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D E C I S I O N
of 16 November 2004

Case Number: T 0443/01 - 3.3.2

Application Number: 92902708.4

Publication Number: 0560928

IPC: A61M 11/00

Language of the proceedings: EN

Title of invention:

Use of NO for the treatment or prevention of
bronchoconstriction

Patentee:

THE GENERAL HOSPITAL CORPORATION

Opponent:

AIR PRODUCTS AND CHEMICALS, INC.
AIR LIQUIDE SANTE France/AIR LIQUIDE SANTE (INTERNATIONAL)

Headword:

Use of NO against broncho- and vasoconstriction/THE GENERAL
HOSPITAL CORPORATION

Relevant legal provisions:

EPC Art. 54

Keyword:

"Main and auxiliary request - novelty - no: claimed use known
from method of treatment disclosed in the prior art"

Decisions cited:

T 0081/84, T 0780/89, T 0024/91, T 0158/96

Catchword:

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Case Number: T 0443/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 November 2004

Appellant: AIR PRODUCTS AND CHEMICALS, INC.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 19 February 2001
rejecting the opposition filed against European
patent No. 0560928 pursuant to Article 102(2)
EPC.

Composition of the Board:
Chairman: U. Oswald
Members: J. Riolo
J. H. P. Willems

Summary of Facts and Submissions

- I. European patent No. 0 560 928, based on application No. 92 902 708.4, was granted on the basis of 21 claims comprising five independent claims, namely claims 1, 2, 3, 7 and 20.

Independent claims 1, 2, 3, 7 and 20 as granted read:

"1. Use of gaseous nitric oxide (NO) for the production of an inhalable medicament for treating or preventing bronchoconstriction in a mammal by a method comprising inhalation of NO in a concentration which is therapeutically effective in the treatment or prevention of said disease."

"2. Use of a gaseous mixture consisting of NO and an inert gas (preferably N₂) for the production of an inhalable medicament for treating or preventing bronchoconstriction or reversible pulmonary vasoconstriction in a mammal."

"3. Use of a source of nitric oxide for the production of an inhalable medicament for treating or preventing reversible pulmonary vasoconstriction in a mammal by a method comprising identification of an individual mammal in need of said treatment or prevention, and inhalation by said mammal of said medicament in an amount which provides an amount of NO which is therapeutically effective in the treatment or prevention of said disease."

"7. A gaseous mixture consisting of NO and an inert gas (preferably N₂) for use in a method of treating bronchoconstriction or reversible pulmonary vasoconstriction in a mammal."

"20. A method of providing an inhalable medicament by continuously mixing NO with an oxygen-containing gas."

II. Notice of opposition was filed against the granted patent by the appellant.

The patent was opposed under Article 100(a) EPC for lack of novelty and lack of an inventive step.

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

- (2) Higebottam et al. " Inhaled endothelium derived-relaxing factor (EDRF) in primary hypertension (PPH)" American Review of Respiratory Disease Supplement, Volume 137, page 107, 1988
- (26) Pepke-Zaba et al. "Inhaled Nitric Oxide (NO), a Selective Pulmonary Vasodilator", Torax, volume 44, page 334p, 1989
- (17) Katsumi et al., "Metabolic Fate of Nitric Oxide" International Archive of Occupational and Environmental Health, vol. 46, pages 71-77, 1980
- (27) Pepke-Zaba et al. "Acute pulmonary vasodilator effects of inhaled nitric oxide (NO) in patients with primary pulmonary hypertension (PPH)" The

European Respiratory Journal, volume 3, Supplement
10, page 313s, abstract 1238, 13 September 1990

III. By its decision pronounced on 18 January 2001, the
opposition division rejected the opposition under
Article 102(2) EPC.

As regards novelty, the opposition division took the
view that:

the subject-matter of claim 1 was novel over the
available prior art because none of the cited documents
disclosed the use of NO for treating or preventing
bronchoconstruction,

the subject-matter of claims 2 and 7 was novel over the
available prior art and in particular over documents
(2), (26) and (27), because these documents did not
disclose a gaseous mixture consisting of NO and an
inert gas,

the subject-matter of claim 3 was novel because no
therapeutical use of NO was disclosed in the prior art,
similar to the situation referred to in decision
T 158/96 (not published in OJ EPO, point 3.4.1, last
sentence),

the subject-matter of claim 20 was novel over the
opposed document (17), because ¹⁵NO did not anticipate
the novelty of ¹⁴NO and because no medicament was
disclosed in document (17).

As regards inventive step, the opposition division
regarded document (26) as the closest prior art for the

subject-matter of claims 1, 2, 3 and 20. It considered that the subject-matter of these claims was inventive vis-à-vis this document, because the tests carried out in document (26) did not render obvious the use of NO as a medicament.

