IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

INO THERAPEUTICS LLC and IKARIA, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. _____
PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC.,	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs INO Therapeutics LLC (hereinafter "INOT"), and Ikaria, Inc. (hereinafter "Ikaria") (collectively, "Plaintiffs") for their Complaint against defendants Praxair Distribution, Inc. and Praxair, Inc. (collectively "Praxair" or "Defendants"), hereby allege as follows:

THE PARTIES

1. Plaintiff INOT is a wholly-owned subsidiary of Ikaria and is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at Perryville III Corporate Park, P. O. Box 9001, 53 Frontage Road, Third Floor, Hampton, New Jersey 08827-9001.

2. Plaintiff Ikaria is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at Perryville III Corporate Park, P.O. Box 9001, 53 Frontage Road, Third Floor, Hampton, New Jersey 08827-9001.

3. Plaintiff Ikaria is a research-driven healthcare company that discovers, develops, manufactures and markets innovative products to address the needs of critically ill patients.

4. On information and belief, Praxair Distribution, Inc. is a corporation organized and existing under the laws of the State of Delaware, with its head office at 28 McCandless Ave, Pittsburgh, Pennsylvania 15201.

5. On information and belief, Praxair, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 39 Old Ridgebury Road, Danbury, Connecticut 06810.

6. On information and belief, Praxair Distribution, Inc. is a wholly-owned subsidiary of Praxair, Inc.

7. On information and belief, Praxair Distribution, Inc. assembled and caused to be filed with the United States Food and Drug Administration ("FDA"), pursuant to 21 U.S.C. § 355(j) (Section 505(j) of the Federal Food, Drug and Cosmetic Act), Abbreviated New Drug Application ("ANDA") No. 207141 (hereinafter "the Praxair ANDA") concerning a proposed drug product, Noxivent, 100 ppm and 800 ppm nitric oxide for inhalation ("Praxair's Proposed ANDA Product").

JURISDICTION AND VENUE

8. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over Praxair Distribution, Inc. On information and belief, Praxair Distribution, Inc. is a corporation organized and existing under the laws of the State of Delaware. On information and belief, Praxair Distribution, Inc. maintains a corporate agent for service of process at 2711 Centerville Road, Suite 400, Wilmington, Delaware 19808.

10. This Court also has personal jurisdiction over Praxair, Inc. On information and belief, Praxair, Inc. is a corporation organized and existing under the laws of the State of Delaware. On information and belief, Praxair, Inc. maintains a corporate agent for service of process at 2711 Centerville Road, Suite 400, Wilmington, Delaware 19808.

11. Venue is proper in this Court at least pursuant to 28 U.S.C. §§ 1391 and 1400(b).

INOmax® (NITRIC OXIDE) FOR INHALATION

12. INOT holds approved New Drug Application ("NDA") No. N020845 for nitric oxide 100 and 800 ppm for inhalation to among other things treat neonates with pulmonary hypertension, and is prescribed and sold in the United States under the trademark INOmax®. The U.S. Food and Drug Administration ("FDA") approved NDA No. N020845 on December 23, 1999.

THE PATENTS-IN-SUIT

13. United States Patent No. 8,282,966 (the "'966 patent," copy attached as Exhibit A) is entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Children in Need of Treatment with Inhaled Nitric Oxide" and was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on October 9, 2012. The '966 patent is listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for INOmax® (NDA No. N020845).

14. The '966 patent is owned by INOT.

15. United States Patent No. 8,293,284 (the "'284 patent," copy attached as Exhibit B) is entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Term or Near-Term Neonates in Need of Treatment with Inhaled Nitric Oxide" and was duly and

legally issued by the USPTO on October 23, 2012. The '284 patent is listed in the FDA's Orange Book for INOmax® (NDA No. N020845).

16. The '284 patent is owned by INOT.

17. United States Patent No. 8,431,163 (the "'163 patent," copy attached as Exhibit C) is entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema Associated with the Inhalation of Nitric Oxide Gas" and was duly and legally issued by the USPTO on April 30, 2013. The '163 patent is listed in the FDA's Orange Book for INOmax® (NDA No. N020845).

18. The '163 patent is owned by INOT.

19. United States Patent No. 8,795,741 (the "'741 patent," copy attached as Exhibit D) is entitled "Methods For Treating Patients Who Are Candidates For Inhaled Nitric Oxide Treatment" and was duly and legally issued by the USPTO on August 4, 2014. The '741 patent is listed in the FDA's Orange Book for INOmax® (NDA No. N020845).

20. The '741 patent is owned by INOT.

21. United States Patent No. 8,846,112 (the "'112 patent," copy attached as Exhibit E) is entitled "Methods Of Distributing A Pharmaceutical Product Comprising Nitric Oxide Gas For Inhalation" and was duly and legally issued by the USPTO on September 30, 2014. The '112 patent is listed in the FDA's Orange Book for INOmax® (NDA No. N020845).

22. The '112 patent is owned by INOT.

23. United States Patent No. 8,291,904 (the "'904 patent," copy attached as Exhibit F) is entitled "Gas Delivery Device And System" and was duly and legally issued by the USPTO on October 23, 2012. The '904 patent is listed in the FDA's Orange Book for INOmax® (NDA No. N020845).

24. The '904 patent is owned by INOT.

25. United States Patent No. 8,573,210 (the "'210 patent," copy attached as Exhibit G) is entitled "Nitric Oxide Delivery Device" and was duly and legally issued by the USPTO on November 5, 2013. The '210 patent is listed in the FDA's Orange Book for INOmax ® (NDA No. N020845).

26. The '210 patent is owned by INOT.

27. United States Patent No. 8,573,209 (the "'209 patent," copy attached as Exhibit H) is entitled "Gas Delivery Device And System" and was duly and legally issued by the USPTO on November 5, 2013. The '209 patent is listed in the FDA's Orange Book for INOmax ® (NDA No. N020845).

28. The '209 patent is owned by INOT.

29. United States Patent No. 8,776,794 (the "'794 patent," copy attached as Exhibit I) is entitled "Nitric Oxide Delivery Device" and was duly and legally issued by the USPTO on July 15, 2014. The '794 patent is listed in the FDA's Orange Book for INOmax ® (NDA No. N020845).

30. The '794 patent is owned by INOT.

31. United States Patent No. 8,776,795 (the "'795 patent," copy attached as Exhibit J) is entitled "Gas Delivery Device and System" and was duly and legally issued by the USPTO on July 15, 2014. The '795 patent is listed in the FDA's Orange Book for INOmax ® (NDA No. N020845).

32. The '795 patent is owned by INOT.

33. On information and belief, Praxair Distribution, Inc. submitted the Praxair ANDA to the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Praxair's Proposed ANDA Product.

34. On information and belief, the Praxair ANDA seeks FDA approval of Praxair's Proposed ANDA Product having the same use as INOmax®, which use is covered by the patents in suit. The Praxair ANDA refers to and relies upon INOT's NDA No. N020845 for INOmax®.

35. On information and belief, Praxair Distribution, Inc. actively collaborated with Praxair, Inc. and/or participated in and/or directed activities related to the submission of the Praxair ANDA and the development of Praxair's Proposed ANDA Product, was actively involved in preparing the ANDA, and/or intends to directly benefit from and has a financial stake in the approval of the ANDA. On information and belief, upon approval of the Praxair ANDA, Praxair Distribution, Inc. will be involved in the manufacture, distribution, and/or marketing of Praxair's Proposed ANDA Product.

36. On information and belief, Praxair, Inc. actively collaborated with Praxair Distribution, Inc. and/or participated in and/or directed activities related to the submission of the Praxair ANDA and the development of Praxair's Proposed ANDA Product, was actively involved in preparing the ANDA, and/or intends to directly benefit from and has a financial stake in the approval of the ANDA. On information and belief, upon approval of the Praxair ANDA, Praxair, Inc. will be involved in the manufacture, distribution, and/or marketing of Praxair's Proposed ANDA Product.

37. By letter dated January 6, 2015 (the "January 6 Letter"), and pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), Praxair Distribution, Inc. notified Plaintiffs that it had submitted to

the FDA the Praxair ANDA, seeking approval to engage in the commercial manufacture, use, or sale of Praxair's Proposed ANDA Product before the expiration of the '966 patent, the '284 patent, the '163 patent, the '741 patent, the '112 patent, the '904 patent, the '210 patent, the '209 patent, the '794 patent, and the '795 patent. The January 6 Letter was received by Plaintiffs on January 8, 2015.

38. In its January 6 Letter, Praxair Distribution, Inc. notified Plaintiffs, as part of the Praxair ANDA, it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification") with respect to the '966 patent, the '284 patent, the '163 patent, the '741 patent, the '112 patent, the '904 patent, the '210 patent, the '209 patent, the '794 patent, and the '795 patent. On information and belief, Praxair Distribution, Inc. certified that, the '966 patent, the '284 patent, the '163 patent, the '741 patent, the '112 patent, the '904 patent, the '210 patent, the '209 patent, the '794 patent, and the '795 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Praxair's Proposed ANDA Product.

COUNT I
INFRINGEMENT OF U.S. PATENT NO. 8,282,966

39. Plaintiffs repeat and reallege paragraphs 1 through 38 above as if fully set forth herein.

40. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '966 patent, Defendants committed an act of infringement of the '966 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '966 patent at the time the Praxair ANDA was submitted.

41. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '966 patent, they would further infringe the '966 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

42. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '966 patent. Plaintiffs do not have an adequate remedy at law.

43. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '966 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT II
INFRINGEMENT OF U.S. PATENT NO. 8,293,284

44. Plaintiffs repeat and reallege paragraphs 1 through 43 above as if fully set forth herein.

45. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '284 patent, Defendants committed an act of infringement of the '284 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '284 patent at the time the Praxair ANDA was submitted.

46. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '284 patent, they would further infringe the '284 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

47. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '284 patent. Plaintiffs do not have an adequate remedy at law.

48. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '284 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT III
INFRINGEMENT OF U.S. PATENT NO. 8,431,163

49. Plaintiffs repeat and reallege paragraphs 1 through 48 above as if fully set forth herein.

50. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '163 patent, Defendants committed an act of infringement of the '163 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '163 patent at the time the Praxair ANDA was submitted.

51. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '163 patent, they would further infringe the '163 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

52. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '163 patent. Plaintiffs do not have an adequate remedy at law.

53. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '163 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT IV
INFRINGEMENT OF U.S. PATENT NO. 8,795,741

54. Plaintiffs repeat and reallege paragraphs 1 through 53 above as if fully set forth herein.

55. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '741 patent, Defendants committed an act of infringement of the '741 patent under 35 U.S.C. § 271(e)(2).

56. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '741 patent, they would further infringe the '741 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

57. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '741 patent. Plaintiffs do not have an adequate remedy at law.

58. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '741 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT V
INFRINGEMENT OF U.S. PATENT NO. 8,846,112

59. Plaintiffs repeat and reallege paragraphs 1 through 58 above as if fully set forth herein.

60. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's

Proposed ANDA Product throughout the United States prior to the expiration of the '112 patent, Defendants committed an act of infringement of the '112 patent under 35 U.S.C. § 271(e)(2).

61. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '112 patent, they would further infringe the '112 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

62. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '112 patent. Plaintiffs do not have an adequate remedy at law.

63. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '112 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT VI
INFRINGEMENT OF U.S. PATENT NO. 8,291,904

64. Plaintiffs repeat and reallege paragraphs 1 through 63 above as if fully set forth herein.

65. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '904 patent, Defendants committed an act of infringement of the '904 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '904 patent at the time the Praxair ANDA was submitted.

66. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product

into the United States, or induce or contribute to any such conduct during the term of the '904 patent, they would further infringe the '904 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

67. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '904 patent. Plaintiffs do not have an adequate remedy at law.

68. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '904 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT VII
INFRINGEMENT OF U.S. PATENT NO. 8,573,210

69. Plaintiffs repeat and reallege paragraphs 1 through 68 above as if fully set forth herein.

70. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '210 patent, Defendants committed an act of infringement of the '210 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '210 patent at the time the Praxair ANDA was submitted.

71. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '210 patent, they would further infringe the '210 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

72. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '210 patent. Plaintiffs do not have an adequate remedy at law.

73. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '210 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT VIII
INFRINGEMENT OF U.S. PATENT NO. 8,573,209

74. Plaintiffs repeat and reallege paragraphs 1 through 73 above as if fully set forth herein.

75. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '209 patent, Defendants committed an act of infringement of the '209 patent under 35 U.S.C. § 271(e)(2). On information and belief, Defendants were aware of the '209 patent at the time the Praxair ANDA was submitted.

76. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '209 patent, they would further infringe the '209 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

77. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '209 patent. Plaintiffs do not have an adequate remedy at law.

78. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '209 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT IX
INFRINGEMENT OF U.S. PATENT NO. 8,776,794

79. Plaintiffs repeat and reallege paragraphs 1 through 78 above as if fully set forth herein.

80. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's Proposed ANDA Product throughout the United States prior to the expiration of the '794 patent, Defendants committed an act of infringement of the '794 patent under 35 U.S.C. § 271(e)(2).

81. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '794 patent, they would further infringe the '794 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

82. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '794 patent. Plaintiffs do not have an adequate remedy at law.

83. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '794 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

COUNT X
INFRINGEMENT OF U.S. PATENT NO. 8,776,795

84. Plaintiffs repeat and reallege paragraphs 1 through 83 above as if fully set forth herein.

85. By submitting the Praxair ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of Praxair's

Proposed ANDA Product throughout the United States prior to the expiration of the '795 patent, Defendants committed an act of infringement of the '795 patent under 35 U.S.C. § 271(e)(2).

86. If Defendants commercially make, use, offer to sell, or sell Praxair's Proposed ANDA Product within the United States, or import Praxair's Proposed ANDA Product into the United States, or induce or contribute to any such conduct during the term of the '795 patent, they would further infringe the '795 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

87. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '795 patent. Plaintiffs do not have an adequate remedy at law.

88. Praxair Distribution, Inc.'s certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) against the '795 patent was wholly unjustified, and thus this case is exceptional under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Defendants have infringed one or more claims of the '966 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '966 patent;

B. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '966 patent;

C. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of

the '966 patent or any later date of exclusivity to which Plaintiffs and/or the '966 patent are or become entitled to;

D. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '966 patent or any later date of exclusivity to which Plaintiffs and/or the '966 patent are or become entitled;

E. A judgment that Defendants have infringed one or more claims of the '284 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '284 patent;

F. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '284 patent;

G. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '284 patent or any later date of exclusivity to which Plaintiffs and/or the '284 patent are or become entitled to;

H. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '284 patent or any later date of exclusivity to which Plaintiffs and/or the '284 patent are or become entitled;

I. A judgment that Defendants have infringed one or more claims of the '163 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '163 patent;

J. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '163 patent;

K. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '163 patent or any later date of exclusivity to which Plaintiffs and/or the '163 patent are or become entitled to;

L. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '163 patent or any later date of exclusivity to which Plaintiffs and/or the '163 patent are or become entitled;

M. A judgment that Defendants have infringed one or more claims of the '741 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '741 patent;

N. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '741 patent;

O. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from

engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '741 patent or any later date of exclusivity to which Plaintiffs and/or the '741 patent are or become entitled to;

P. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '741 patent or any later date of exclusivity to which Plaintiffs and/or the '741 patent are or become entitled;

Q. A judgment that Defendants have infringed one or more claims of the '112 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '112 patent;

R. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '112 patent;

S. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '112 patent or any later date of exclusivity to which Plaintiffs and/or the '112 patent are or become entitled to;

T. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration

date of the '112 patent or any later date of exclusivity to which Plaintiffs and/or the '112 patent are or become entitled;

U. A judgment that Defendants have infringed one or more claims of the '904 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '904 patent;

V. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '904 patent;

W. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '904 patent or any later date of exclusivity to which Plaintiffs and/or the '904 patent are or become entitled to;

X. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '904 patent or any later date of exclusivity to which Plaintiffs and/or the '904 patent are or become entitled;

Y. A judgment that Defendants have infringed one or more claims of the '210 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '210 patent;

Z. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '210 patent;

AA. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '210 patent or any later date of exclusivity to which Plaintiffs and/or the '210 patent are or become entitled to;

BB. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '210 patent or any later date of exclusivity to which Plaintiffs and/or the '210 patent are or become entitled;

CC. A judgment that Defendants have infringed one or more claims of the '209 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '209 patent;

DD. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '209 patent;

EE. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '209 patent or any later date of exclusivity to which Plaintiffs and/or the '209 patent are or become entitled to;

FF. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '209 patent or any later date of exclusivity to which Plaintiffs and/or the '209 patent are or become entitled;

GG. A judgment that Defendants have infringed one or more claims of the '794 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '794 patent;

HH. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '794 patent;

II. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '794 patent or any later date of exclusivity to which Plaintiffs and/or the '794 patent are or become entitled to;

JJ. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '794 patent or any later date of exclusivity to which Plaintiffs and/or the '794 patent are or become entitled;

KK. A judgment that Defendants have infringed one or more claims of the '795 patent by filing ANDA No. 207141 relating to Praxair's Proposed ANDA Product before the expiration of the '795 patent;

LL. A judgment that the manufacture, use, offer for sale, sale and/or importation of Praxair's Proposed ANDA Product will infringe the '795 patent;

MM. A permanent injunction restraining and enjoining Defendants, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Praxair's Proposed ANDA Product until the expiration of the '795 patent or any later date of exclusivity to which Plaintiffs and/or the '795 patent are or become entitled to;

NN. An order that the effective date of any approval of Praxair's ANDA No. 207141 relating to Praxair's Proposed ANDA Product under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date that is not earlier than the expiration date of the '795 patent or any later date of exclusivity to which Plaintiffs and/or the '795 patent are or become entitled;

OO. A declaration that this case is "exceptional" within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, costs, expenses, and disbursements of this action; and

PP. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

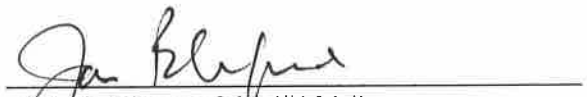

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EXHIBIT A

US008282966B2

(12) **United States Patent**
Baldassarre et al.

(10) **Patent No.: US 8,282,966 B2**
(45) **Date of Patent: *Oct. 9, 2012**

(54) **METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN CHILDREN IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE**

(75) Inventors: **James S. Baldassarre**, Doylestown, PA (US); **Ralf Rosskamp**, Chester, NJ (US)

(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/821,020**

(22) Filed: **Jun. 22, 2010**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned.

(51) **Int. Cl.**

A01N 59/00	(2006.01)
A61K 33/00	(2006.01)
C01B 21/24	(2006.01)
A61M 16/00	(2006.01)

(52) **U.S. Cl.** **424/718**; 128/200.24; 423/405

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(57) **ABSTRACT**

The invention relates methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

29 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN CHILDREN IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. patent application Ser. No. 12/494,598, entitled "Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension", filed on Jun. 30, 2009, incorporated herein by reference.

BACKGROUND OF THE INVENTION

INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108 (Suppl II):II-167-II-173; Lepore J J et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler J W et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a.) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b.) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a.) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a.) identifying a patient in need of receiving iNO treatment; (b.) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c.) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP$\geqq$20 mm Hg.

In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or, associations thereof.

In another exemplary embodiment of the method, the patient population comprises children.

In another exemplary embodiment of the method, the patient population comprises adults.

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing and increased rate of one or more AEs or SAEs selected

from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm)>25 mm Hg at rest, PCWP≦15 mm Hg, and, a pulmonary vascular resistance index (PVRI)> 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; cardiomyopathy characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety. The CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including U.S. Pat. Nos. 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; U.S. patent application Ser. Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery and a backup NO delivery capability.

As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

As used herein, the terms "adverse event" or "AE" (and variations thereof) mean any untoward occurrence in a subject, or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

As used herein, the terms "adverse drug reaction" or "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

As used herein, the terms "serious adverse event" or "SAE" (or "serious adverse drug reaction" or "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or, is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above—these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related

or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measure by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measure of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

In cardiac physiology, afterload is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore only of direct relevance in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

The terms "left ventricular afterload" (and variations thereof) refer to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (Increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increase pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole increasing forward blood flow by reducing afterload thus, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (See Rubin L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult,* 2*d Ed*., Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906;

Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

CINRGI study. (See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a PaO_2>60 mm Hg and a pH<7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 4. ECMO was the primary endpoint of the study.

TABLE 1

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax ®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants≦14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response=>20 mmHg, partial=10-20 mm Hg, no response=<10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

TABLE 2

Summary of Clinical Results from NINOS Study

	Control (n = 121)	NO (n = 114)	P value
Death or ECMO *, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological squeal.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

TABLE 3

ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n = 89)	Inhaled NO (n = 97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The

listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

Example 1

INOT22 Study

The INOT22, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to access the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI)>3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criteria of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) (p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). While the change from baseline in SVRI with NO alone was −0.2 WU·m^2 (p=0.899) which demonstrates a lack of systemic effect.

TABLE 4

SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU · m^2)	NO Plus O_2 (n = 109)	O_2 (n = 106)	NO (n = 106)
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	−7.6, 55.6	−7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	−0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	−20.5, 19.1	−18.1, 17.7	−12.5, 12.7
p-value[a]	0.007	0.004	0.899

Pairwise comparisons
NO plus O_2 versus O_2, p = 0.952
NO plus O_2 versus NO, p = 0.014
O_2 versus NO, p = 0.017

[a]p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.
Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

TABLE 5

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56

TABLE 5-continued

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Change from Baseline			
Mean	−0.2	−0.1	−0.1
SD	0.52	0.31	0.54
Median	−0.1	−0.1	0.0
Minimum, Maximum	−4.4, 2.0	−1.6, 2.0	−4.4, 1.6
P Value[1]	<0.001	<0.001	0.002

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

TABLE 6

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Percent Change from Baseline			
Mean	−33.5	−19.3	−6.2
SD	36.11	34.59	64.04
Median	−34.0	−21.3	−13.8
Minimum, Maximum	−122.2, 140.1	−122.7, 93.3	−256.1, 294.1
P Value[1]	<0.001	<0.001	0.006

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG) decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 5 below.

TABLE 5

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine

whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline PCWP≧18 mm Hg (7.5%), of which, 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%) compared to 6.5% for the entire cohort.

Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor C J et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP>20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

We claim:

1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;

(b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim **1**, wherein the child is a neonate.

3. The method of claim **1**, wherein step (b) comprises measuring the child's pulmonary capillary wedge pressure.

4. The method of claim **1**, wherein the child's left ventricular dysfunction is attributable to congenital heart disease.

