

**Internal distribution code:**

- (A) [ ] Publication in OJ  
(B) [ ] To Chairmen and Members  
(C) [X] To Chairmen  
(D) [ ] No distribution

**Datasheet for the decision  
of 10 October 2013**

**Case Number:** T 0809/10 - 3.3.02  
**Application Number:** 04029366.4  
**Publication Number:** 1516639  
**IPC:** A61M 15/00, A61P 9/12  
**Language of the proceedings:** EN

**Title of invention:**

Use of NO for treating persistent pulmonary hypertension of the newborn

**Patent Proprietor:**

THE GENERAL HOSPITAL CORPORATION

**Opponents:**

AIR PRODUCTS AND CHEMICALS, INC.  
Westfalen AG Münster  
AIR LIQUIDE SANTE (INTERNATIONAL) et al.

**Headword:**

Use of NO for treating persistent pulmonary hypertension of the newborn/THE GENERAL HOSPITAL

**Relevant legal provisions:**

EPC Art. 100(c), 123(2), 76(1), 84  
EPC Art. 100(a), 54, 56, 100(b), 83  
RPBA Art. 12, 13  
EPC R. 80

**Keyword:**

"Main request: added matter (yes)"  
"Auxiliary request 1C' filed in appeal proceedings: admissible and allowable"

**Decisions cited:**

T 0443/01

**Catchword:**

-



Case Number: T 0809/10 - 3.3.02

**DECISION**  
of the Technical Board of Appeal 3.3.02  
of 10 October 2013

**Appellant O1:** AIR PRODUCTS AND CHEMICALS, INC.  
(Opponent 1) 7201 Hamilton Boulevard  
Allentown, PA 18195-1501 (US)

**Representative:** Muir, Benjamin M. J.  
Beck Greener  
Fulwood House  
12 Fulwood Place  
London WC1V 6HR (GB)

**Appellant O2:** Westfalen AG Münster  
(Opponent 2) Industrieweg 43-63  
D-48155 Münster (DE)

**Representative:** Weiss, Peter  
Dr. Weiss & Arat  
Zeppelinstrasse 4  
D-78234 Engen (DE)

**Appellant O3:** AIR LIQUIDE SANTE (INTERNATIONAL) et al.  
(Opponent 3) 75 Quai d'Orsay  
F-75007 Paris (FR)

**Representative:** Pittis, Olivier  
L'Air Liquide, S.A.  
Direction de la Propriété Intellectuelle  
75, Quai d'Orsay  
F-75321 Paris Cedex 07 (FR)

**Respondent:** THE GENERAL HOSPITAL CORPORATION  
(Patent Proprietor) 55 Fruit Street  
Boston, MA 02114 (US)

**Representative:** Dörries, Hans Ulrich  
df-mp  
Fünf Höfe  
Theatinerstrasse 16  
D-80333 München

**Decision under appeal:**            **Decision of the Opposition Division of the European Patent Office posted 25 March 2010 rejecting the opposition filed against European patent No. 1516639 pursuant to Article 101(2) EPC.**

**Composition of the Board:**

**Chairman:**            U. Oswald  
**Members:**            M. C. Ortega Plaza  
                             R. Cramer

## Summary of Facts and Submissions

I. European patent No. 1 516 639, based on European patent application No. 04029366.4, which was filed as a divisional application of European patent application No. 97105021.6, which was filed as a divisional application of European patent application No.92902708.4, which was filed as an international patent application published as WO 92/10228 (root application as filed), was granted with four claims.

II. Claim 1 as granted read as follows:

"1. Use of a gaseous mixture consisting of NO and an inert gas (preferably N<sub>2</sub>) for the production of an inhalable medicament for treating persistent pulmonary hypertension of the newborn".

Claim 3 as granted read as follows:

"3. Use as specified in any of Claims 1 or 2, wherein the concentration of NO<sub>2</sub> in said inhalable medicament is maintained at less than 1 ppm".

III. Oppositions were filed and revocation of the patent in its entirety was requested in particular pursuant to Article 100(a) and (b) EPC (the subject-matter of the opposed patent is not new, does not involve an inventive step and is insufficiently disclosed) and Article 100(c) EPC (added subject-matter).

IV. The following documents *inter alia* were cited in the opposition and appeal proceedings:

D2 Higenbottam et al., Am. Rev. Resp. Dis. Suppl. 1988; 137:107

D3 Pepke-Zaba and Higenbottam, Thorax, 44, 334P

D4 Pepke-Zaba et al., Eur. Resp. J., Suppl., 1990, 313s, Abstract 1238

D5 Dinh Xuan, JIMR 17: 305-315, 1989

D6 Dinh Xuan, Therapie, 45: 111-118, 1990

D10 Graves et al., Chest, 93: 638-641, 1988

D11 Dresdale et al., Bull NY Acad. Med., 30(3), 195-207, 1954

D12 Special gases and equipment from Air Products (Air Products Limited pre-1982 catalogue: front and rear cover pages; 3-5 (index pages & 59)

D13 Rolls Royce Exhaust Emission Requirements (June 1989)

D14 Moinard and Guenard, Eur. Respir. J., 3, 318-322, 1990

D15 Borland and Higenbottam, Eur. Respir. J., 2, 58-63, 1989

D20 CFPO delivery slip for a mixture of NO/N<sub>2</sub> to the Lyon hospital dated 13 March 1990

D21 CFPO invoice for a mixture of NO/N<sub>2</sub> sold to the Lyon hospital in October 1990

D24 Barst, Chest, 89(4), 497-503, 1986

D32 Clutton-Brock, Brit. J. Anaesth. 39, 388-392, 1967

D33 Shiel, Brit. J. Anaesth. 39, 413-424, 1967

D35 NO gas tank label

D37 Maeda et al., Environmental Health Perspectives, 73: 171-177, 1987

D38 Oda et al., Arch. Environ. Health 30: 453-456, 1975

D39 von Nieding, Luft, 35, 175-178, 1975

- D44 Butt and Higenbottam, Chest, 105, 1994, Supplement 21S-25S
- D41 Copy of correspondence dated 5 September 1991 between the editor Mr. Clusin and Mr. Hedenstierma
- D47 Meyer and Piiper, Eur. Respir. J., 2, 494-496, 1989
- D49 Gosselin et al., Clinical Toxicology of Commercial Products, 5th edition, 1984
- D58 Palevsky et al., Circulation, 82, 2018-2026, 1990
- D60 Beutler in Hematology, McGraw-Hill, New York 1977, Chapter 54, 491-494
- D63 Lynne M. Reid, The American Journal of Cardiovascular Pathology, vol. 1(2), 287-299, 1987
- D80 Summary of Product Characteristics (SmPC) for INOmax<sup>TM</sup>
- D85 Copy of a letter to Higenbottam dated 2 June 1989 from the editor of The American Physiological Society, with comments of the reviewers

- V. The present appeal lies from a decision of the opposition division (posted on 25 March 2010) rejecting the oppositions (Article 101(2) EPC).
- VI. The opposition division considered that the claims as granted did not contain added subject-matter vis-à-vis the root application. Moreover, it considered that the deviations in Table 5 of the published patent from Table 5 in the root application were the result of printing errors.

The opposition division considered that the patent in suit disclosed how to obtain the proper dosages and the suitable ranges in order to put the invention into practice. In the opposition division's opinion the fact that a certain dosage of NO caused damage and was toxic

did not mean that the patent did not disclose the invention in a manner sufficiently clear and complete to be reproduced, since the skilled person would avoid such damaging doses when treating persistent pulmonary hypertension of the newborn (PPHN).

Additionally, the opposition division considered that the subject-matter claimed in claim 1 of the main request met the requirements of novelty (Article 54 EPC). In particular, the root application did not form part of the prior art. In the opposition division's opinion, board of appeal decision T 443/01 of 16 November 2004, which revoked the patent derived from the root application, did not constitute *res judicata* since the subject-matter claimed in the patent in suit was not the same as that serving as the basis for decision T 443/01. Additionally, the subject-matter claimed was novel vis-à-vis document D2 since PPHN was a particular disorder, suffered by a particular group of patients, which was distinct from primary pulmonary hypertension.

The opposition division considered either document D2 or document D10 to represent the closest prior art. It was of the opinion that the subject-matter claimed in the patent as granted involved an inventive step (Article 56 EPC).

VII. Opponent 01 (appellant 01), opponent 02 (appellant 02) and opponent 03 (appellant 03) lodged appeals against the opposition division's decision and filed grounds of appeal. They requested that the decision under appeal be set aside and the patent be revoked in its entirety.

VIII. With a letter dated 25 October 2010 the patent proprietor (respondent) filed a reply to the opponents' appeals. The respondent requested that the appeals be dismissed (that the opposition division's decision be upheld). It further requested that, alternatively, the patent be maintained in amended form on the basis of one of auxiliary requests I to III, filed with the letter of 25 October 2010.