The opposition division also took the view that the subject-matter of claim 7 was inventive over document (17), in particular because the person skilled in the art would not use a gaseous mixture comprising NO and CO for therapeutical purposes in the light of its content.

- IV. The appellant (opponent 01) lodged an appeal against the said decision.

- V. On 19 June 2002, an intervention under Article 105 EPC was filed. The patent was attacked under Article 100(a) EPC for lack of novelty, lack of an inventive step and because the use claims concerned a method for therapeutical treatment, and under Article 100(c) EPC on account of added matter in claims 20 and 21. Furthermore, the priority right was contested.

- VI. In the communication accompanying the summons to the oral proceedings, the opinion was expressed that there was no new matter added to claims 20 and 21 and the transfer of the priority right was valid.

- VII. On 16 September 2004, the respondent filed 10 auxiliary requests, i.e. auxiliary request 1A, 1B, 2A, 2B, 3A, 3B, 4, 5A, 5B and 6.

VIII. Oral proceedings were held before the board on 16 November 2004.

At the beginning of the oral proceedings, the admissibility of the 10 auxiliary requests filed on 16 September 2004 was discussed. These auxiliary requests were then rejected by the board as late-filed.

During the oral proceedings, the respondent filed four other auxiliary requests, namely auxiliary requests 1 to 4, which were then replaced by another set of five auxiliary requests, ie auxiliary requests 1 to 5.

At the very end of the oral proceedings, the respondent filed two further auxiliary requests, auxiliary requests 6 and 7.

All auxiliary requests were rejected by the board as late-filed, excepted auxiliary request 1.

IX. The submissions of the appellant and of the intervener can be summarised as follows:

The objection of added matter was not maintained during the oral proceedings.

As regards the question of novelty under Article 54 EPC, they took the view that the features of claim 3 of the patent in suit were all anticipated by each of documents (2), (26) and (27).

As to inventive step, the appellant contended that the claimed matter was moreover obvious over the same prior art documents.

X. In the respondent's view, the subject-matter of claim 3 of the patent in suit was novel and involved an inventive step over documents (2), (26) and (27) because these documents neither disclosed nor suggested a therapeutical use but merely a scientific experiment which did not suggest that any therapeutical effectiveness could be achieved with NO.

Finally, it argued that, having regard to the toxicity of NO, there was a technical prejudice against its therapeutic use, in particular for the treatment of persistent pulmonary hypertension of newborns.

XI. The appellant and intervener (opponents) requested that the decision under appeal be set aside and that European patent No. 0560 298 be revoked.

The respondent (patentee) requested that the appeal be dismissed and that the patent be maintained as granted (main request) or, alternatively, on the basis of the auxiliary request, the only auxiliary request admitted in the proceedings.

Reasons for the decision

1. The appeal is admissible.
2. *Admissibility of the auxiliary requests*
 - 2.1 Auxiliary requests filed with letter of 16 September 2004.

In the absence of any valid arguments from the appellant as to why these requests could not have been filed earlier, they are considered as late-filed and are not therefore admitted into the proceedings.

2.2 Auxiliary requests 1 to 4 filed during the oral proceedings.

The only argument submitted by the respondent for the filing of these requests at that stage was that there was a reaction to the disclosure of document (2). However, as this document was already in file before the opposition division, the same conclusion as under point 2.1 applies.

2.3 Auxiliary requests 1 to 5 (filed in place of the previously filed auxiliary requests 1 to 4; see 2.2 above) and auxiliary requests 6 to 7 filed at the very end of the oral proceedings.

2.3.1 Auxiliary request 1

The set of claims of the first auxiliary request differs from the set of claims of the main request only in that all claims or the part of claims directed to a product for a first medical use were deleted.

As this auxiliary request was filed as a direct response to the board's observation made during the oral proceedings as to the scope of claims directed to a product for a first medical use, this set of claims is admitted into the procedure.

2.3.2 Auxiliary requests 2 to 5

The respondent argued that the amended claims in these requests have been filed in response to an argument put forward for the first time during the oral proceedings, namely that the expression "therapeutically effective" could not be regarded as a distinguishing technical feature in the present case.

Since claim 2 of each of auxiliary requests 2 to 5 was amended, although it did never contain the expression "therapeutically effective", the board cannot accept the respondent's submission.

The more so, since the contested expression was in fact introduced in most of the newly filed sets of claims (see claim 2 of auxiliary requests 2, 4, 5).

Accordingly, the same conclusion as under point 2.1 applies to auxiliary requests 2 to 5.

2.3.3 Auxiliary requests 6 and 7

These requests were filed when the board was announcing its intention to deliberate on the admissibility of auxiliary requests 1 to 5.

Therefore, the board cannot see any justification for the filing of these requests at that stage as it can be neither a reaction to observations made by it nor a reaction to submissions made by the other parties.

Accordingly, the same conclusion as under point 2.1 applies to these requests.