5. The method of claim **1**, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide.

6. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) carrying out a diagnostic process comprising measuring blood oxygen level, to identify a child as being in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the child is not dependent on right-to-left shunting of blood;

(b) determine determining that the child has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from treatment with inhaled nitric oxide based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

7. The method of claim **6**, wherein the diagnostic process of step (a) further comprises performing echocardiography.

8. The method of claim **6**, wherein the child is a neonate.

9. The method of claim **6**, wherein step (b) comprises measuring the child's pulmonary capillary wedge pressure.

10. The method of claim **6**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

11. The method of claim **6**, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk not only

of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

12. The method of claim **11**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

13. A method of treatment comprising:

(a) performing echocardiography to identify a plurality of children who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the children are not dependent on right-to-left shunting of blood;

(b) determining that a first child of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second child of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second child; and

(e) excluding the first child from treatment with inhaled nitric oxide, based on the determination that the first child has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

14. The method of claim **13**, wherein step (a) further comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic.

15. The method of claim **13**, wherein the second child has congenital heart disease.

16. The method of claim **13**, wherein step (b) comprises measuring the first child's pulmonary capillary wedge pressure.

17. The method of claim **13**, wherein determining that the second child of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography.

18. The method of claim **13**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

19. The method of claim **13**, wherein the left ventricular dysfunction of the first child is attributable to congenital heart disease.

20. The method of claim **13**, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

21. The method of claim **20**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

22. A method of treatment comprising:

(a) identifying a plurality of children who are in need of 20 ppm inhaled nitric oxide treatment, wherein the children are not dependent on right-to-left shunting of blood;

(b) in the first child of the plurality, measuring pulmonary capillary wedge pressure to determine that the first child of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) in the second child of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the second child of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second child; and

(e) excluding the first child from treatment with inhaled nitric oxide, based on the determination that the first child has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

23. The method of claim **22**, wherein step (a) comprises performing echocardiography to determine that the first and second children have pulmonary hypertension.

24. The method of claim **22**, wherein step (a) comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic.

25. The method of claim **22**, wherein the second child has congenital heart disease.

26. The method of claim **22**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

27. The method of claim **22**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

28. The method of claim **22**, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

29. The method of claim **28**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

* * * * *

EXHIBIT B

US008293284B2

(12) **United States Patent**
Baldassarre et al.

(10) **Patent No.: US 8,293,284 B2**
(45) **Date of Patent: *Oct. 23, 2012**

(54) **METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN TERM OR NEAR-TERM NEONATES IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE**

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See application file for complete search history.

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(57) **ABSTRACT**

The invention relates methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

30 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN TERM OR NEAR-TERM NEONATES IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of and claims priority to U.S. patent application Ser. No. 12/494,598, entitled "Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension", filed on Jun. 30, 2009, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

INOmax®(nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108 (Suppl II):II-167-II-173; Lepore J J et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler J W et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a.) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b.) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a.) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a.) identifying a patient in need of receiving iNO treatment; (b.) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c.) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP≧20 mm Hg.

In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or, associations thereof.

In another exemplary embodiment of the method, the patient population comprises children.

In another exemplary embodiment of the method, the patient population comprises adults.

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing and increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm)>25 mm Hg at rest, PCWP≦15 mm Hg, and, a pulmonary vascular resistance index (PVRI)> 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; cardiomyopathy characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety. The CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®), INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including U.S. Pat. Nos. 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; U.S. patent application Ser. Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery and a backup NO delivery capability.

As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

As used herein, the terms "adverse event" or "AE" (and variations thereof) mean any untoward occurrence in a subject, or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

As used herein, the terms "adverse drug reaction" or "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

As used herein, the terms "serious adverse event" or "SAE" (or "serious adverse drug reaction" or "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or, is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above—these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with

cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measure by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measure of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

In cardiac physiology, afterload is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore only of direct relevance in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

The terms "left ventricular afterload" (and variations thereof) refer to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (Increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increase pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole increasing forward blood flow by reducing afterload thus, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

A small proportion of INOmax sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax® in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening

arterial oxygenation. (See Rubin L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

CINRGI Study.

(See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (01) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a PaO_2>60 mm Hg and a pH<7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 4. ECMO was the primary endpoint of the study.

TABLE 1

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax ®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

NINOS study.

(See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9,597).

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≦14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response=>20 mmHg, partial=10-20 mm Hg, no response=<10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

TABLE 2

Summary of Clinical Results from NINOS Study

	Control (n = 121)	NO (n = 114)	P value
Death or ECMO *, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological squeal.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

TABLE 3

ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n = 89)	Inhaled NO (n = 97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1

INOT22 Study

The INOT22, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to access the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI)>3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criteria of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI)(Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2)(p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). While the change from baseline in SVRI with NO alone was −0.2 WU·m^2 (p=0.899) which demonstrates a lack of systemic effect.

TABLE 4

SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU · m^2)	NO Plus O_2 (n = 109)	O_2 (n = 106)	NO (n = 106)
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	−7.6, 55.6	−7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	−0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	−20.5, 19.1	−18.1, 17.7	−12.5, 12.7
p-value[a]	0.007	0.004	0.899

Pairwise comparisons

NO plus O_2 versus O_2, p = 0.952

NO plus O_2 versus NO, p = 0.014

O_2 versus NO, p = 0.017

[a]p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

TABLE 5

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Change from Baseline			
Mean	−0.2	−0.1	−0.1
SD	0.52	0.31	0.54
Median	−0.1	−0.1	0.0
Minimum, Maximum	−4.4, 2.0	−1.6, 2.0	−4.4, 1.6
P Value[1]	<0.001	<0.001	0.002

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

TABLE 6

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Percent Change from Baseline			
Mean	−33.5	−19.3	−6.2
SD	36.11	34.59	64.04
Median	−34.0	−21.3	−13.8
Minimum, Maximum	−122.2, 140.1	−122.7, 93.3	−256.1, 294.1
P Value[1]	<0.001	<0.001	0.006

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG) decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 5 below.

TABLE 5

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline PCWP≧18 mm Hg (7.5%), of which, 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%) compared to 6.5% for the entire cohort.

Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor C J et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP>20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

We claim:

1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the patient is not dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim **1**, wherein step (b) comprises performing echocardiography.

3. The method of claim **1**, wherein step (b) comprises measuring the patient's pulmonary capillary wedge pressure.

4. The method of claim **1**, wherein the patient's left ventricular dysfunction is attributable to congenital heart disease.

5. The method of claim **1**, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide.

6. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) carrying out a diagnostic process comprising measuring blood oxygen level, to identify a term or near-term neonate patient as being in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;

(b) determining that the patient has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from treatment with inhaled nitric oxide based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

7. The method of claim **6**, wherein the diagnostic process of step (a) further comprises performing echocardiography.

8. The method of claim **6**, wherein step (b) comprises performing echocardiography.

9. The method of claim **6**, wherein step (b) comprises measuring the patient's pulmonary capillary wedge pressure.

10. The method of claim **6**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

11. The method of claim 6, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

12. The method of claim 11, wherein the left ventricular dysfunction is attributable to congenital heart disease.

13. A method of treatment comprising:

(a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the patients are not dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second patient of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and

(e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

14. The method of claim 13, wherein step (a) further comprises measuring blood oxygen levels in the first and second patients and thereby determining that the first and second patients are hypoxic.

15. The method of claim 14, wherein the left ventricular dysfunction is attributable to congenital heart disease.

16. The method of claim 13, wherein the second patient has congenital heart disease.

17. The method of claim 13, wherein step (b) comprises measuring the first patient's pulmonary capillary wedge pressure.

18. The method of claim 13, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

19. The method of claim 13, wherein the left ventricular dysfunction is attributable to congenital heart disease.

20. The method of claim 13, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

21. The method of claim 13, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

22. The method of claim 21, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

23. A method of treatment comprising:

(a) identifying a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment, wherein the patients are not dependent on right-to-left shunting of blood;

(b) in a first patient of the plurality, measuring pulmonary capillary wedge pressure to determine that the first patient of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) in a second patient of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the second patient of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and

(e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

24. The method of claim 23, wherein step (a) comprises performing echocardiography to determine that the first and second patients have pulmonary hypertension.

25. The method of claim 23, wherein step (a) comprises measuring blood oxygen levels in the first and second patients and thereby determining that the first and second patients are hypoxic.

26. The method of claim 23, wherein the second patient has congenital heart disease.

27. The method of claim 23, wherein step (b) comprises measuring the first patient's pulmonary capillary wedge pressure.

28. The method of claim 23, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

29. The method of claim 23, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

30. The method of claim 29, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

* * * * *

EXHIBIT C

US008431163B2

(12) **United States Patent**
Baldassarre et al.

(10) **Patent No.: US 8,431,163 B2**
(45) **Date of Patent: *Apr. 30, 2013**

(54) **METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA ASSOCIATED WITH INHALATION OF NITRIC OXIDE GAS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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USPC **424/718**; 128/200.24; 423/405

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are methods of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas.

25 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA ASSOCIATED WITH INHALATION OF NITRIC OXIDE GAS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of and claims priority to U.S. patent application Ser. No. 12/821,041, filed on Jun. 22, 2010, now U.S. Pat. No. 8,293,284, which claims priority to U.S. patent application Ser. No. 12/494,598, filed on Jun. 30, 2009 and now abandoned. The contents of both prior applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108 (Suppl II):II-167-II-173; Lepore J J et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler J W et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a) identifying a patient in need of receiving iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geqq$20 mm Hg.

In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or associations thereof.

In another exemplary embodiment of the method, the patient population comprises children.

In another exemplary embodiment of the method, the patient population comprises adults.

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing an increased rate of one or more AEs or SAEs selected

from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia, or associations thereof.

In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) >25 mm Hg at rest, PCWP ≦15 mm Hg, and a pulmonary vascular resistance index (PVRI) >3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm >25 mm Hg at rest and PVRI >3 u·m^2; cardiomyopathy characterized by PAPm >25 mm Hg at rest and PVRI >3 u·m^2; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety. The CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including U.S. Pat. Nos. 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; U.S. patent application Ser. No. 11/355,670 (US 2007/0190184); Ser. No. 10/520,270 (US 2006/0093681); Ser. No. 11/401,722 (US 2007/0202083); Ser. No. 10/053,535 (US 2002/0155166); Ser. No. 10/367,277 (US 2003/0219496); Ser. No. 10/439,632 (US 2004/0052866); Ser. No. 10/371,666 (US 2003/0219497); Ser. No. 10/413,817 (US 2004/0005367); Ser. No. 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

As used herein, the terms "adverse event" and "AE" (and variations thereof) mean any untoward occurrence in a subject or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

As used herein, the terms "adverse drug reaction" and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

As used herein, the terms "serious adverse event" and "SAE" (or "serious adverse drug reaction" and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above—these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopa-

thy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measuring by inserting a balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore of direct relevance only in the laboratory; in the clinic, the term "end-systolic pressure" is usually more appropriate, although not equivalent.

The term "left ventricular afterload" (and variations thereof) refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (See Rubin L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diag-*

nosis and Management in the Adult, 2d Ed., Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course,* 2d Ed., Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

CINRGI Study.

(See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a PaO_2>60 mm Hg and a pH <7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 1. ECMO was the primary endpoint of the study.

TABLE 2

Summary of Clinical Results from NINOS Study

	Control (n = 121)	NO (n = 114)	P value
Death or ECMO *, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

NINOS Study.