IX. The board sent a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings which contained *inter alia* a preliminary opinion in relation to Article 100(c) EPC.

With said communication the board drew the parties' attention to the fact that an inspection of the file had shown that the deviations in the printed patent document from table 5 of the root application originated from printer's errors, and that the differences were not present on page 37 of the "Druckexemplar" serving as the basis for the examining division's decision to grant the application.

The board also expressed a preliminary opinion in relation to some of appellant O1's objections concerning the status as divisional application and cited Enlarged Board of Appeal decisions G 1/05, OJ EPO 2008, 271, and G 1/06, OJ EPO 2008, 307.

X. With a letter dated 9 August 2013 the respondent filed a reply to the board's communication (in particular in relation to Article 100(c) EPC).



Moreover, with said letter the respondent clarified that auxiliary requests I to III filed with the letter dated 25 October 2010 corresponded to auxiliary requests filed with the letter of 12 December 2008 in response to the oppositions.

The respondent requested that the appeals be dismissed, alternatively, it requested that the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 3 filed with the letter of 12 December 2008 (it filed a copy of these auxiliary requests 1 to 3 with the letter of 9 August 2013), or, further alternatively, on the basis of one of the auxiliary requests 1B, 1C, 1D, 2B, 3B, filed for the first time with said letter of 9 August 2013.

- XI. With a letter dated 9 September 2013 appellant O2 filed a reply to the respondent's arguments. Appellant O2 submitted arguments against the respondent's auxiliary requests.
- XII. With a letter dated 4 October 2013 the respondent filed a further auxiliary request, auxiliary request 1C'. With said letter the respondent stated that the ranking of its requests was the following: main request (that the appeals be dismissed), auxiliary requests 1, 1B, 1C, 1C', 1D, 2, 2B, 3, 3B.
- XIII. Claim 1 of auxiliary request 1 is identical to claim 1 as granted.

Claim 1 of auxiliary request 1B reads as follows:

"1. Use of a gaseous mixture consisting of NO and N<sub>2</sub> for the production of an inhalable medicament for treating persistent pulmonary hypertension of the newborn".

Claim 1 of auxiliary request 1C reads as follows:

"1. Use of a gaseous mixture consisting of NO and N<sub>2</sub> for the production of an inhalable medicament for treating pulmonary hypertension in a patient with persistent pulmonary hypertension of the newborn".

Claim 1 of auxiliary request 1C' reads as follows:

"1. Use of a gaseous mixture consisting of NO and N<sub>2</sub> for the production of an inhalable medicament for reversing acute pulmonary vasoconstriction resulting from persistent pulmonary hypertension of the newborn".

XIV. Oral proceedings took place on 9 and 10 October 2013.

XV. The appellants' arguments, as far as relevant for the present decision, may be summarised as follows.

*(a) Admission of auxiliary requests 1 to 3, 1B, 1C, 1D, 2B, 3B and 1C'*

The appellants objected to the admission of auxiliary request 1C' filed with the letter of 4 October 2013 but did not object to the admission of the other auxiliary requests. The appellants submitted that auxiliary request 1C' could have been filed earlier. In their view, there was no justification for its late filing (only two working days before the oral proceedings). The board's communication was sent on 6 May 2013 as an

annex to the summons to oral proceedings; thus in the appellants' view the respondent had had ample opportunity to file auxiliary request 1C' earlier, at the latest with the letter of 9 August 2013. The appellants denied that the amendment responded to objections raised in appellant O2's letter dated 9 September 2013.

Appellant O3 further submitted that, although it did not request postponement of the oral proceedings, admission of auxiliary request 1C' into the proceedings would require adjournment of the oral proceedings. Thus auxiliary request 1C' should not be admitted.

*(b) Main request (Article 100(c) EPC)*

The appellants referred to the board's communication sent as an annex to the summons and shared the board's analysis in relation to claim 1 as granted.

Moreover, it was not disputed that pulmonary hypertension was the result of pulmonary vasoconstriction, but that there was no basis in the root application as filed for treating PPHN other than linked to vasoconstriction.

The passages concerning inhalation devices cited by the respondent were not an adequate basis for the therapy in claim 1 as granted since they did not concern the administration of gaseous NO for treating any condition, in particular PPHN. The portable inhalation devices mentioned were not suitable for treating newborns. Moreover, said passages addressed vasoconstriction such as in asthma, which was not the medical condition in claim 1 as granted.

Moreover, there was no feature in granted claim 1 indicating that gaseous NO would be effective in pulmonary vasodilation in PPHN.

Appellant O1 further stated that although document D10 was very relevant for inventive step assessment, it did not represent the whole common general knowledge in the field since there were also idiopathic forms of PPHN, which were also encompassed by the claim's wording, in which the lungs were perfectly normal. The reasons for persistent pulmonary hypertension did not always have to be linked to vasoconstriction. Since the symptoms to be treated were not defined in granted claim 1, the medical treatment also encompassed the treatment of other aetiologies of PPHN which were not necessarily linked to vasoconstriction.

Appellant O2 further mentioned that the reference on page 14 to the treatment of hyaline membrane disease was a proof that there were different aetiologies and symptoms embraced by the syndrome PPHN and the root application as filed did not provide a basis for all of them.

Appellant O3 pointed to the three types of PPHN mentioned in document D3 and stated that the treatment disclosed in the root application as filed did not concern all of them.

Additionally, appellant O3 also objected under Article 100(c) EPC to claim 3 of the main request.

(c) *Auxiliary requests 1, 1B, 1C, 1C' (formal requirements)*

The appellants submitted that the objections raised against claim 1 of the main request pursuant to Article 100(c) EPC applied *mutatis mutandis* to the auxiliary requests.

As regards auxiliary request 1C the appellants submitted the following:

the root application as filed did not refer to the treatment of pulmonary hypertension but to the treatment of acute, persistent or chronic pulmonary hypertension (page 7). Therefore, the amendments introduced in claim 1 of auxiliary request 1C did not find an allowable basis in the root application as filed, and/or introduced a lack of clarity into the subject-matter claimed. Page 21 did not refer to NO/N<sub>2</sub> mixtures.

Appellant 02 further stated that since claim 1 as granted concerned the treatment of the newborn (up to 28 days) the amendment introduced in claim 1 of auxiliary request 1C either extended the scope of protection over that of granted claim 1 (Article 123(3) EPC) (i.e. the patient to be treated was not necessarily a newborn but also included older infants), or the claim lacked clarity in relation to the patient undergoing the treatment. Moreover, this new wording in claim 1 also introduced added matter within the meaning of Articles 123(2) and 76(1) EPC.

Appellant 03 also mentioned that there was an additional problem in respect of Article 123(3) EPC

since the subject-matter now claimed related to a shifting of the subject-matter in claim 1 as granted. The subject-matter now claimed was not fully covered by the scope of granted claim 1 (partial treatment *versus* total treatment), and the amended claim lacked clarity in relation to the nature of the treatment. Moreover, there was an Article 123(2)/Article 123(3) EPC trap deriving from the fact that the granted claim contained added matter which did not allow that amended claim of auxiliary request 1C be retained. Moreover, as reflected in document D10 (page 639) there were newborns with underdevelopment of the vascular bed for which the treatment with NO addressing pulmonary hypertension would have no effect. Thus, the amended claim had a different scope to that of the granted claim, which addressed all forms of PPHN.

As regards auxiliary request 1C' the appellants submitted the following:

Appellant O1 submitted that the passages cited by the respondent as basis also mentioned administration of oxygen for hypoxic newborns. The disclosure on page 22 required that the NO-N<sub>2</sub> mixture be blended with O<sub>2</sub>.

Appellant O3 further submitted that the replacement of the expression "for treating" by the expression "for reversing" contravened the requirements of Article 84 EPC. Moreover, since PPHN was not treated but only a certain symptom, there was a problem in respect of Article 123(3) EPC. It also raised an objection under Rule 80 EPC against the amendment concerning the definition of the medical condition in claim 1.

In relation to claim 3 appellant 03 stated that monitoring NO<sub>2</sub> only made sense if there was oxygen. Therefore, there was a lack of consistency between the claims (Article 84 EPC). Appellant 02 also contested the clarity of amended claim 3.

*(d) Sufficiency of disclosure*

Appellant 01 submitted that its arguments in relation to lack of sufficiency of disclosure went parallel to the arguments submitted in relation to added matter. The medical treatment now defined was not exemplified in the specification as filed. The experiments with lambs with induced pulmonary vasoconstriction could not serve as a valid model for PPHN. The protocol for administration of gaseous NO to newborn infants on pages 33 and 34 was a theoretical protocol. The results displayed on page 36 and onwards concerned the treatment of an infant suffering from PPHN and congenital heart failure, but the aim was not the treatment of PPHN. Appellant 01 further submitted that it was not clearly stated in the examples on page 36 and onwards whether the infants were newborns. Moreover, normal neonates with PPHN did not have a congenital heart failure with atrial septal defect.

