those derivatives which are not toxic or which naturally occur within the body or have been approved for other therapeutic uses.

The list of derivatives suggested in document (1) for the inactivation of viruses comprises two groups of agents, there are specific compounds, such as neutral red, methylene blue and classes of derivatives, such as porphyrins, psoralens, acridines, toluidines, flavine and phenothiazine derivatives.

When considering the list, the skilled person would first be directed to the individual compounds mentioned, since there is no need to make the further step of selecting a derivative within the class.

There are only two individual derivatives mentioned, i.e. methylene blue and neutral red.

Methylene blue is a molecule which has been intensively studied for its applicability in various therapeutical uses (also see page 5, line 41, to page 6, line 9, of the patent in suit).

Moreover, methylene blue can be regarded as one of the most popular agents having a wide spectrum of applications in organic, inorganic and particularly medical research laboratories. Methylene blue indeed belongs to the basic equipment of any student in the field of chemistry and biochemistry respectively.

The skilled man would thus automatically first try to carry out experimental work in order to test the efficacy of methylene blue for the inactivation of HIV and would thus arrive at the subject-matter of claim 1 of the main and first auxiliary request without the exercise of inventive skill.

4.3.5 The appellant's submission that methylene blue being an HIV-inactivating agent proved to be the most effective compound compared to closely related phenothiazine derivatives, was active though another mechanism and was non toxic could not lead the Board to a different conclusion.

The HIV inactivating activity of methylene blue was compared with that of toluidine blue, azure A, azure B and thionine.

All derivatives of these comparative studies are phenothiazine derivatives. None of them are cited in document (1), except methylene blue.

Since, for the above reasons, the skilled person would automatically first have envisaged the use of the methylene blue without the exercise of inventive ingenuity, any additional advantage (e.g. high activity, different mechanism of action), even if it was unexpected, could only be considered as a gratis effect which would inevitably have resulted from the skilled person's non-inventive activity.

5. *Auxiliary request 2: added matter*

Claim 5 of this auxiliary request is directed to an "*ex vivo*" method.

The description as originally filed does not contain any support for a method which is carried out *ex vivo*.

The specification as originally filed relates to methods carried out independently *in vivo* or *in vitro*, e.g. examples 9 and 10 as pointed out by the appellant, but fails to disclose the treatment of cells *in vitro* followed by their reintroduction into a body.

Consequently, the Board concludes that an *ex vivo* method, i.e. requiring the reintroduction of cells into a body subsequent to an *in vitro* treatment of the

cells, is not disclosed in the application as originally filed.

The subject-matter of claim 5 of auxiliary request 2 therefore infringes the requirements of Article 123(2) EPC.

6. *Auxiliary request 3*

As claim 1 of this auxiliary request is identical to claim 5 of auxiliary request 2, the reasoning and conclusion in point 5 hold good for this request as well.

7. *Remittal to the first instance*

Under Article 111(1) EPC, following the examination as to the allowability of the appeal, the Board may exercise any power within the competence of the first-instance department or remit the case to that department.

Having arrived at the present stage of the proceedings, the Board is thus not obliged to remit the case but has the power to assess the appropriateness of a remittal in each case on its merits. More particularly, a remittal to the department of first instance would be appropriate if a new submission were made by an opposing party which could jeopardise the maintenance of the patent.

In the present case, the examination as to the allowability of the claims is made in respect of the

same documents as those taken into consideration by the department of first instance.

It is indeed a fact that the appellant was confronted for the first time during the oral proceedings with the new argument that there was no support for any "*ex vivo*" method in the description as originally filed. The board also did not overlook the fact that the opposition division did not explicitly take position on the allowability under Article 123(2) EPC of granted claim 10.

However, the appellant had ample opportunity and enough time during the oral proceedings before the Board to submit arguments and to file amendments. The arguments regarding the support in the original application have been heard by the Board.

As regards the omitted declarations of experts provided in the opposition proceedings, the Board cannot agree that they were not considered by the opposition division simply because there are no explicit comments on them in the written reasons regarding assessment of inventive step. On the contrary, as they are mentioned in the decision under appeal (see point I.3 of the facts and submissions), the board can only conclude that they were considered by the opposition division.

The Board does not therefore see any justification for a remittal and exercises its discretionary power under Article 111(1) EPC to take a final decision in the interest of overall procedural economy and effectiveness.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

A. Townend U. Oswald