(See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≦14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response=>20 mmHg, partial=10-20 mm Hg, no response=<10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

TABLE 1

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax ®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

TABLE 3

ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n = 89)	Inhaled NO (n = 97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

Example 1

INOT22 Study

The INOT22 study, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing," was conducted both to assess the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) >3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criterion of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter (WU·m^2) (p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). While the change from baseline in SVRI with NO alone was −0.2 WU·m^2 (p=0.899) which demonstrates a lack of systemic effect.

TABLE 4

SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU · m^2)	NO Plus O_2 (n = 109)	O_2 (n = 106)	NO (n = 106)
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	−7.6, 55.6	−7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	−0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	−20.5, 19.1	−18.1, 17.7	−12.5, 12.7
p-value[a]	0.007	0.004	0.899

Pairwise comparisons

NO plus O_2 versus O_2, p = 0.952

NO plus O_2 versus NO, p = 0.014

O_2 versus NO, p = 0.017

[a]p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

TABLE 5

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Change from Baseline			
Mean	−0.2	−0.1	−0.1
SD	0.52	0.31	0.54
Median	−0.1	−0.1	0.0
Minimum, Maximum	−4.4, 2.0	−1.6, 2.0	−4.4, 1.6
P Value[1]	<0.001	<0.001	0.002

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

TABLE 6

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Percent Change from Baseline			
Mean	−33.5	−19.3	−6.2
SD	36.11	34.59	64.04
Median	−34.0	−21.3	−13.8
Minimum, Maximum	−122.2, 140.1	−122.7, 93.3	−256.1, 294.1
P Value[1]	<0.001	<0.001	0.006

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG) decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 7 below.

TABLE 7

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No

TABLE 7-continued

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline CWP ≧18 mm Hg (7.5%), of which 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor C J et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP >20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

We claim:

1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from inhaled nitric oxide treatment, based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim **1**, wherein the determination in (b) comprises performing echocardiography.

3. The method of claim **1**, wherein the patient's left ventricular dysfunction is attributable to congenital heart disease.

4. The method of claim **1**, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide.

5. The method of claim **4**, wherein the patient's left ventricular dysfunction is attributable to congenital heart disease.

6. A method of treatment comprising:

(a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second patient of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and

(e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first

patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

7. The method of claim **6**, wherein the second patient has congenital heart disease.

8. The method of claim **6**, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

9. The method of claim **6**, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

10. The method of claim **9**, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

11. The method of claim **6**, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

12. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from inhaled nitric oxide treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the treatment after it has begun, the exclusion or discontinuation being based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

13. The method of claim **12**, wherein the determination in (b) comprises performing echocardiography.

14. The method of claim **12**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

15. The method of claim **12**, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, the patient's treatment with inhaled nitric oxide is discontinued after it was begun, the exclusion or discontinuation being based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

16. The method of claim **15**, wherein the left ventricular dysfunction of the patient is attributable to congenital heart disease.

17. The method of claim **13**, wherein the left ventricular dysfunction of the patient is attributable to congenital heart disease.

18. The method of claim **13**, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, the patient's treatment with inhaled nitric oxide is discontinued after it was begun, the exclusion or discontinuation being based on the determination that the patient has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

19. The method of claim **18**, wherein the left ventricular dysfunction of the patient is attributable to congenital heart disease.

20. A method of treatment comprising:

(a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second patient of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and

(e) excluding the first patient from treatment with inhaled nitric oxide, or, despite the first patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the first patient's treatment with inhaled nitric oxide after it was begun, the exclusion or discontinuation being based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

21. The method of claim **20**, wherein the second patient has congenital heart disease.

22. The method of claim **20**, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

23. The method of claim **20**, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment, or, despite the first patient's ongoing need for treatment for hypoxic respiratory failure, the first patient's treatment with inhaled nitric oxide is discontinued after it was begun, the exclusion or discontinuation being based on the determination that the first patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

24. The method of claim **23**, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

25. The method of claim **20**, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

* * * * *

EXHIBIT D

US008795741B2

(12) **United States Patent**
Baldassarre

(10) **Patent No.: US 8,795,741 B2**
(45) **Date of Patent: *Aug. 5, 2014**

(54) **METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(63) Continuation of application No. 12/820,866, filed on Jun. 22, 2010, now abandoned, which is a continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned, application No. 13/683,417, which is a continuation of application No. 13/651,660, filed on Oct. 15, 2012, which is a continuation of application No. 12/821,041, filed on Jun. 22, 2010, now Pat. No. 8,293,284, which is a continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned.

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G06Q 99/00	(2006.01)
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USPC **424/718**; 128/200.24; 423/405; 600/483; 600/484; 600/485

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in the patient, leading to pulmonary edema.

44 Claims, No Drawings

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METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/820,866, filed Jun. 22, 2010, which is a continuation of U.S. Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned. This application is also a continuation of U.S. Ser. No. 13/651,660, filed Oct. 15, 2012, which is a continuation of U.S. application Ser. No. 12/821,041 (now U.S. Pat. No. 8,293,284), filed Jun. 22, 2010, which is a continuation of U.S. application Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned.

BACKGROUND OF THE INVENTION

INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108 (Suppl II):II-167-II-173; Lepore J J et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler J W et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a) identifying a patient in need of receiving iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP≥20 mm Hg.

In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or associations thereof.

In another exemplary embodiment of the method, the patient population comprises children.

In another exemplary embodiment of the method, the patient population comprises adults.

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia, or associations thereof.

In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm)>25 mm Hg at rest, PCWP≤15 mm Hg, and a pulmonary vascular resistance index (PVRI)>3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; cardiomyopathy characterized by PAPm>25 mm Hg at rest and PVRI>3 u·m^2; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation, and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including U.S. Pat. Nos. 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; U.S. patent application Ser. Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

As used herein, the terms "adverse event" and "AE" (and variations thereof) mean any untoward occurrence in a subject or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

As used herein, the terms "adverse drug reaction" and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

As used herein, the terms "serious adverse event" and "SAE" (or "serious adverse drug reaction" and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above—these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug

abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measuring by inserting a balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore of direct relevance only in the laboratory; in the clinic, the term "end-systolic pressure" is usually more appropriate, although not equivalent.

The term "left ventricular afterload" (and variations thereof) refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the

treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (See Rubin L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

CINRGI Study.

(See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a PaO_2>60 mm Hg and a pH<7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 1. ECMO was the primary endpoint of the study.

TABLE 1

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax ®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

NINOS Study.

(See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response=>20 mmHg, partial=10-20 mm Hg, no response=<10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

TABLE 2

Summary of Clinical Results from NINOS Study

	Control (n = 121)	NO (n = 114)	P value
Death or ECMO *, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

TABLE 3

ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n = 89)	Inhaled NO (n = 97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

Example 1

INOT22 Study

The INOT22 study, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing," was conducted both to assess the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI)>3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criterion of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) (p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). While the change from baseline in SVRI with NO alone was −0.2 WU·m^2 (p=0.899) which demonstrates a lack of systemic effect.

TABLE 4

SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU · m^2)	NO Plus O_2 (n = 109)	O_2 (n = 106)	NO (n = 106)
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	−7.6, 55.6	−7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	−0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	−20.5, 19.1	−18.1, 17.7	−12.5, 12.7
p-value[a]	0.007	0.004	0.899

Pairwise comparisons

NO plus O_2 versus O_2, p = 0.952

NO plus O_2 versus NO, p = 0.014

O_2 versus NO, p = 0.017

[a]p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

TABLE 5

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Change from Baseline			
Mean	−0.2	−0.1	−0.1
SD	0.52	0.31	0.54
Median	−0.1	−0.1	0.0
Minimum, Maximum	−4.4, 2.0	−1.6, 2.0	−4.4, 1.6
P Value[1]	<0.001	<0.001	0.002

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

TABLE 6

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Percent Change from Baseline			
Mean	−33.5	−19.3	−6.2
SD	36.11	34.59	64.04
Median	−34.0	−21.3	−13.8

TABLE 6-continued

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Minimum, Maximum	−122.2, 140.1	−122.7, 93.3	−256.1, 294.1
P Value[1]	<0.001	<0.001	0.006

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG) decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation.

A list of subjects who died, discontinued or experienced an SAE is provided in Table 7 below.

TABLE 7

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline PCWP>18 mm Hg (7.5%), of which 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor C J et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP>20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

We claim:

1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim **1**, wherein the first patient has congenital heart disease.

3. The method of claim **1**, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

4. The method of claim **1**, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

5. The method of claim **4**, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

6. The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

7. The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

8. The method of claim 1, wherein the second patient has a PCWP that is greater than or equal to 20 mm Hg.

9. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said method comprising:

(a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

10. The method of claim 9, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

11. The method of claim 10, wherein the adverse event comprises pulmonary edema.

12. The method of claim 10, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

13. The method of claim 9, wherein (c) comprises determining that the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

14. The method of claim 9, wherein the first patient has congenital heart disease.

15. The method of claim 9, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

16. The method of claim 14, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

17. The method of claim 9, wherein

the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and

either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide.

18. The method of claim 17, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

19. The method of claim 17, wherein the discontinuation is in view of: the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

20. The method of claim 19, wherein the adverse event experienced by the second patient comprises pulmonary edema.

21. The method of claim 19, wherein the adverse event experienced by the second patient comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

22. The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

23. The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on each of the first and second patients.

24. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk of inducing an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

(c) administering a first treatment regimen to the first patient, wherein the first treatment regimen comprises administration of 20 ppm inhaled nitric oxide for 14 days or until the first patient's hypoxia has resolved;

(d) determining that a second patient of the plurality has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide; and

(e) administering a second treatment regimen to the second patient, wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved.

25. The method of claim 24, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide.

26. The method of claim 24, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide but discontinuing the administration upon determination that inhaling nitric oxide has increased the second patient's PCWP and/or induced pulmonary edema in the second patient.

27. The method of claim 24, wherein the first patient has congenital heart disease.

28. The method of claim 24, wherein the pre-existing left ventricular dysfunction of the second patient is attributable to congenital heart disease.

29. The method of claim 24, wherein the diagnostic process comprises echocardiography.

30. The method of claim 24, wherein the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

31. The method of claim 1, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

32. The method of claim 9, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

33. The method of claim 24, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

34. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema, the method comprising:

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

35. The method of claim 34, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

36. The method of claim 34, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

37. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said method comprising:

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

38. The method of claim 37, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

39. The method of claim 38, wherein the adverse event comprises pulmonary edema.

40. The method of claim 38, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

41. The method of claim 37, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

42. The method of claim 37, wherein

the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and

either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide.

43. The method of claim 42, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

44. The method of claim 42, wherein the discontinuation is in view of:

the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

* * * * *

EXHIBIT E

US008846112B2

(12) **United States Patent**
Baldassarre

(10) **Patent No.: US 8,846,112 B2**
(45) **Date of Patent: *Sep. 30, 2014**

(54) **METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION**

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USPC **424/718**; 128/200.24; 423/405

(58) **Field of Classification Search**

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(57) **ABSTRACT**

Disclosed are methods of distributing a pharmaceutical product comprising nitric oxide gas. The methods include supplying a source of nitric oxide gas to a medical provider, informing the medical provider about a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure, and providing a warning about use of inhaled nitric oxide in patients with pre-existing left ventricular dysfunction.

19 Claims, No Drawings

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METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. application Ser. No. 12/820,866, filed Jun. 22, 2010, which is a continuation of U.S. Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned. This application is also a divisional of U.S. Ser. No. 13/651,660, filed Oct. 15, 2012, which is a continuation of U.S. application Ser. No. 12/821,041 (now U.S. Pat. No. 8,293,284), filed Jun. 22, 2010, which is a continuation of U.S. application Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned.