Appellant 02 shared the arguments of appellant 01, and appellant 03 stated that there was no example showing how the acute pulmonary vasoconstriction was reversed.

(e) *Novelty*

Appellants O1 and O3 did not have any comments on novelty.

Appellant O2 objected to the novelty of claim 1 of auxiliary request 1C' and referred to the reasons given in decision T 443/01 of 16 November 2004 for revoking the patent deriving from the root application since claim 3 in decision T 443/01 encompassed the subject-matter now claimed. Claim 3 in T 443/01 concerned the treatment or prevention of pulmonary vasoconstriction in a mammal and was found to lack novelty over D2, which disclosed the vasodilatory effects of inhaled NO in seven patients with primary pulmonary hypertension. There was no new technical effect for newborns, and thus the claim lacked novelty.

(f) *Inventive step*

Appellant O1 submitted that document D10 represented the closest prior art since it dealt with the same indication and technical problem (document D10, page 638 and figure 1). In newborns suffering from PPHN, pulmonary hypertension persisted after birth and led to a right-to-left shunt through persistent foetal channels (patent foramen ovale and patent ductus arteriosus). Pulmonary hypertension was the state of the normal newborn at term, and normally during adaptation to air breathing pulmonary dilation occurred and compliance increased. In PPHN pulmonary vascular resistance was increased, preventing normal pulmonary blood flow and leading to hypoxia. A vicious cycle was thus initiated causing further vasoconstriction and



loss of compliance. Therefore, the pharmacological treatment of PPHN was to lower pulmonary pressure without affecting systemic pressure; however, the pulmonary vasodilators currently used, as mentioned in document D10 (page 640), were not selective vasodilators of pulmonary vasculature. Document D63 also mentioned that PPHN could be treated with vasodilators, but at the time of publication of document D63 (1987) there was no satisfactory and selective vasodilator available (page 288, left-hand column, first paragraph). Document D10 taught that if the vasodilator influenced the systemic pressure, the effect might even be undesirable for the newborn with PPHN. The difference between the content of document D10 and the subject-matter of claim 1 was that the pharmacological agents disclosed in D10 were not selective vasodilators. The problem to be solved was to provide an alternative vasodilatory treatment that is selective to the pulmonary system. Document D58 taught that pharmacological agents had been tested over the years for their ability to induce pulmonary vasodilation in patients with primary (idiopathic) pulmonary hypertension (PPH). Some cases of PPHN were also idiopathic since document D10 taught that the lung did not necessarily have to be damaged for persistent pulmonary hypertension to exist. Thus, in order to find a selective vasodilator the skilled person would look at document D2 which dealt with the treatment of PPH. In fact document D2 compared the vasodilatory effects of inhaled NO with those of prostacyclin (mentioned in document D10 as lacking selectivity). Document D2 disclosed NO as a selective pulmonary vasodilator. Thus the proposed solution was obvious. Document D2 disclosed that NO (40 ppm in air) was inhaled, so

document D2 did not specifically mention a gaseous mixture consisting of NO and N<sub>2</sub>, but no pharmacological effect over that of NO known from document D2 was attributable to this difference. Additionally, it was well known to the skilled person that NO oxidises to the toxic NO<sub>2</sub>, and thus safety standards, such as gaseous mixtures of NO and N<sub>2</sub> as inert gas, were well-known sources for NO. In this context appellant O1 cited documents D12, D13, D20 and D21. Appellant O1 recalled that the respondent had stated that NO was the active agent. Appellant O1 further submitted that at the effective date of the invention PPHN had a 40% mortality rate and 50-60% of survivors suffered from neurological damage. ECMO was one of the treatments known from document D10, but it was a very invasive procedure and was only available in certain hospitals in intensive care. Therefore, there was an urgent need for an alternative. The chemical treatments involved vasodilators as disclosed in document D10, but the results were very variable. The gold standard for PPH, PGI<sub>2</sub>, was also used for PPHN (this drug was mentioned in documents D2 and D10). Document D10 was the natural starting point and documents D2, D3 and D4 belonged to a similar field relating to the use of NO in treating PPH. In the light of these documents the skilled person would conclude that NO was a selective vasodilator. D58 showed prostacyclin as a gold standard for PPH with decrease in PVR equal to or greater than 30% in seven out of 23 patients and a response of more than 20% in more than one third of the patients. As regards correspondence D41, there was no copy on file of the scientific article it referred to. However, the results with NO were good enough (three out of ten patients) for an alternative to prostacyclin, since the essential

factor for treating PPHN was that NO was a selective vasodilator. The results in document D2 showed that NO was a selective vasodilator; an absolute reduction of pulmonary hypertension was not the point. The treatment of PPH and of PPHN appertained to related fields since the patients suffering from primary pulmonary hypertension (PPH) in document D11 had idiopathic pulmonary hypertension (page 186, no vascular changes present) and some of the patients suffering from PPHN were idiopathic. Appellant O1 also referred to document D58, page 2019.

Appellant O1 recalled that the skilled person was the notional skilled person and not a particular scientist working in the field. The safety and security standards were known, as acknowledged in paragraph [0010] of the patent in suit; 25 ppm NO or below was safe. The skilled person had no reason to have concerns if the safety standards mentioned in paragraph [0010] of the patent in suit were met. Appellant O1 cited *inter alia* documents D14 and D15 in order to show that treatment with inhaled NO was safe if maintained at an adequate dose. Moreover, there was no indication to be found in the prior art as to whether the administration of inhaled NO would open more ductus arteriosus as alleged by the respondent. The problems related to methemoglobin would only be relevant when a massive inhalation of NO took place (it was also possible to kill a patient with an anticancer drug). The levels of methemoglobin in document D37 (figure 2) would not have dissuaded the skilled person from trying inhaled NO since they referred to 100 ppm NO. Document D49 mentioned 5% methemoglobin in experiments with mice exposed to 40 ppm of NO.

Appellant O2 clarified that it did not dispute the submissions of appellants O1 and O3, but in its opinion document D2 was the closest prior art, and it again referred to board of appeal decision T 443/01. The problem was to provide the method for newborns. It was not excluded that the patients in document D2 were children. If the physician were faced with an infant such as that described on page 36 he would have no doubt about treating him with NO before he died. The skilled person was not only a neonatologist but a team also including a pharmaceutical developer. Moreover, the prior art (documents D2, D3, D4, D5) taught that when NO gas was diluted it was not toxic. In the concentration used in document D2 it was a selective vasodilator.

Appellant O3 shared appellant O1's arguments. D10 was the best starting point since it related to the same disease, PPHN, the same patients (newborns with PPHN), and proposed the same line of treatment (vasodilators). In fact document D10 disclosed three types of treatment: assisted ventilation, with the problem of damage to the trachea, ECMO which was quite invasive and thus was reserved for extreme cases, and treatment with vasodilators (page 640). Prostaglandin I<sub>2</sub> (prostacyclin) worked well in some cases and badly in others. The problem to be solved was to find an alternative treatment without negative side effects linked to systemic vasodilatation. The skilled person would look for documents which disclosed selective vasodilators. He would then find document D2 which concerned the problem of vasoconstriction in patients with PPH and disclosed the use of NO as a selective vasodilator. PPH

could also affect children. Document D24 showed that nine-month-old babies could suffer from primary pulmonary hypertension, and not only adults. This knowledge would have been an incentive to the skilled person, who would have tried to apply the knowledge of document D10 which concerned PGI<sub>2</sub> (providing a link to document D2) and NO. The use of any medicament required a risk/benefit analysis and careful tests to establish the appropriate dose in order to avoid toxic side effects. Patients with PPHN were in a critical state, so the skilled person had the choice of either letting them die or performing the appropriate tests. He would perform the tests. Moreover, document D2 was not isolated. Other publications were similar, such as documents D3 (where there was an amelioration of at least 15%), D4, D5, page 309, and D6. These documents taught that NO was efficient, as a selective vasodilator, for treating pulmonary pathologies, and that the treated patients did not die. Thus, NO was obviously an alternative to PGI<sub>2</sub>. As regards the NO/N<sub>2</sub> mixture, it was in 1990 delivered to hospitals for medical uses (documents D20 and D21). NO was the active agent and N<sub>2</sub> was an inert gas.

XVI. The respondent's arguments, as far as relevant for the present decision, may be summarised as follows.

*(a) Admission of auxiliary requests 1 to 3, 1B, 1C, 1D, 2B, 3B and 1C'*

The respondent noted that no objections were raised against the admission of auxiliary requests 1 to 3, 1B, 1C, 1D, 2B, 3B.