3. *Main request*

Novelty

3.1 Claim 3 of the patent in suit is a Swiss-type claim, which can be analysed as follows:

1. use of a source of nitric oxide
2. for the production of an inhalable medicament
3. for treating or preventing reversible pulmonary vasoconstriction in a mammal
4. by a method comprising
 - 4.1 identification of an individual mammal in need of said treatment or prevention, and
 - 4.2 inhalation by said mammal of said medicament in an amount which provides an amount of NO which is therapeutically effective in the treatment or prevention of said disease.

According to the patent in suit, the source of nitric oxide can be "... any [other] known source of the chemical NO, so long as NO is delivered to the site within the airways ..." (page 6, lines 17 to 21).

3.2 Document (2) discloses, as acknowledged on page 4, lines 20 to 25 of the description of the patent in suit, the vasodilatory effects of inhaled NO in seven patients with primary pulmonary hypertension.

From the table in this document, it is apparent that the average pulmonary artery pressure ($\overline{\text{PAP}}$) of these patients when breathing 40 ppm NO in air was 56.7 mm Hg, compared to 59.6 mm Hg when breathing air

without added NO, a difference in the mean values of 2.9 mm Hg.

The pulmonary resistance (PR) was also decreased from 17.7 to 16.1 (PR is the quotient of $\overline{\text{PAP}}$ divided by \dot{Q} , cardiac output).

NO was inhaled from Douglas bags at a concentration of 40 ppm in air over two periods of five minutes each.

Thus, (2) discloses

1. the use of a source of nitric oxide (Douglas bag containing 40 ppm NO in air, ie a source of nitric oxide within the meaning of the patent in suit - see point 3.1 above).
2. for the production of an inhalable gas (40 ppm NO in air)
3. for treating reversible pulmonary vasoconstriction in a mammal (seven patients with primary pulmonary hypertension (PPH) - see also the table in (2) where the vasodilatation effects are reported showing that the condition is reversible)
4. by a method comprising
 - 4.1 identification of an individual mammal in need of said treatment or prevention (seven patients with PPH).

3.3 Having regard to the characteristics 2 and 4.2 of the analysis of claim 3, it remains to be examined whether the amount of NO according to document (2) provided by

the administration of 40 ppm NO in air from a Douglas bag during a period of 5 minutes is therapeutically effective as an inhalable medicament.

In the cases considered, the patients who were treated suffered from primary pulmonary hypertension, which is characterised inter alia by an elevated pulmonary artery pressure (Δ PAP) and by a higher pulmonary vascular resistance (Δ PVR) in the lungs.

Δ PAP is the difference between the elevated PAP and "normal" PAP (about 14 mm Hg at rest).

PVR (pulmonary vascular resistance) is computed by subtracting the pulmonary capillary wedge pressure (PCWP) (or left atrial pressure when available) from the mean pulmonary artery pressure (PAP), and dividing by the cardiac output (see page 5, lines 7 to 9 of the patent in suit).

As explained in the footnote bridging page 6 and page 7 of the respondent's submission of 12 February 1999, Δ PVR, which is the difference between the patient's elevated PVR and "normal" PVR, can be calculated from the data of document (2) making the assumption that PCWP remains constant whether the patient breathes air or 40 ppm NO in air, that a patient without cardiac disease will have a PCWP ranging from 5 to 10 mmHg and that normal PVR is 1 mm Hg.min/litre.

The estimated reduction in $\overline{\Delta$ PVR in document (2)'s patients who breathed 40 ppm NO in air is 11% to 12%, depending on whether a 5 mm Hg or 10 mm Hg PCWP is

assumed (see the last three lines of the footnote on page 7 of the respondent's letter of 12 February 1999).

From document (2), it also appears, as acknowledged by the respondent's letter of 12 February 1999 (see the last three lines of the footnote on page 7), that the average of the abnormal elevated pulmonary artery pressure ($\overline{\Delta\text{PAP}}$) of the patients decreased by about 6%.

Thus, the question arises whether or not the diminution by 6% of the $\overline{\Delta\text{PAP}}$ or by about 11% of the $\overline{\Delta\text{PVR}}$ is such that the treatment should fall under the category of therapeutic treatment.

According to the case law of the board of appeal (see T 81/84, OJ EPO 1988, 207, point 4; T 780/89, OJ EPO 1993, 440, point 3.3) "the use of medicaments may be called for whenever the human body is suffering from a disease, illness, pain or discomfort or incapacity, and the administration thereof could provide or contribute to either full or partial healing, or relief or restoration of fitness".

Accordingly, even a partial healing, such as the one achieved by the administration of NO according to the disclosure in document (2), is to be construed as "therapy" or "therapeutic use".

It must therefore be concluded that the treatment described in (2) is therapeutically effective within the meaning of the established case law of the boards of appeal and that a gas mixture containing 40 ppm NO in air is in fact a medicament.