BACKGROUND OF THE INVENTION

INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108 (Suppl II):II-167-II-173; Lepore J J et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler J W et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a) identifying a patient in need of receiving iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP≥20 mm Hg.

In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or associations thereof.

In another exemplary embodiment of the method, the patient population comprises children.

In another exemplary embodiment of the method, the patient population comprises adults.

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia, or associations thereof.

In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm)>25 mm Hg at rest, PCWP≤15 mm Hg, and a pulmonary vascular resistance index (PVRI)>3 $u \cdot m^2$; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm>25 mm Hg at rest and PVRI>3 $u \cdot m^2$; cardiomyopathy characterized by PAPm>25 mm Hg at rest and PVRI>3 $u \cdot m^2$; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation, and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including U.S. Pat. Nos. 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; U.S. patent application Ser. No. 11/355,670 (US 2007/0190184); Ser. No. 10/520,270 (US 2006/0093681); Ser. No. 11/401,722 (US 2007/0202083); Ser. No. 10/053,535 (US 2002/0155166); Ser. No. 10/367,277 (US 2003/0219496); Ser. No. 10/439,632 (US 2004/0052866); Ser. No. 10/371,666 (US 2003/0219497); Ser. No. 10/413,817 (US 2004/0005367); Ser. No. 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

As used herein, the terms "adverse event" and "AE" (and variations thereof) mean any untoward occurrence in a subject or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

As used herein, the terms "adverse drug reaction" and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

As used herein, the terms "serious adverse event" and "SAE" (or "serious adverse drug reaction" and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above—these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug

abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measuring by inserting a balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore of direct relevance only in the laboratory; in the clinic, the term "end-systolic pressure" is usually more appropriate, although not equivalent.

The term "left ventricular afterload" (and variations thereof) refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the

treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (See Rubin L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

CINRGI Study.

(See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a PaO_2>60 mm Hg and a pH<7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 1. ECMO was the primary endpoint of the study.

TABLE 1

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax ®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

NINOS Study.

(See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response=>20 mmHg, partial=10-20 mm Hg, no response=<10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

TABLE 2

Summary of Clinical Results from NINOS Study

	Control (n = 121)	NO (n = 114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

*Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

TABLE 3

ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n = 89)	Inhaled NO (n = 97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

Example 1

INOT22 Study

The INOT22 study, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing," was conducted both to assess the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI)>3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criterion of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) (p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). While the change from baseline in SVRI with NO alone was −0.2 WU·m^2 (p=0.899) which demonstrates a lack of systemic effect.

TABLE 4

SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU · m^2)	NO Plus O_2 (n = 109)	O_2 (n = 106)	NO (n = 106)
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	−7.6, 55.6	−7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	−0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	−20.5, 19.1	−18.1, 17.7	−12.5, 12.7
p-value[a]	0.007	0.004	0.899

Pairwise comparisons

NO plus O_2 versus O_2, p = 0.952

NO plus O_2 versus NO, p = 0.014

O_2 versus NO, p = 0.017

[a]p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

TABLE 5

Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Change from Baseline			
Mean	−0.2	−0.1	−0.1
SD	0.52	0.31	0.54
Median	−0.1	−0.1	0.0
Minimum, Maximum	−4.4, 2.0	−1.6, 2.0	−4.4, 1.6
P Value[1]	<0.001	<0.001	0.002

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

TABLE 6

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	−1.6, 4.7	−1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	−1.2, 2.2
Percent Change from Baseline			
Mean	−33.5	−19.3	−6.2
SD	36.11	34.59	64.04
Median	−34.0	−21.3	−13.8

TABLE 6-continued

Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
Minimum, Maximum	−122.2, 140.1	−122.7, 93.3	−256.1, 294.1
P Value[1]	<0.001	<0.001	0.006

[1]Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 124 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG), decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation.

A list of subjects who died, discontinued or experienced an SAE is provided in Table 7 below.

TABLE 7

Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 124 patients had a baseline PCWP≥18 mm Hg (7.5%), of which 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor C J et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP>20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

I claim:

1. A method of providing pharmaceutically acceptable nitric oxide gas, the method comprising:

obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen;

supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction;

providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide

and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

2. The method of claim **1**, wherein the information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

3. The method of claim **1**, further comprising:

performing at least one diagnostic process to identify a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;

determining that the first neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to

arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

4. The method of claim **1**, further comprising:

performing at least one diagnostic process to identify a plurality of neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction;

determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

treating the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;

for each patient of the plurality determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one patient of the plurality determined to have pre-existing left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

5. The method of claim **3**, wherein the information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

6. The method of claim **4**, wherein the information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

7. A method of providing pharmaceutically acceptable nitric oxide gas, the method comprising:

obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen;

supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction; and

providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide,

(ii) information that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and (iii) a recommendation that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

8. The method of claim **7**, wherein the information of (i) and (ii) and the recommendation of (iii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

9. The method of claim **7**, further comprising:

performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide that the neonatal patient has pre-existing left ventricular dysfunction;

treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the neonatal patient experiences pulmonary edema; and

in accordance with the recommendation of (iii), discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema.

10. The method of claim **4**, wherein the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

11. The method of claim **9**, wherein the neonatal patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

12. A method comprising:

obtaining a source of nitric oxide gas comprising a cylinder of compressed gas and/or a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit, for inhalation by a patient;

supplying the source of nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction; and

providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide

and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

13. The method of claim **12**, wherein the information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

14. A method comprising:

obtaining a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit, for inhalation by a patient;

supplying the device to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction;

providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide

and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for multiple neonatal patients who (a) are suffering from

hypoxic respiratory failure, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the multiple patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

15. The method of claim **14**, wherein the information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the device.

16. The method of claim **12**, further comprising:

identifying a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;

determining that the first neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction; and

using the source of nitric oxide gas to treat the second neonatal patient with 20 ppm inhaled nitric oxide.

17. The method of claim **12**, further comprising:

identifying a plurality of neonatal hypoxic respiratory failure patients who are candidates for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

using the source of nitric oxide gas to treat the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;

for each patient of the plurality who is determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one of the evaluated patients, determining that the potential benefit of the treatment outweighs the potential risk; and

using the source of nitric oxide gas to treat the at least one patient with 20 ppm inhaled nitric oxide.

18. The method of claim **14**, further comprising:

identifying a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;

determining that the first neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction; and

using the device to treat the second neonatal patient with 20 ppm inhaled nitric oxide.

19. The method of claim **14**, further comprising:

identifying a plurality of neonatal hypoxic respiratory failure patients who are candidates for inhaled nitric oxide treatment;

determining, prior to treatment with inhaled nitric oxide, whether or not each patient of the plurality has pre-existing left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

using the device to treat the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;

for each patient of the plurality who is determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one of the evaluated patients, determining that the potential benefit of the treatment outweighs the potential risk; and

using the device to treat the at least one patient with 20 ppm inhaled nitric oxide.

* * * * *

EXHIBIT F

US008291904B2

(12) **United States Patent**
Bathe et al.

(10) **Patent No.: US 8,291,904 B2**
(45) **Date of Patent: *Oct. 23, 2012**

(54) **GAS DELIVERY DEVICE AND SYSTEM**

(75) Inventors: **Duncan P. Bathe**, Fitchburg, WI (US); **John Klaus**, Cottage Grove, WI (US); **David Christensen**, Cambridge, WI (US)

(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/493,493**

(22) Filed: **Jun. 11, 2012**

(65) **Prior Publication Data**

US 2012/0240927 A1 Sep. 27, 2012

Related U.S. Application Data

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(51) **Int. Cl.**
A61M 15/00 (2006.01)
F16K 31/02 (2006.01)
A62B 9/02 (2006.01)

(52) **U.S. Cl.** **128/205.24**; 128/203.14; 128/204.22

(58) **Field of Classification Search** 128/204.18, 128/204.21–204.23, 205.24, 203.12, 203.14, 128/200.24, 205.11, 205.23

See application file for complete search history.

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Primary Examiner — Kristen Matter
(74) *Attorney, Agent, or Firm* — Diehl Servilla LLC

(57) **ABSTRACT**

A gas delivery system including a gas delivery device, a control module and a gas delivery mechanism is described. An exemplary gas delivery device includes a valve assembly with a valve and circuit including a memory, a processor and a transceiver in communication with the memory. The memory may include gas data such as gas identification, gas expiration and gas concentration. The transceiver on the circuit of the valve assembly may send wireless optical line-of-sight signals to communicate the gas data to a control module. Exemplary gas delivery mechanisms include a ventilator and a breathing circuit. Methods of administering gas are also described.

16 Claims, 12 Drawing Sheets

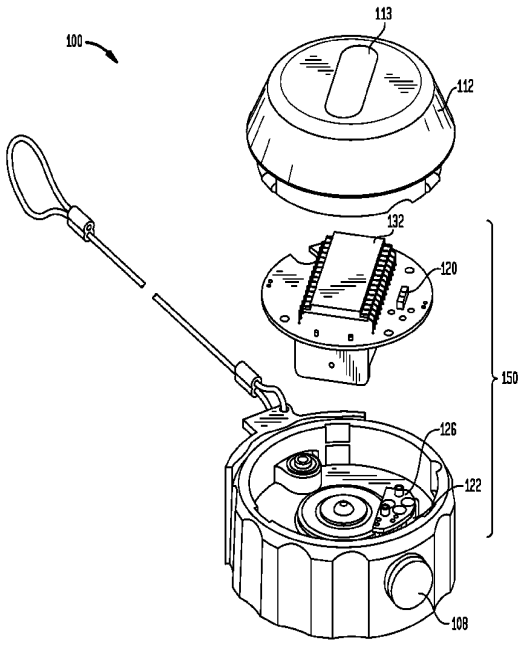
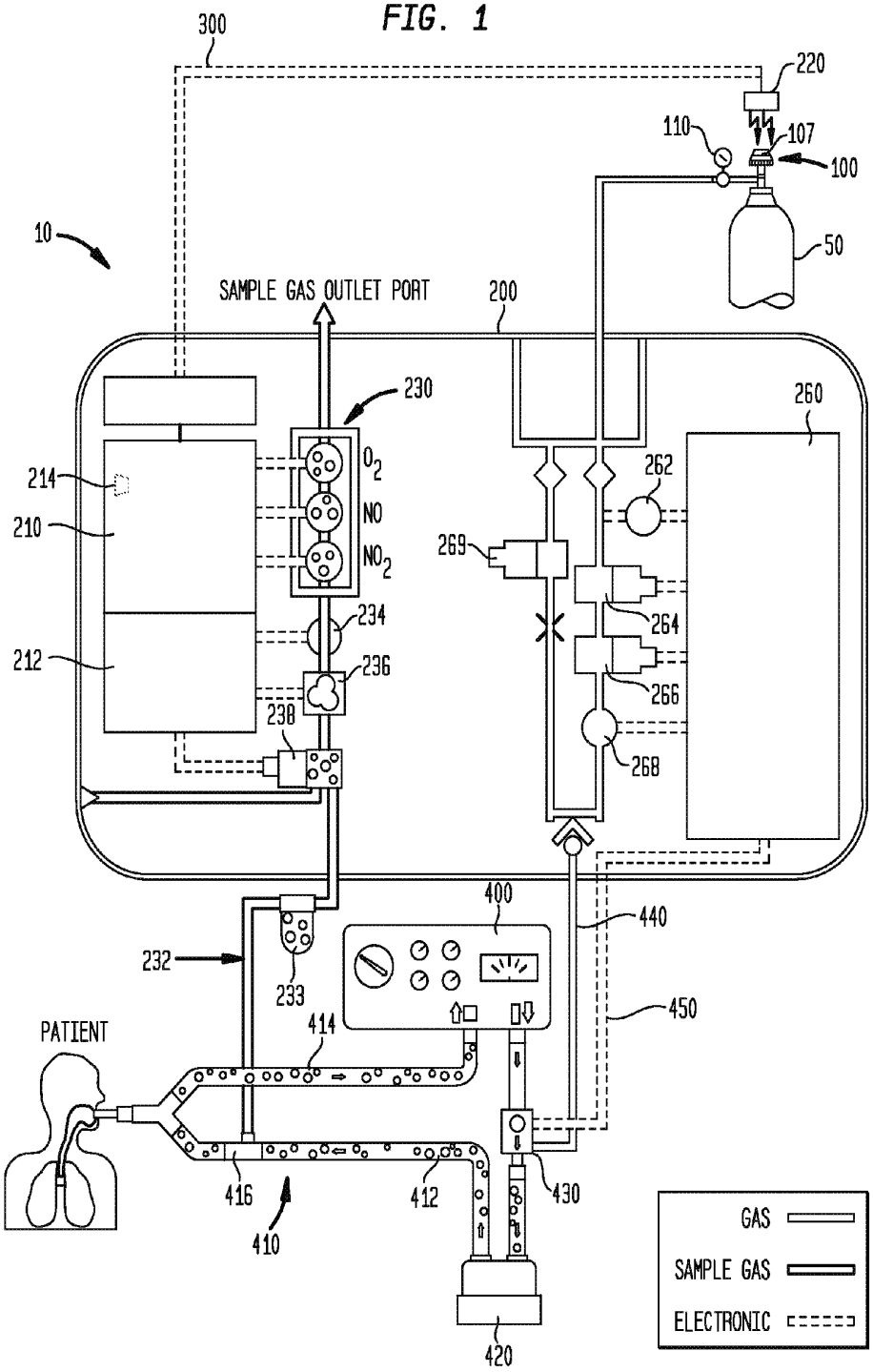