As regards auxiliary request 1C', the respondent submitted that it was filed as a direct reaction to appellant O2's letter dated 9 September 2013 (i.e. only one month before the oral proceedings) which contained a new attack, namely against the clarity and sufficiency of the subject-matter claimed in auxiliary request 1C. Auxiliary request 1C' was filed as soon as possible after that letter. Moreover, the amendments introduced were an attempt to respond to appellant O2's objections by taking into consideration at the same time all observations relating to the main request. The amendments were clear and easy to handle since they reflected the teaching on pages 7 and 8, as well as page 21, of the root application as filed. Therefore, the other parties could reasonably be expected to deal with such a request without adjournment of the oral proceedings (Article 13(3) RPBA). Additionally, this request had not been filed earlier since the respondent did not wish to encumber the proceedings (and earn criticism for doing so) filing a high number of auxiliary requests even before some objections became relevant.

*(b) Main request (Article 100(c) EPC)*

The root application as filed provided ample basis for claim 1 as granted, in particular for identifying NO as the agent to be able to treat various forms of pulmonary hypertension and pulmonary vasoconstriction (page 6, lines 16-21, lines 21-25). The respondent also cited page 6, lines 27-30, and "therapeutically effective treatment" defined as "it reduces the patient's airway resistance by 20% or more, as measured by standard methods of pulmonary mechanics". It also

cited page 3, lines 27-30, and the passage bridging pages 3 and 4, which disclosed that pulmonary hypertension had been implicated in life-threatening clinical conditions such as adult respiratory distress syndrome (ARDS) and persistent pulmonary hypertension of the newborn (PPHN). It also cited page 21, *inter alia* lines 13, 19 and 26, page 18, lines 14-20, page 7, lines 20-29, page 16, lines 22-29, and pages 33 to 40. Page 21 gave a literal basis for granted claim 1. Additionally, according to EPO practice it was not necessary to specify the technical effect in a second medical use claim directed to the treatment of a disease (it mentioned by analogy the treatment of rheumatoid arthritis and immunosuppression, and the treatment of cancer and anti-proliferative effect). The respondent also mentioned that the claim was not meant to encompass things that did not work. It cited in this context board of appeal decisions T 1069/08 of 8 September 2011, T 601/05 of 2 November 2009 and T 1696/08 of 3 February 2011.

The exclusion criteria on page 34 did not mean that NO did not work but that newborns with pulmonary hypoplasia were difficult patients in view of ECMO (extracorporeal membrane oxygenation). Moreover, one of the aims of the treatment was that there would be no need to go to ECMO and therefore it did not make sense to start with newborns that already had ECMO when tailoring the experimental treatment for testing inhaled NO. There was, however, no indication in the root application that treatment with gaseous NO would not work for such patients since at least hypoxia could be reversible.

The respondent also cited page 14, lines 3-8, page 15, lines 9-11, 17, lines 7-22, page 20 and page 26, line 4, in relation to inhalation devices and gas mixtures to be inhaled. The portable inhalation devices might not be specific for newborns but their use for such treatment of newborns was not excluded. The treatment of hyaline membrane disease was a treatment concerning newborns (page 14, lines 11-12, of the root application as filed).

The respondent argued that inhalation of gaseous NO applied to the newborn relieved pulmonary vasoconstriction and caused pulmonary vasodilation and that as a result the situation of right-to-left shunting of blood through the patent ductus arteriosus would improve. The respondent cited document D10 as appertaining to the common general knowledge of the skilled person about persistent pulmonary hypertension in the newborn.

The respondent further submitted that before birth there was the embryonic respiration mode with oxygen supply by placenta and after birth air had to be supplied by the lung. Normally, the ductus arteriosus closed at birth and then it would eventually be sealed. However, as stated in document D10 the pathophysiologic key in the syndrome PPHN prevents normal pulmonary blood flow and causes a right-to-left shunt through the patent foramen ovale and patent ductus arteriosus (i.e. the old channels). The results are hypoxia and cyanosis. The effect of inhaled gaseous NO is that it opens up the lungs, then causing improvement in the right-to-left shunting of blood. Babies who turned blue (cyanosis) turned pink after the treatment.



The respondent clarified, however, that it did not submit that treatment with inhaled NO cured every infant with PPHN but it helped many of them, in particular those with a constricted lung. Thus, all three groups of patients in document D10 could in principle benefit from treatment with inhaled NO.

In relation to claim 3 as granted the respondent stated that it was self-explanatory that the monitoring was necessary in order to maintain the concentration of NO<sub>2</sub> at less than 1 ppm.

*(c) Auxiliary requests 1, 1B, 1C, 1C' (formal requirements)*

The arguments presented for the main request applied mutatis mutandis to auxiliary requests 1, 1B, 1C and 1C'. Additionally, the basis for the specification of N<sub>2</sub> as the inert gas was to be found on pages 21, 22, 34 and 35 of the root application as filed.

As regards claim 1 of auxiliary request 1C, the claim addressed those forms of PPHN which were treatable. Moreover, the respondent stated that patients with PPHN did not have chronic pulmonary hypertension since they just had been born and were not adults (i.e. did not have adult lungs). The respondent submitted that the appellants' arguments lacked consistency with some of the arguments they had presented before for the main request. In this context the respondent cited document D63, page 287, right-hand column, last paragraph of the introduction, in order to show that persistence of pulmonary hypertension was not only a

cause but a very dramatic symptom. Moreover, the respondent stressed that even if difficult newborn patients could be encountered, newborns with PPHN became hypoxic and thus inhalation treatment with NO would at least allow them to be stabilized.

As regards auxiliary request 1C' the respondent submitted the following:

Claim 1 related to the medical use of a gaseous mixture of NO and N<sub>2</sub> (inert gas) in which NO was the active agent (page 21 of the root application as filed). The preferred mode disclosed was to administer NO as a mixture with N<sub>2</sub>. There was no valid justification for the appellants' request to include oxygen in the claim's wording. The claim had to be read in its technically meaningful sense with a will to understand. The claim concerned a medical treatment. Since pulmonary vasoconstriction had increased at birth and had become acute, the aim was to reverse that process. Auxiliary request 1C' had been filed as a direct response to the objections against auxiliary request 1C raised in the course of the proceedings. Therefore, it could not be any problem in relation to Rule 80 EPC. Moreover, the three anatomical types mentioned in document D10 should not be artificially construed as separate options, since documents D10 and D63 made it clear that one main characteristic or most common symptom of PPHN was that there was pulmonary vasoconstriction. Therefore there was no contravention of Article 123(3) EPC.

In relation to claim 3 the respondent submitted that the fact that the concentration of NO<sub>2</sub> was monitored had

to do with the toxicity of NO<sub>2</sub> (e.g. page 5, lines 33-34, and page 8 of the root application as filed) and thus was of general applicability to all the methods disclosed in the root application as filed. Even the source of NO might have been contaminated. Therefore, there was no problem of lack of consistency.

*(d) Sufficiency of disclosure*

The specification contained examples of the treatment of three newborn infants suffering from PPHN. Page 35 disclosed detailed instructions how to administer gaseous NO and how to measure the pressure and the improved oxygenation, which is the most important effect. The infant suffering from PPHN and congenital heart disease mentioned on page 36 underwent treatment within the meaning of claim 1. The patient had not been included in the PPHN studies mentioned before on pages 33 to 34 because it was a complicated and severe case in view of the existence of the atrial-ventricular (AV) canal. The results on page 2, table 2, line 24, showed that even in this difficult case there had been success with oxygenation. It was disclosed on page 39 that two more infants with PPHN had been treated by NO inhalation and both had survived long term. The appellants had not discharged their burden of proof in relation to the alleged lack of sufficiency of disclosure. It was generally easy to identify whether pulmonary vasoconstriction was reduced. The skilled pulmonologist would know how to put the claimed invention into practice. In common terms if the baby turned pink vasoconstriction was relieved. The patients treated and referred to in the experiments were newborns. Although the normal newborn patients had

normal foramen and the case with congenital heart failure did not, there were still the same problems of right-to-left shunt and vasoconstriction, naturally with aggravated conditions. Finally, the appellants' criticism of the term "reversing" was not supported by any substantive argument showing why the skilled person would not be able to understand the treatment in the claim and measure and determine the mentioned effect.

(e) *Novelty*

The respondent pointed to the differences between claim 3 in decision T 443/01 and claim 1 of auxiliary request 1C'. Moreover, the analysis to be made was whether or not a particular piece of prior art was novelty-destroying for the subject-matter claimed. The group of patients suffering from PPHN was not disclosed in document D2. This particular group of patients was not an arbitrary choice since it was clearly identifiable, in particular in view of the right-to-left shunting of blood. The respondent again referred to document D10. In the newborns with PPHN the lung did not open up and thus the embryonic channels were still used. This had nothing to do with primary pulmonary hypertension in adult lungs.