Therefore, document (2) anticipates the subject-matter of claim 3.

- 3.4 The respondent alleges that no therapeutically effective treatment within the meaning of claim 3 of the patent in suit was achieved in document(2).
- 3.4.1 The respondent refers to the passage on page 4, line 58, to page 5, line 10, of the description of the patent in suit where it is stated that a pulmonary vasodilatory treatment is herein said to be "therapeutically effective" in a given patient if it can induce any one or more of the following:
- (1) prevention of the onset of pulmonary vasoconstriction following an injury (such as aspiration or trauma) that could be expected to result in pulmonary vasoconstriction;
 - (2) a 20% or more decrease in the patient's Δ PVR (the difference between the patient's elevated PVR and "normal" PVR, with normal PVR assumed to be below 1 mm Hg.min/litre for an adult human, unless found to be otherwise for a given patient);
 - (3) a 20% or greater decrease in the patient's Δ PAP;
 - (4) in adults with acute or chronic respiratory failure (eg due to asthma or pneumonia), an improvement in arterial oxygen tensions by at least 10 mm Hg; or

- (5) in an infant, improved transpulmonary O₂ transport, as measured by a 10% or greater increase in upper body (pre-ductal) arterial O₂ saturation.

The respondent observed that the treatment in document (2) only achieved a decrease of 6% of the $\overline{\Delta PAP}$ or about 11% of the $\overline{\Delta PVR}$ as opposed to the 20% decrease required and thus the subject-matter of claim 3 was novel over (2).

It must firstly be pointed out that these requirements are not in the claims and thus cannot delimit the claimed matter vis-à-vis prior art document (2).

Moreover, when the technical information of the patent in suit is compared with the disclosure of document (2), the patent in suit appears not to teach any additional specific means or treatment conditions for achieving these values.

It is in any case doubtful whether their introduction into claim 3 would have conferred novelty on this claim.

Indeed, the term "therapy" is not restricted to curing a disease and removing its causes. Rather, as mentioned above (see point 3.3), this term also encompasses treatments which are designed to lessen the symptoms (see also T 24/91, OJ EPO 1995, 512).

The present situation is therefore to be distinguished from the circumstances which led to decision T 158/96 (not published in OJ EPO; cited in CLBA 2001, I.C.2, page 55), cited by the opposition division in its

decision for the assessment of novelty of the subject-matter of claim 3 over (2).

In fact, the study reported in (2) is not at all equivalent to the particular "phase II evaluation" considered by the board of appeal in case T 158/96.

In that specific case, the prior art document merely reported that phase II clinical trials were being undertaken to evaluate sertaline for the treatment of obsessive-compulsive disorder (OCD).

The board considered that the skilled person, reading in the prior art that sertraline was undergoing phase II trials for OCD, had no means of concluding from this information, reliably and beyond mere speculation, that the drug finally proved, during this phase, any therapeutic effect potentially useful in the treatment of OCD (reasons 3.4.1).

Under these specific circumstances, the board recognised as plausible the appellant's arguments that experimentation in animals was not indicative of any therapeutic effectiveness of sertraline for OCD since **no model for OCD actually existed**, but was simply intended to prove the lack of any form of toxicity and to gain early knowledge about the metabolism of the substance (reasons 3.6).

In contrast, in the present case, the state of the art represented by document (2) clearly and unambiguously demonstrated that nitric oxide was a pulmonary vasodilator as shown under 3.3.

3.4.2 The respondent also submitted that document (2) failed to develop an administration mode for NO that would have been considered suitable for therapeutic use since the use of a Douglas bag is not a safe administration mode on account of the concentration of NO₂ which is toxic and which rapidly increases, while the concentration of NO decreases.

The board observes that claim 3 of the patent in suit is not limited to any mode of administration, so that this argument cannot be taken into account in any case.

3.4.3 In addition, the respondent further stated that, given the toxicity of NO, the skilled person would have been prejudiced against using NO in the treatment of persistent pulmonary hypertension of the newborn.

Again, claim 3 is not limited to any population and therefore this argument cannot be taken into account when assessing novelty of claim 3.

3.4.4 Finally, the respondent pointed out that document (2) disclosed a scientific study as opposed to the claimed method of treatment.

The board agrees that (2) discloses a scientific study.

However, for the reasons pointed out above (point 3.3), this study is at the same time a disclosure of a therapeutic treatment having regard to the effects which were achieved.

3.5 Under these circumstances, the board concludes that the subject-matter of claim 3 of the main request lacks novelty under Article 54 EPC.

There is therefore no need to examine the remaining independent claims

4. *Auxiliary request 1*

As claim 3 of the main request is still present in this auxiliary request, the reasoning and conclusion in point 3.3 hold good for this request as well.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

A. Townend

U. Oswald