FIG. 1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10
50
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230
260
214
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212
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NO
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236
238
262
269
264
266
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FIG. 2

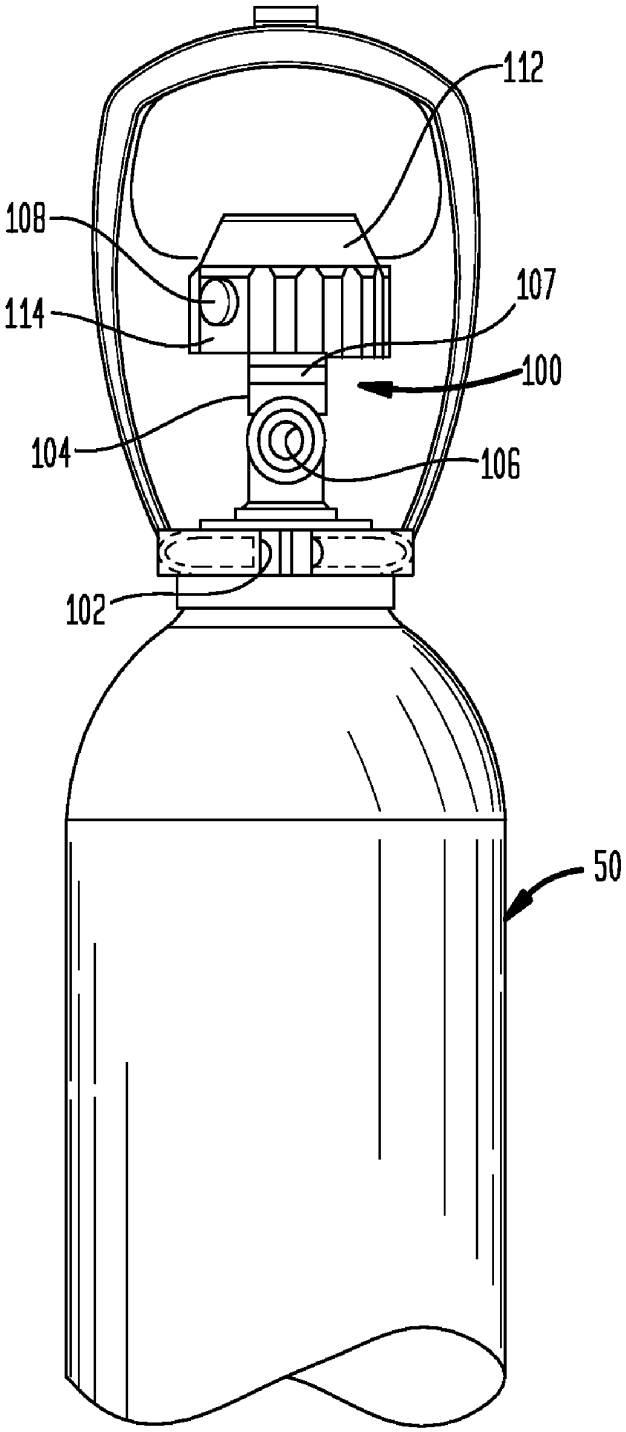


FIG. 3

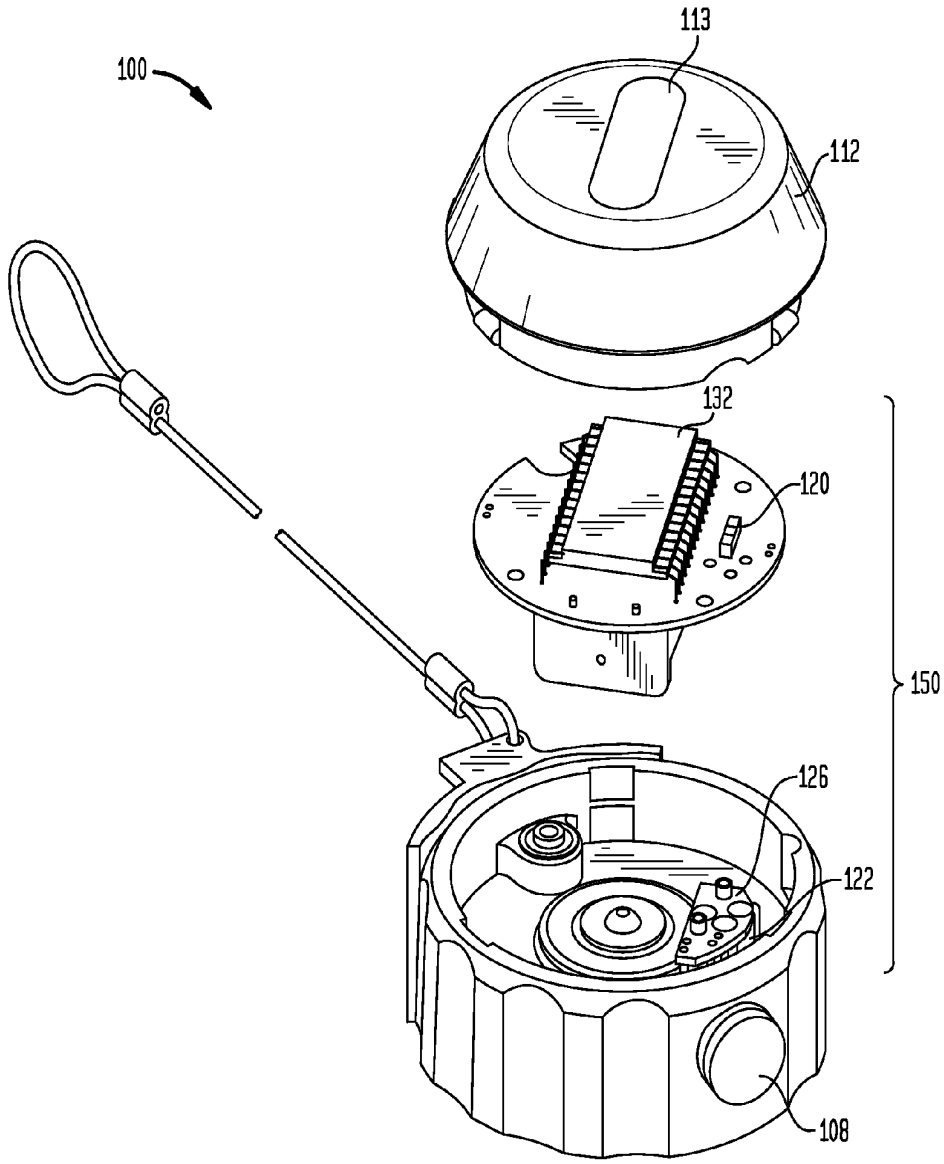
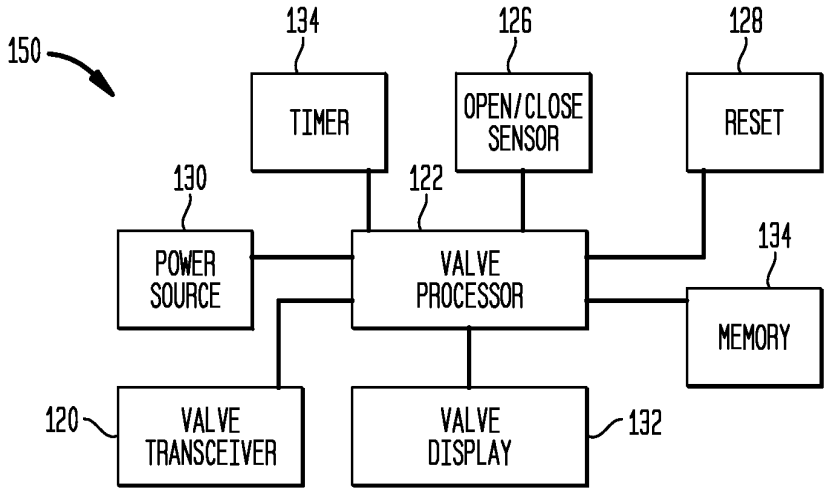


FIG. 4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OPEN/CLOSE SENSOR
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RESET
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POWER SOURCE
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MEMORY
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VALVE TRANSCEIVER
VALVE DISPLAY
132

FIG. 5

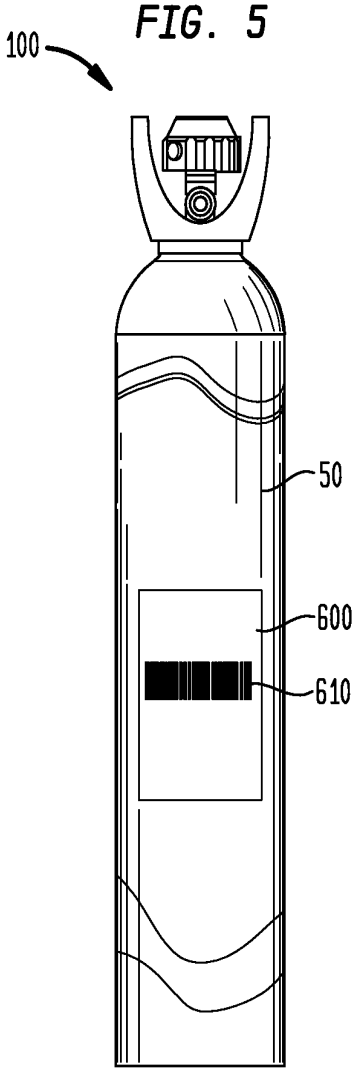
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FIG. 6