(f) *Inventive step*

The respondent did not acknowledge document D10 as the closest prior art since it was not a promising starting point, as it did not concern the drug NO. It did not, however, develop a separate line of argument with a different starting point.

The respondent submitted that document D10 taught that the newborn suffered from life-threatening hypoxia (page 638), and that document D63 (pages 287-288) acknowledged that to its date of publication PPHN still had a high mortality. PPHN was something different from PPH. Newborns suffering from PPHN did not have any chance of alleviating from cyanosis (blue babies). In patients with PPHN their capacity for exercising was reduced but they did not have oxygenation problems causing cyanosis. What document D10 actually taught was that there was no known drug that was a "**powerful** and selective dilator of the pulmonary vasculature" (emphasis added). Thus, what was needed was a powerful and effective selective vasodilator. Document D2 did not necessarily appertain to a field related to that of document D10 since PPHN was a totally different disease treated by neonatologists. The lungs were constricted in both PPH and PPHN patients but due to very different causes. Therefore, the definition of the problem to be solved had to include that the treatment had to be safe and effective. The respondent referred to document D80 (as post-published evidence) and to paragraph [0040] of the patent in suit. Moreover, the fact that the patients suffering from PPH in document D58 were idiopathic did not mean that they had normal lungs, it only meant that the cause of PPH was not known. Document D11 showed that it had been long known that PPH occurred in lungs with anatomical changes such as lung fibrosis, sclerotic changes or increase in muscle cell lines (document D11, page 197, "fibrous intimal thickening and narrowing, or obliteration of the smaller arteries"), anomalies which were unlikely to be present in PPHN. Document D11 explained that PPH could be present in patients as young as twenty months, but

the majority of patients were adults (page 198) with pulmonary changes. Moreover, PPH was a disease of an adult lung as shown in document D24, and confirmed in the post-published document D44. The patients with PPHN treated in document D10 had very young lungs which were still not fully developed and had an open ductus. The lungs of the anatomical type mentioned in document D10 as excessive muscularization of the pulmonary vascular bed were different from those of PPH patients. Document D63 (page 291, figures 5 and 7) confirmed that the "idiopathic" variety of persistent pulmonary hypertension of the newborn was characterized by excessive muscularization of the intraacinar arteries in utero. The preacinar arteries were normal and the pulmonary veins and intraacinar arterial density were also normal. Document D58 merely mentioned on page 2019 that there was no coexisting illness, which did not mean that the lungs suffering from PPH were not affected.

There were essential differences between the newborns suffering from idiopathic persistent pulmonary hypertension and the older patients suffering from primary (idiopathic) pulmonary hypertension. For those newborns with underdevelopment of the pulmonary vascular bed the differences were even greater since their lungs were closer to those of the embryonic stage than to adult lungs. The skilled person would not know how newborns with hypoplasia react to NO.

Additionally, the effect shown in document D2 for NO was quite low or moderate, and this teaching did not let the skilled person predict whether or not

administration of NO in newborns with PPHN would be effective.

Document D2 showed a much more significant decrease in mean pulmonary arterial pressure which was attained with prostacyclin (PGI<sub>2</sub>) than that which was attained with NO. The respondent referred to the values established in decision T 443/01 in relation to the effects attained by inhalation of NO disclosed in document D2 (pages 11 and 12) and cited document D24, which mentioned a 20% or greater decrease in mean pulmonary arterial pressure as a valid criterion for effective treatment in children and young adults suffering from primary pulmonary hypertension. Thus, even looking at document D2, the skilled person would not consider the administration of gaseous NO as a successful therapeutic alternative. In this context the respondent referred to the comments of the reviewers in document D85 that the effects of NO inhalation did not show significant changes and that the overall impression was that there was a response in only 3 out of 10 PPH patients. Document D2 related to a comparison of administration of inhaled NO with the golden standard at the time, PGI<sub>2</sub>. NO did not achieve the values of the standard and was not particularly selective. The skilled person (pulmonologist, physician and neonatologist) looking for a treatment of PPHN would not have been impressed by the data displayed in document D2. The respondent also cited document D47, paragraph bridging pages 495-496. Document D47 concerned studies testing pulmonary diffusion capacity and it could not be concluded whether NO had a vasodilator effect on pulmonary vessels. Therefore, there was no proof that the skilled person would have

reasonable expectations of success on the lungs of the newborn with PPHN in relation to oxygenation and avoidance of cyanosis and acidosis.

The respondent also mentioned the toxicity concerns of the skilled person in relation to NO gas and cited *inter alia* documents D32, D33, D35 and D36. It further cited documents D37 and D38 in order to show that NO impaired the oxygen transport capacity of hemoglobin owing to formation of nitrosylhemoglobin and methemoglobin. Figure 2 in document D37 showed that after one hour's exposure to NO a level of 20% methemoglobin was attained. Document D37's experiments were performed on animals. Such levels of methemoglobin would lead to death in 40 to 60% of patients. The respondent also cited document D60 in order to show that newborn infants were particularly susceptible to the development of methemoglobinemia (page 492, left-hand column) and document D49 (III-323). The last thing the skilled person wanted was to affect oxygenation capacity in newborns. It had long been known that inhalation of more than 15 ppm of NO over more than 15 minutes caused a significant drop in arterial oxygen partial pressure (document D39).

Therefore, the skilled person would not think of NO as a solution to the problem since he would expect that administration of NO would even worsen hypoxia. The respondent denied that document D15 disclosed that inhalation with NO was safe, as it mentioned toxicity only in relation to the formation of NO<sub>2</sub>.

Document D24 did not relate to the treatment of PPHN, nor did it say anything about NO. Document D24 related to the treatment of PPH with *inter alia* the vasodilator



prostacyclin and stressed that pulmonary arterial pressure had to decrease by more than 20% with acute vasodilator therapy to be considered a significant change (page 502, right-hand column). Even considering the teaching in document D2, NO would not be seriously contemplated according to the criteria in document D24. Moreover, D2 did not check the side-effects of the treatment with inhaled NO and therefore it could not be said that the document D2 disclosed that treatment with NO was safe for babies. It was not only a question of toxicity, but also a question of worsening the symptoms. The skilled person would not have taken too much risk in view of the aetiology of the disease. The respondent cited documents D85 and D41 and the ethical concerns expressed by the reviewers in relation to the inhalation treatment with NO and, in the case of document D41, the expectations of profound negative effects on oxygenation.

The respondent mentioned that appellant O2's arguments related to hindsight. The knowledge in the patent could not be used to allege that the invention was obvious. Moreover, the treatment of babies had to undergo serious ethical examination, as they were not guinea pigs. The inventor could do the experimental treatment since it had previously performed studies on lambs. This had nothing to do with the obviousness of the claimed invention.

XVII. The appellants (opponents) requested that the decision under appeal be set aside and that European patent No. 1 516 639 be revoked.

The respondent requested that the appeals be dismissed, or alternatively, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 3 filed with the letter of 12 December 2008, or further alternatively, on the basis of one of auxiliary requests 1B, 1C, 1D, 2B, 3B, filed with the letter of 9 August 2013, or on the basis of auxiliary request 1C' filed with the letter of 4 October 2013.

### **Reasons for the Decision**

#### 1. *Admissibility*

1.1 The appeals are admissible.

1.2 *Admissibility of auxiliary requests 1 to 3 and of auxiliary requests 1B, 1C, 1D, 2B, 3B*

None of the appellants have objected to the admissibility of auxiliary requests 1 to 3 and of auxiliary requests 1B, 1C, 1D, 2B and 3B, and the board sees no reason not to admit them into the proceedings.

Therefore, auxiliary requests 1 to 3 (Article 12 RPBA) and auxiliary requests 1B, 1C, 1D, 2B and 3B (Article 13(1) RPBA) are admissible.

1.3 *Admissibility of auxiliary request 1C'*

Auxiliary request 1C' was filed with the respondent's letter dated 4 October 2013.

Auxiliary request 1C had been filed with the respondent's letter of 9 August 2013 as an attempt to respond to the observations within the meaning of Article 100(c) EPC in the board's communication sent as an annex to the summons to oral proceedings. The amendments undertaken in claim 1 of auxiliary request 1C were contested with appellant O2's letter dated 9 September 2013, in particular within the meaning of Articles 84, 83, 123(2) and 76(1) EPC. The filing of auxiliary request 1C' relates to a fair attempt to respond to said objections while coming at the same time as close as possible to the disclosure in the relevant pages of the description of the root application as filed, which were explicitly cited in the board's communication sent as an annex to the summons to oral proceedings. Thus the board is convinced that the amendments did not raise issues which could not reasonably be expected to be dealt with by the parties without adjournment of the proceedings.

Therefore, the board making use of its discretionary power admits auxiliary request 1C' into the proceedings (Article 13 RPBA).

2. The patent in suit derives from European patent application 04029366.4, which was filed as a divisional application of European patent application 97105021.6, which was filed as a divisional application of European patent application 92902708.4, which was filed as an international application, published as WO 92/10228 (root application as filed).

2.1 The root application, which was granted as EP-B1-0560928, underwent opposition proceedings and was

revoked by board of appeal decision T 443/01 of 16 November 2004 (same board as the present board in another composition).

2.2 The documents concerning the description and examples as originally filed are identical for the three applications: root (GA), parent (PA) and its divisional (OA) (i.e. the application from which the patent in suit derives); the sets of claims of the three applications as filed differ from each other.

3. *Main request (set of claims as granted)*

3.1 *Article 100(c) EPC*

3.1.1 According to Article 100(c) EPC, opposition may be filed on the grounds that:

"the subject-matter of the European patent extends beyond the content of the application as filed, **or, if the patent was granted on a divisional application** or on a new application filed under Article 61, **beyond the content of the earlier application as filed**" (emphasis added).

3.2 Claim 1 as granted relates to a second or (further) medical use claim in the Swiss-type form and relates to

- . the **use of a gaseous mixture**
  - consisting of **NO and an inert gas**
  - . for the production of an **inhalable** medicament
  - . for **treating persistent pulmonary hypertension of the newborn.**

The expression which appears in claim 1 as granted in brackets, namely "(preferably N<sub>2</sub>)", has no limitative character as to the scope of the subject-matter claimed.

Moreover, claim 1 as granted does not address a generic treatment of pulmonary hypertension in infants, but it addresses the treatment of a disorder, known as persistent pulmonary hypertension of the newborn (PPHN), which encompasses different associated aetiologies and symptoms in a particular group of patients, namely **neonates** (newborns or newborn infants).

The content of document D10, which concerns a review of "*Persistent pulmonary hypertension in the neonate*" in a well-known publication, namely "Chest" (Official Publication of the American College of Chest Physicians), appertains to the common general knowledge of the skilled person. This does not mean, however, that document D10 exhaustively discloses the whole common general knowledge of the notional skilled person in the field. Document D10 defines PPHN as a syndrome in which the **pathophysiologic** key is "increased pulmonary vascular resistance that prevents normal pulmonary blood flow and causes a right-to-left shunt through persistent fetal channels (ie., the patent foramen ovale [PFO] and patent ductus arteriosus [PDA])". Document D10 further states that the result of PPHN is "life-threatening hypoxia, cyanosis, and acidosis" (page 638, left-hand column, first paragraph under the summary). Additionally, according to document D10, the syndrome PPHN includes three different anatomic types: maladaptation, excessive muscularization and underdevelopment of the pulmonary vascular bed (D10, page 638, left-hand column).

Claim 1 as granted is not restricted in relation to the treatment of a particular aetiology or symptom associated with PPHN. However, the description of the root application as filed states that "the methods herein disclosed are useful for preventing (if given prior to the onset of symptoms) or reversing **acute pulmonary vasoconstriction**, such as may result from pneumonia, traumatic injury, ..., asthma, post cardiac surgery acute pulmonary hypertension, **persistent pulmonary hypertension of the newborn**, perinatal aspiration syndrome", etc. (page 7, lines 20-33) (*emphasis added*). Therefore, the administration of gaseous NO as active ingredient (page 8, lines 3-5 of root application as filed) addresses the treatment of acute pulmonary vasoconstriction, and the patients who undergo the treatment are generally defined as "a **mammal with pulmonary vasoconstriction** or asthma" (page 8, lines 4-5 of the root application as filed) (*emphasis added*).

The description of the root application as filed further states in general terms: "The invention allows for effective reversal of **pulmonary hypertension** without the risk of underperfusion of vital organs, venous pooling, ischemia, and heart failure that may accompany systemic vasodilation. Such **isolated pulmonary vasodilation** is also important **in treating PPHN in newborn infants**, as systemic vasodilation aggravates the undesired mixing of oxygenated and de-oxygenated blood through the ductus arteriosus or the foramen ovale of newborns" (page 18, lines 20-28, of the root application as filed) (*emphasis added*).

As regards the paragraph under the heading "NO **Inhalation Therapy for Pulmonary Vasoconstriction**" on page 21 of the root application as filed, it states the following: "Pulmonary hypertension is a widespread clinical manifestation, afflicting diverse groups of patients. Use of inhaled NO is currently envisioned for, ..., **patients afflicted with** or at risk of developing the following: ARDS, pneumonia, asthma, acute pulmonary edema, ..., **PPHN**, etc. (emphasis added). This paragraph is followed by the heading "Method for administration". Under the method for administration disclosed for the therapy for treating pulmonary hypertension, "a mixture of 200-800 ppm **NO in pure N<sub>2</sub> gas**" is disclosed (page 22, lines 5-6, of the root application as filed) (emphasis added). Moreover it is also disclosed that in "a hospital or emergency field situation, administration of NO gas could be accomplished, for example, by attaching a tank of **compressed NO gas in N<sub>2</sub>**, and a second tank of oxygen or an oxygen/N<sub>2</sub> mixture ..." (page 22, lines 27-30) (emphasis added).

The vasodilatory action of inhaled NO as a local or selective effect in the blood vessels of the lungs is further disclosed on page 24 of the root application as filed.

The examples concern *inter alia* a protocol for administration of gaseous NO to infants: "The following is a description of an approved experimental protocol **for the administration of NO to newborns** at Massachusetts General Hospital" (*emphasis added*). They illustrate the invention disclosed in the description, which addresses **acute pulmonary vasoconstriction** and

pulmonary hypertension by achieving **local vasodilation** (see also page 35, lines 4 to 6 of the root application as filed).

Thus, even assuming that all newborns suffering from PPHN (e.g. those having pulmonary hypoplasia which are excluded from the experimental treatment on pages 33-34) present acute pulmonary vasoconstriction, claim 1 as granted extends the treatment of PPHN to any form (regardless of aetiology and symptoms) of the syndrome since the functional link between the inhalation of a gaseous mixture of NO (and N<sub>2</sub>) and reversing acute vasoconstriction is not necessarily required. However, the description of the root application as filed discloses the treatment of PPHN only as far as it concerns reversing acute pulmonary vasoconstriction.

Additionally, there is a lack of disclosure in the root application as filed for singularising the treatment of PPHN together with the administration of a gaseous mixture of NO and an inert gas other than N<sub>2</sub>. The disclosure on page 14 of the root application as filed relating to a "portable inhaler similar to those typically used by persons with asthma" does not concern the treatment of newborns with PPHN. The root application as filed does not explain how much similarity is required between the portable inhaler for adults and a portable inhaler suitable for inhalation of newborns, or what differences are involved in order to adapt a portable inhaler designed for adults suffering from vasoconstriction such as in asthma to make it suitable for inhalation therapy in newborns with PPHN. The description on page 14, first paragraph, does not mention treatment of PPHN, but it indicates



that the "pharmaceutically-active agent included in the device of the invention may be an antimicrobial agent, or a surfactant suitable for the treatment of hyaline membrane disease" (according to document D10, page 638, the syndrome PPHN may be primary or secondary to *inter alia* hyaline membrane disease). Moreover, the contents of the device as disclosed in the same paragraph on page 14 are to be chosen among several options: "a pressurised mixture of nitrogen gas (or another inert gas) and nitric oxide (**instead or in addition to** an inert, liquified propellant such as a fluorocarbon, e.g. freon)" (*emphasis added*) and do not serve to single out the mixture of NO and an inert gas for the treatment of newborns.

Similar comments also apply to the content on page 15 of the root application as filed. As regards the disclosure on page 17, it concerns the inhalation of a **NO-releasing compound** in solid or liquid form by means of a portable inhaler. Furthermore, the disclosure on page 26 in relation to the inhalation devices refers to those previously disclosed and hence the same arguments apply by analogy to those given in relation to a lack of basis for the inhalation therapy of newborns with PPHN.

Therefore, the treatment of PPHN by inhalation with a gaseous mixture of NO and an inert gas claimed in claim 1 as granted extends beyond the content of the root application as filed (Article 100(c) EPC).

- 3.3 As regards the respondent's arguments concerning the cited passages, e.g. page 6 under the heading "Summary of the invention", they do not refer exclusively to the

use of gaseous NO, but also refer to the use of a nitric oxide-releasing compound. Therefore, a choice between two different options must be made by the skilled person when selecting gaseous nitric oxide, in addition to the selection of PPHN as the medical condition to be treated. Moreover, some of the passages cited by the respondent do not specify the treatment of PPHN, but relate to pulmonary hypertension in general or to primary pulmonary hypertension, and thus they cannot be arbitrarily combined with the disclosure which is specifically directed to newborns suffering from PPHN.