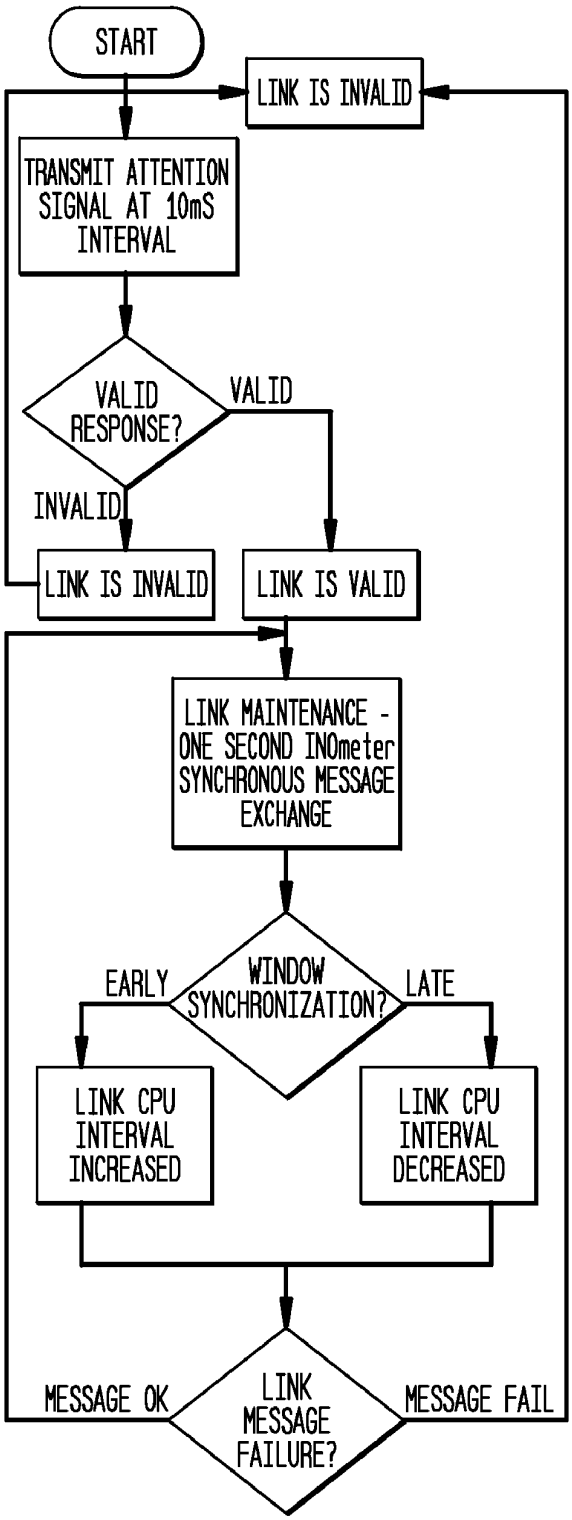

START
LINK IS INVALID
TRANSMIT ATTENTION SIGNAL AT 10mS INTERVAL
VALID RESPONSE?
VALID
INVALID
LINK IS INVALID
LINK IS VALID
LINK MAINTENANCE - ONE SECOND INOmeter SYNCHRONOUS MESSAGE EXCHANGE
WINDOW SYNCHRONIZATION?
EARLY
LATE
LINK CPU INTERVAL INCREASED
LINK CPU INTERVAL DECREASED
LINK MESSAGE FAILURE?
MESSAGE OK
MESSAGE FAIL