The passage bridging pages 3 and 4 teaches that pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome (ARDS) and persistent pulmonary hypertension of the newborn (PPHN), but this information cannot serve as a delimitation of the subject-matter in claim 1 as granted, which encompasses in its technically meaningful sense any form of treatment of PPHN by inhalation of a gaseous mixture of NO and an inert gas.

Additionally, although claim 1 as granted is not restricted in relation to the aetiology and symptoms of PPHN the claim is not ambiguous, and thus the description cannot be invoked to delimit what is the subject-matter claimed in said claim. The respondent cited document D10 as appertaining to the common general knowledge of the skilled person. Therefore, the description cannot be invoked to artificially delimit claim 1 as granted in relation to the meaning of the syndrome PPHN, known to the skilled person in the light

of his common general knowledge (see document D10). Therefore, the fact that the description discloses that the treatment may serve to reverse acute pulmonary vasoconstriction or reduce the patient's airway resistance does not restrict the subject-matter claimed in claim 1 as granted, since these features are not reflected by claim 1 as granted. When investigating whether there is added matter within the meaning of Article 100(c) EPC it has to be assessed whether the granted claim contains technical information which is not directly and unambiguously derived from the (root) application as filed. This is the case in the patent in suit for claim 1 as granted, which addresses as the therapeutic use the treatment of PPHN without any particular restriction, whereas the description of the root application as filed links the therapeutic treatment of PPHN to a particular technical effect (non-systemic, pulmonary vasodilation, see root application as filed, *inter alia* page 8, lines 15-16, lines 24-25 "such isolated pulmonary vasodilation is also important in treating PPHN in newborn infants") which translates into reversing acute pulmonary vasoconstriction or reducing the patient's airway resistance. Thus claim 1 as granted encompasses forms for the treatment of PPHN which are not disclosed in the root application as filed.

Finally, establishing whether the granted claim includes added matter within the meaning of Article 100(c) EPC requires an assessment of the overall technical circumstances of the individual case under consideration. Whether there is a basis in the application as filed for medical use claims and whether or not a particular technical effect has to be

reflected by the claim's wording depends on the particular circumstances of each case. Moreover, the board of appeal decisions cited by the respondent (T 1069/08, T 601/05 and T 1696/08) do not deal with the question of added matter (Articles 100(c), 123(2) and 76(1) EPC). Assessment of the disclosure as originally filed as an adequate basis for amendments is something different from assessment of the requirements of Article 83 EPC and can also not be made dependent on assessment of the novelty and inventive step of the subject-matter claimed.

3.4 Therefore, the main request fails since claim 1 extends beyond the content of the root application as filed (Article 100(c) EPC).

4. *Auxiliary request 1*

4.1 Claim 1 of auxiliary request 1 is identical to claim 1 as granted. Therefore, auxiliary request 1 fails for the same reasons as the main request (Article 100(c) EPC).

5. *Auxiliary request 1B*

5.1 Claim 1 of auxiliary request 1B differs from claim 1 of the main request merely in that the inert gas is restricted to N<sub>2</sub>. Therefore the reasons concerning added matter in relation to the treatment of any form of PPHN without indication as to aetiology or symptoms apply mutatis mutandis to auxiliary request 1B.

The passages on page 22 concern the use of NO inhalation therapy for **pulmonary vasoconstriction** in

*inter alia* PPHN, which is not reflected by the claim's wording. The experiments on pages 34 and 35 concerned PPHN, but they also address vasoconstriction and the vasodilatory response to NO inhalation.

Therefore, auxiliary request 1B fails since it contains added matter pursuant to Articles 100(c), 123(2) and 76(1) EPC.

6. *Auxiliary request 1C*

- 6.1 The amendment introduced in claim 1 of auxiliary request 1C relates to the definition of the medical treatment: "for treating **pulmonary hypertension in a patient** with persistent pulmonary hypertension of the newborn" (*emphasis added*). This amendment introduces into the claim a lack of clarity (Article 84 EPC) in relation to the patient and the condition to be treated. As regards the patient to be treated the new definition now includes not only newborns but also older infants, which is in contradiction with the content of the description (Article 84 EPC, lack of support). Moreover, document D63, which was cited by the respondent during the discussion of auxiliary request 1C, relates to constrictive and restrictive pulmonary hypertension in the newborn and infant (see title). Document D63 clearly states that the lung of the newborn is not that of the adult in miniature (page 288, right-hand column). Furthermore, document D63 distinguishes between persistent pulmonary hypertension in the newborn and postnatal pulmonary hypertension (pages 290, 296). However, it is unclear whether claim 1 of auxiliary request 1C only addresses the treatment of persistent pulmonary hypertension of the newborn or also extends

to the treatment of postnatal pulmonary hypertension. Thus assessment of the requirements of Article 123(3) EPC is hindered owing to the lack of clarity of the amendment introduced into the claim.

Therefore, auxiliary request 1C fails since the subject-matter claimed in claim 1 does not meet the requirements of Article 84 EPC.

7. *Auxiliary request 1C'*

7.1 Claim 1 of auxiliary request 1C' differs from claim 1 as granted in the specification of N<sub>2</sub> as the inert gas, and in the definition of the medical treatment, which reads as follows: "for reversing acute pulmonary vasoconstriction resulting from persistent pulmonary hypertension of the newborn".

The amendments concerning the wording of the medical treatment were occasioned by the grounds of opposition pursuant to Article 100(b) and (c) EPC raised by the appellants in the course of the proceedings. Moreover, the choice of the wording concerning the medical treatment was made on the basis of the original disclosure in the root application as filed, in order to pre-empt further objections under Article 76(1) EPC.

Therefore the amendments meet the requirements of Rule 80 EPC.

7.1.1 Claim 1 as granted addressed the treatment of the syndrome PPHN in generic terms. In other words, claim 1 as granted does not require the treatment to be causative and/or symptomatic, but encompasses all

possible forms of treatment for PPHN in general. Therefore, amended claim 1 does not extend the protection it confers over claim 1 as granted (Article 123(3) EPC) since the treatment now claimed is restricted to one particular treatment which falls within the scope of claim 1 as granted.

7.1.2 Moreover, "acute pulmonary vasoconstriction resulting from PPHN" is a serious symptom of PPHN which can be linked *inter alia* to hypoxia and cyanosis in the newborn. Therefore "reversing" (the constrictive component is reversed by dilation) acute pulmonary vasoconstriction represents a treatment of the newborn suffering from the syndrome PPHN.

Furthermore, the claim has to be read in a technically meaningful sense. The claim relates to the medical use of a gaseous mixture consisting of NO and N<sub>2</sub>. Thus it is self-evident that treatment by inhalation with such a gaseous mixture is not meant to hinder administration of oxygen and/or air, and the claim cannot be understood as meaning that during the treatment no oxygenation takes place, since this would immediately cause the patient's death.

Therefore, auxiliary request 1C' meets the requirements of Article 84 EPC.

7.1.3 Additionally, the medical use of a gaseous mixture consisting of NO and N<sub>2</sub> according to claim 1 derives directly and unambiguously from the root application as filed (Articles 123(2) and 76(1) EPC), *inter alia* from page 7, lines 22 and 29-30, and pages 21 to 23 of the root application as filed. The specific disclosure on

page 22 only mentions that "the NO-N<sub>2</sub> mixture may be blended with air or O<sub>2</sub> through calibrated rotameters". However, this particular embodiment does not restrict the more general disclosure of the medical use achieved by administration of gaseous NO in relation to acute pulmonary vasoconstriction and PPHN.

7.1.4 Additionally, the amendment in claim 3 of auxiliary request 1C' concerns the expression "monitored and" before the expression "maintained at less than 1 ppm". This amendment was introduced as a clear and direct response to appellant O3's objection pursuant to Article 100(c) EPC against claim 3 as granted. Additionally, it is self-explanatory that in order that the concentration of NO<sub>2</sub> can be maintained at certain levels it has to be monitored. The monitoring of the concentration of NO<sub>2</sub> has to do with the fact that NO is unstable and undergoes spontaneous oxidation to NO<sub>2</sub>, which is toxic to the lungs (see passage bridging pages 5 and 6). Therefore, the amendment does not cause problems within the meaning of Article 84 EPC.

7.1.5 Therefore, auxiliary request 1C' meets the requirements of Articles 123(2), 76(1), 123(3) and 84 EPC.

## 7.2 *Sufficiency of disclosure*

7.2.1 The arguments provided by the appellants do not raise serious doubts about the reproducibility of the invention claimed in auxiliary request 1C'. In particular, there is no evidence on file showing that the symptom of acute pulmonary vasoconstriction resulting from PPHN cannot be determined. The appellants' arguments in relation to the term



"reversing" do not cast serious doubts on sufficiency of disclosure either, as the medical treatment in claim 1 relates to relieving the severe symptom.

The specification contains sufficient and detailed instructions for the skilled person to reproduce the invention claimed. Moreover, even if one of the patients treated was a complex case owing to the congenital heart failure and had to be returned to the newborn intensive care unit, the patient also suffered from PPHN, and thus the disclosure that in such a patient inhalation of NO improves oxygen saturation and blood gas tension is relevant for the technical effect and invention claimed. Moreover, there are at least two further newborn infants with PPHN (paragraph [0054] of the patent in suit) treated with inhaled NO showing increases in preductal oxygenation.

It has not been proven that the teaching contained in the whole patent in suit, including the experimental part beginning with the Protocol for administration of gaseous NO to infants with PPHN (where the infants are clearly newborns) and the reported results of actual experiments *in vivo*, is insufficient for the skilled person to reproduce the claimed invention.

Therefore, the patent in suit discloses the invention claimed in the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Articles 100(b) and 83 EPC).

### 7.3 *Novelty*

- 7.3.1 Document D2 does not disclose the treatment of patients with persistent pulmonary hypertension of the newborn. The syndrome PPHN is diagnosed in a particular group of patients, namely the neonate, and leads to respiratory failure and death unless treated (see document D10, page 638, left-hand column, and page 639 under the heading "Diagnosis"). Therefore, the patients treated according to claim 1 of auxiliary request 1C' are not the same as the patients with primary pulmonary hypertension treated in document D2.

The conclusion in decision T 443/01 that a different claim lacked novelty is not directly applicable to the subject-matter claimed in claim 1 of auxiliary request 1C' since its subject-matter is different from the subject-matter defined in the claim dealt with in point 3.1 ff of T 443/01.

### 8. *Inventive step*

- 8.1.1 Document D10, which discloses several approaches to the treatment of persistent hypertension of the newborn (PPHN), represents the closest prior art.

Document D10 discloses *inter alia* the pharmacologic treatment with vasodilators (page 640). Document D10 states: "There is currently no known drug that is a powerful and selective dilator of pulmonary vasculature" and gives a brief discussion of some of the more commonly used pharmacologic agents used to its publication date (1988). Among these prostaglandin I<sub>2</sub> (prostacyclin) is mentioned and it is explained that

reports vary widely concerning the use of this vasodilator. Document D10 states in relation to prostaglandin I<sub>2</sub>: "It has been very useful in some neonates, but equally unhelpful in others due to **devastating complications**" (page 640, right-hand column) (emphasis added).

In the light of the closest prior art the problem to be solved lies in the provision of an alternative treatment for PPHN.

The solution defined in claim 1 is to use inhaled NO. The fact that NO is administered in a gaseous mixture with N<sub>2</sub> as inert gas merely reflects the knowledge in the field, since NO was known to oxidize to toxic NO<sub>2</sub> in the presence of oxygen, as acknowledged in the patent in suit (paragraph [0010]). Moreover, gaseous NO/N<sub>2</sub> mixtures suitable for inhalation were commercially available to hospitals (documents D20 and D21).

The board is satisfied that the problem has been solved in view of the content of the specification, in particular in view of the results of administering NO to infants with persistent pulmonary hypertension of the newborn (PPHN). Apart from the fact that the respondent has confirmed that the patients treated in the experiments were newborns, it becomes apparent from the content of the specification in paragraphs [0046] to [0054]. Moreover, as already mentioned in connection with the assessment of sufficiency of disclosure, the *in vivo* experiments concerned the treatment with inhaled NO of at least two newborn infants suffering from PPHN but without congenital heart failure, and showed increases in preductal oxygenation and long term

survival (paragraph [0054] of the patent in suit). One the patients had such a rapid improvement with NO inhalation alone that ECMO was avoided altogether. This teaching clearly indicates that vasoconstriction (which is an accompanying symptom to PPHN) was relieved and thus acute vasoconstriction is reversed.

It now has to be investigated whether the proposed solution is obvious in the light of the prior art.

The passage in document D10 expressing that "there is currently no known drug that is a **powerful** and **selective** dilator of pulmonary vasculature" (emphasis added) incites the skilled person to look for powerful and selective dilators of pulmonary vasculature. The skilled person is not only a neonatologist but he is the notional skilled person possessing several related technical expertises, such as pulmonologist or pharmaceutical technologist. Therefore, the skilled person would also consider document D2.

Document D2 compares the vasodilatory effects of inhaled NO in patients with primary pulmonary hypertension with those of an intravenous infusion of prostacyclin (PGI<sub>2</sub>). Document D2 discloses that the average of the abnormal elevated pulmonary artery pressure of the patients suffering from PPH decreased by about 6%. A document similar to document D2 relating to experiments of inhaled NO in patients suffering PPH, namely document D3, discloses a decrease in the **average pulmonary arterial pressure** below 15%. The further documents cited, namely D4, D5 and D6 confirm that inhaled NO represents a valid pharmacologic treatment

for PPH since it does not cause systemic hypotension, but they do not mention PPHN in any way.

For the treatment of PPH a certain relief attained by a moderate decrease in the pulmonary arterial pressure may suffice for a valid therapy. However, in newborn patients PPHN results in life-threatening hypoxia or cyanosis (document D10, page 638, left-hand column). Therefore, they need a powerful pulmonary vasodilator. Moreover, even if some patients of PPH may be children, they are at least nine months old (document D24). Therefore, their lungs and anatomic condition are not those of a newborn who has an open ductus arteriosus and a right-to-left shunt through foetal channels (document D10, page 638, left-hand column), and thus the results of the experiments on patients with PPH are not conclusive for PPHN.

Furthermore, document D24 defines a 20% or greater decrease in **mean pulmonary arterial pressure** as a criterion for considering the patients (children and young adults suffering from primary pulmonary hypertension) to be responders to pharmacologically induced vasodilatation (prostacyclin and nifedipine were tested). This teaching serves to indicate the actual magnitude of vasodilatation that the skilled person would be looking for in order to consider a certain drug to be a powerful pulmonary vasodilator in order to be expected to be a successful candidate for treating PPHN, where vasoconstriction becomes acute and life-threatening if not treated.

Document D2 teaches that inhaled NO causes no systemic vasodilatation, but the actual decrease in pulmonary

arterial pressure shown in document D2 (and document D3) is moderate. The skilled person would not expect from the data displayed in document D2 that inhaled NO would be a successful therapeutic alternative for the treatment of PPHN.

Therefore, the proposed solution is not rendered obvious by the cited prior art since the skilled person would not seriously contemplate NO as solution to the problem.

8.1.2 Turning now to further arguments submitted by the appellants, the following has been considered:

It is not relevant for the assessment of inventive step in the present case that some of the patients suffering from primary pulmonary hypertension and some of the newborns suffering from PPHN may be idiopathic. This only means that the causes for the pulmonary hypertension are not known. However, lack of knowledge in relation to the causes does not make the aetiologies identical. Moreover, the physical and anatomical conditions of the newborn lungs are not comparable to those of patients suffering from PPH, who may be children (older than nine months) but are not newborns turning hypoxic and cyanotic and eventually dying if not immediately treated. As stated in document D63, "the lung of a newborn is not that of the adult in miniature" (page 288) and "the continuing elevation of pulmonary vascular resistance results in right-to-left shunting across **still patent foetal channels**,..., this causes central cyanosis" (pages 287-288) (emphasis added). It has not been proven that this is also the case of the nine-month-old children suffering from PPH.

The argument that the mere knowledge that inhaled NO did not cause selective vasodilatation in PPH patients was incentive enough for the skilled person to consider NO as the solution to the problem is denied, since there was no expectation of success in view of the moderate values attained in document D2.

As regards the argument that the skilled person had no other choice than to administer inhaled NO to the newborns fighting for their lives, it has to be said that this situation does not reflect reality, where ethical considerations are seriously taken into account before starting an experimental treatment unpromising in the light of the prior art. The physician treating those patients would have stuck, without making use of inventive skills, to other treatments, which were known and currently used, as disclosed in document D10.

Additionally, document D58 does not concern the use of NO as vasodilator and did not concern newborns with PPHN.

As regards the arguments concerning methemoglobinemia, the extent to which methemoglobinemia develops depends on the dose of inhaled NO which is administered. The skilled person would not have been deterred from the use of NO in general terms. However, the reasons why the skilled person would disregard NO as a successful alternative concern the lack of knowledge in the prior art to qualify this particular drug as a selective pulmonary vasodilator powerful enough to be seriously considered for the treatment of PPHN.

8.1.3 Therefore, auxiliary request 1C' meets the requirements of Article 56 EPC.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of auxiliary request 1C' filed with the letter of 4 October 2013 and a description to be adapted thereto.

The Registrar:

The Chairman:

A. Counillon

U. Oswald