FIG. 7

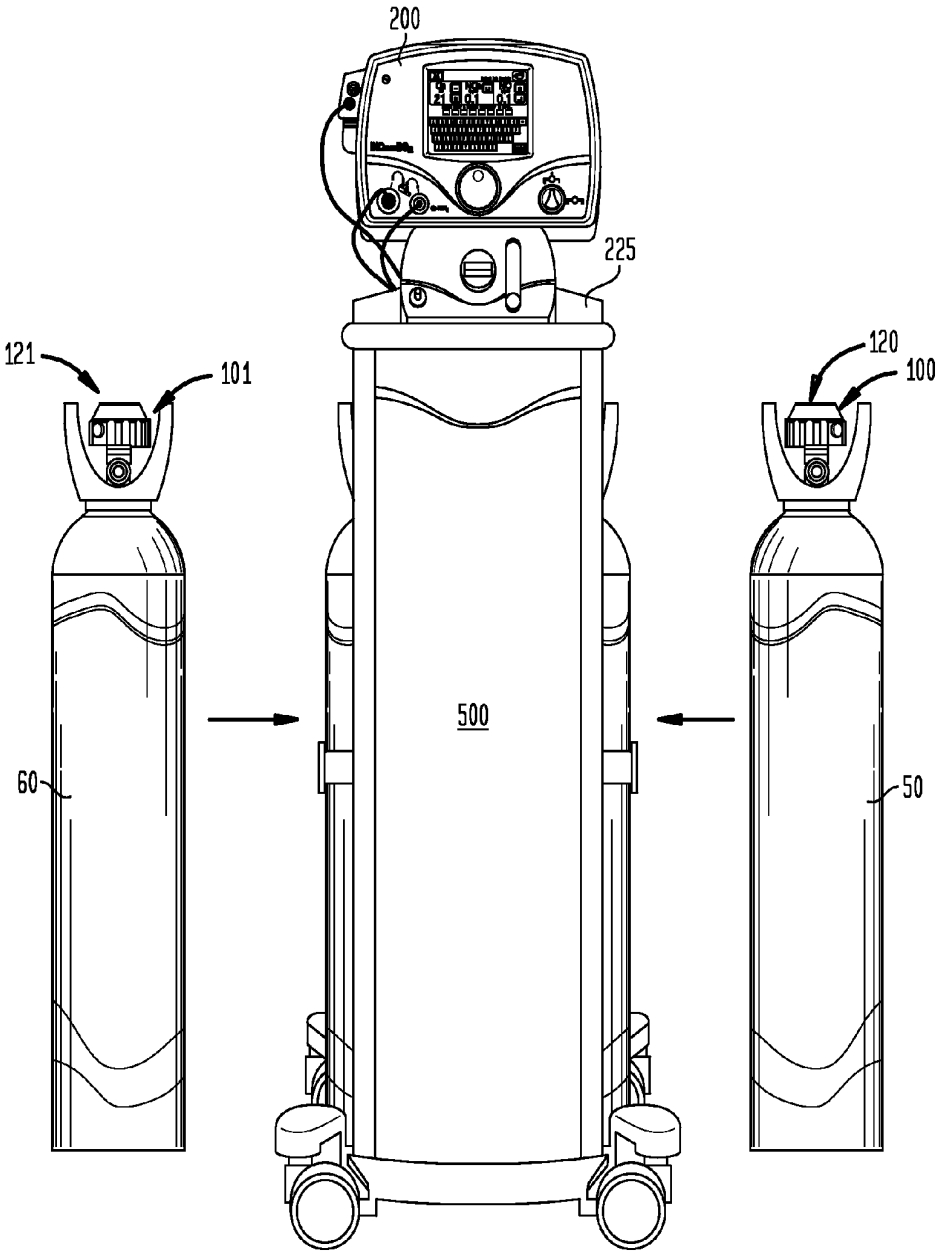


FIG. 8

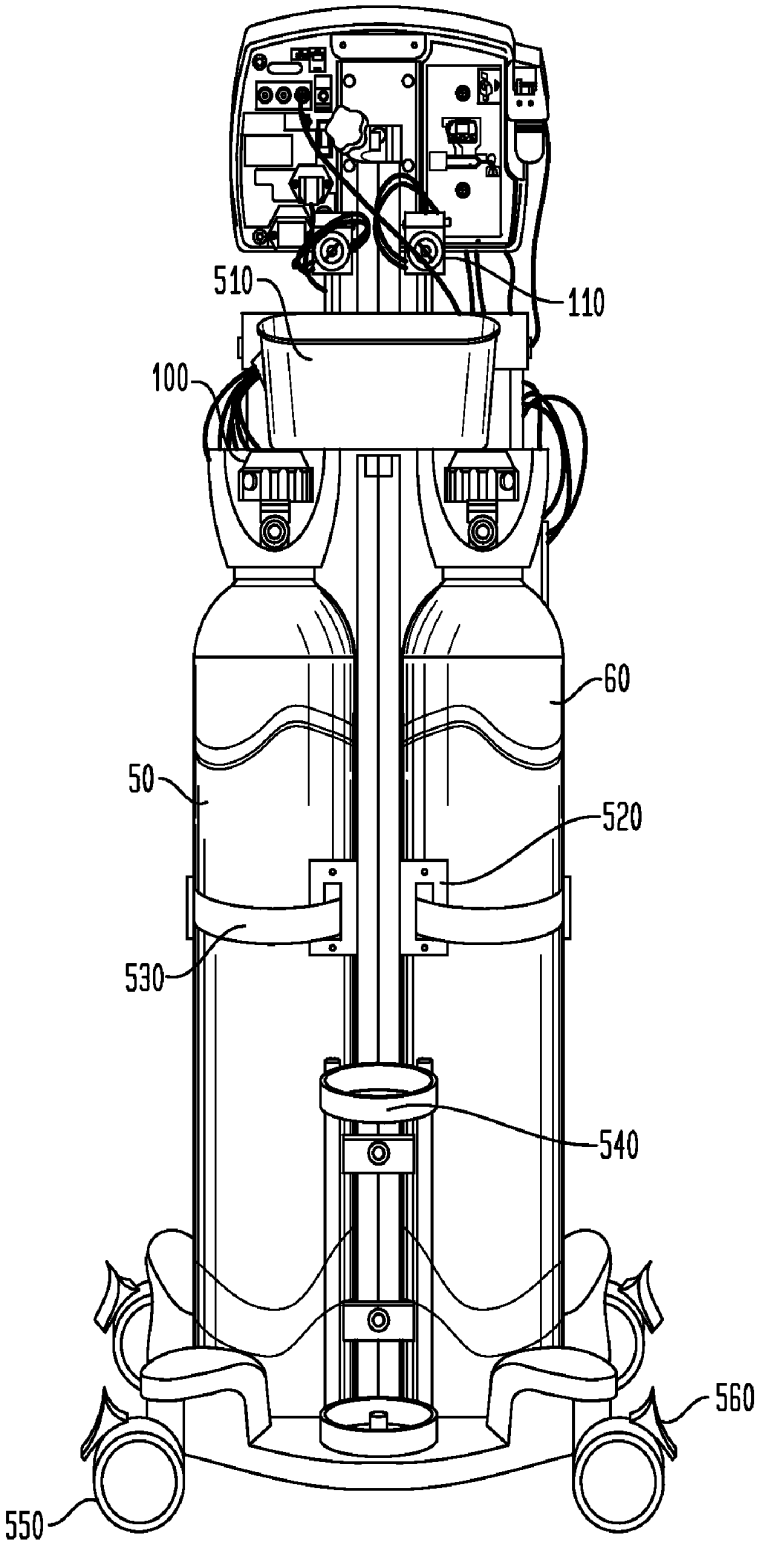


FIG. 9

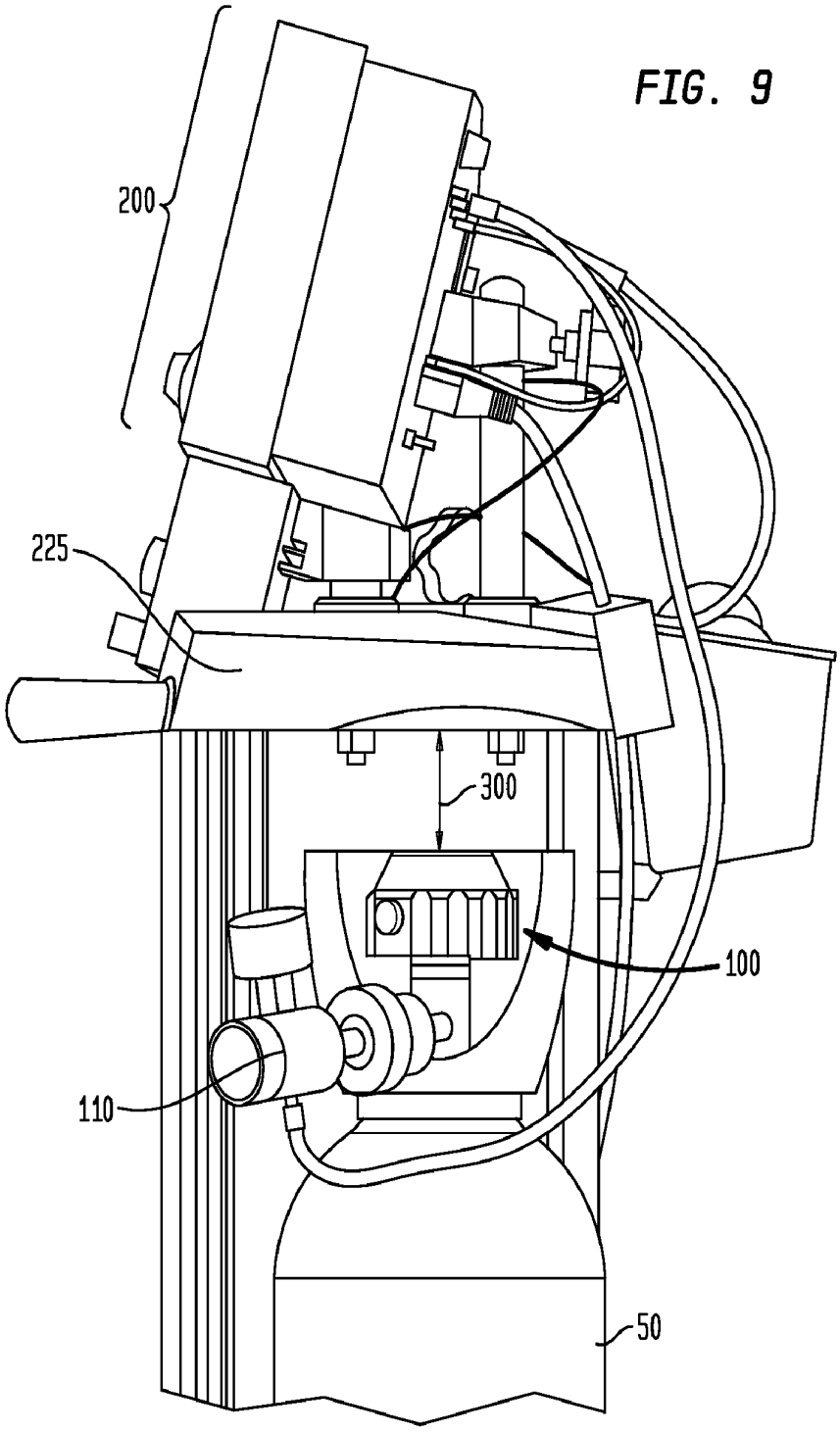
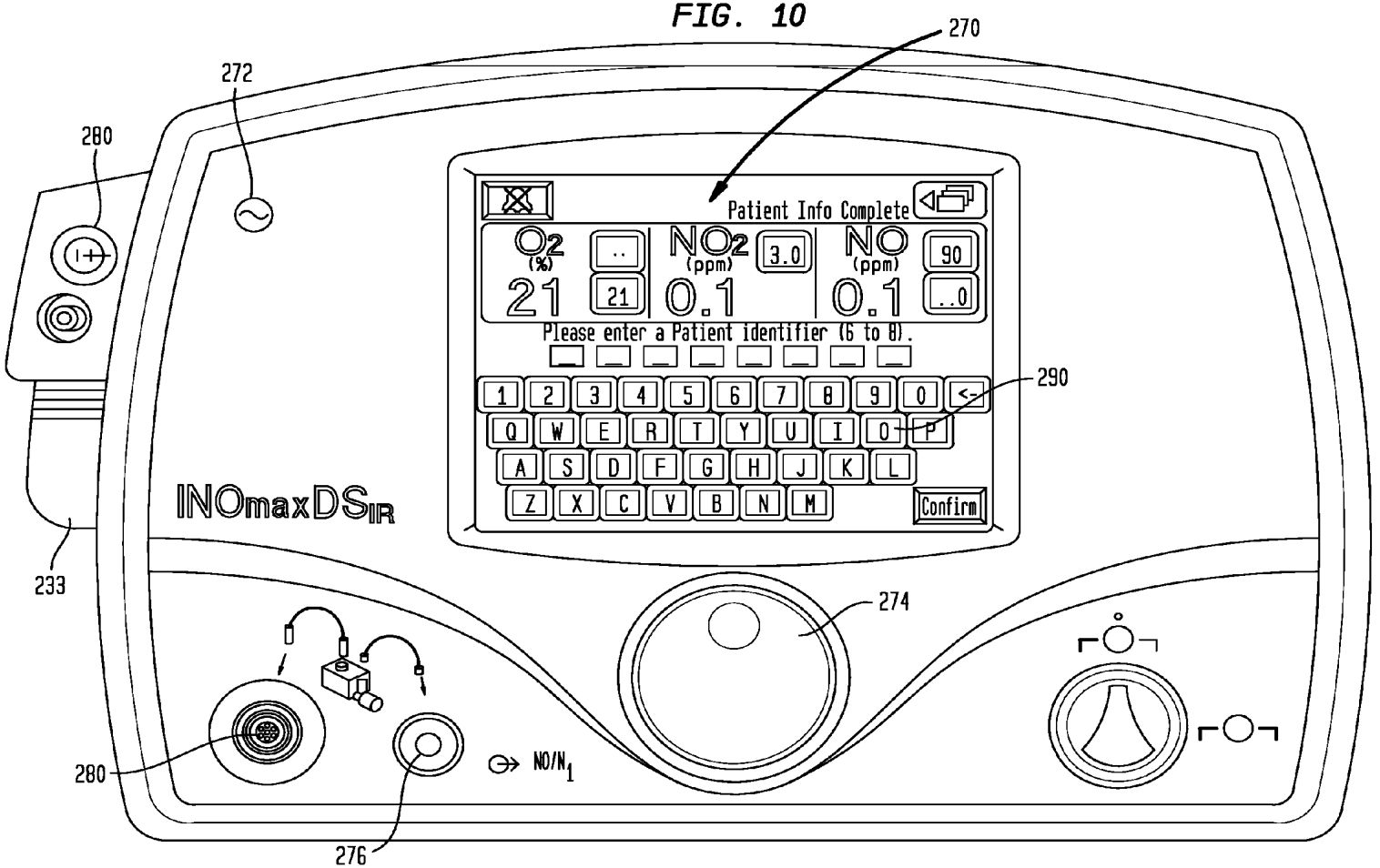


FIG. 10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272
280
Patient Info Complete
O2 (%)
NO2 (ppm)
3.0
NO (ppm)
90
21
21
0.1
0.1
..0
Please enter a Patient identifier (6 to 8).
1 2 3 4 5 6 7 8 9 0 <-
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
Confirm
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INOmaxDS IR
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NO/N1
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FIG. 11

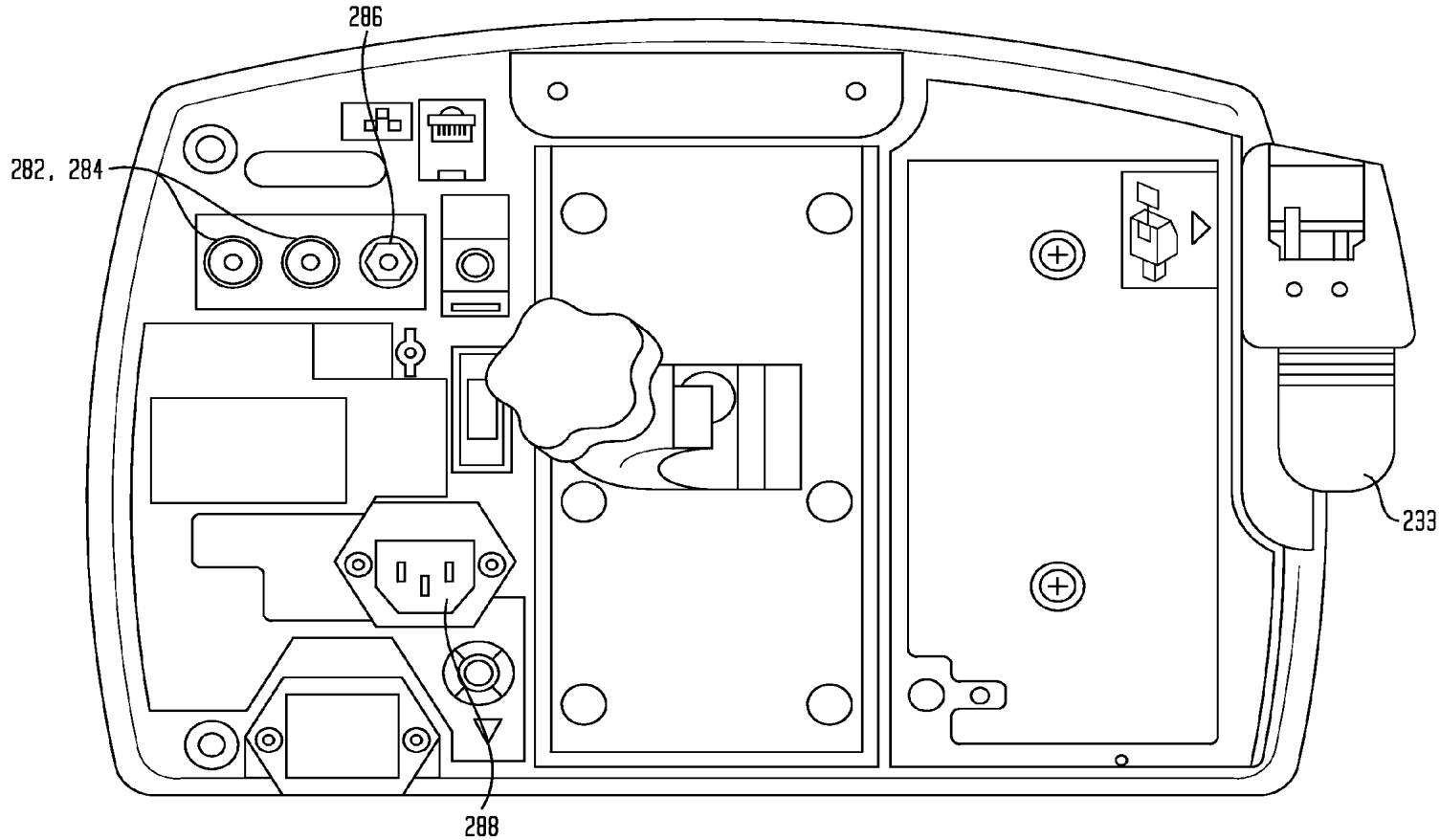


FIG. 12

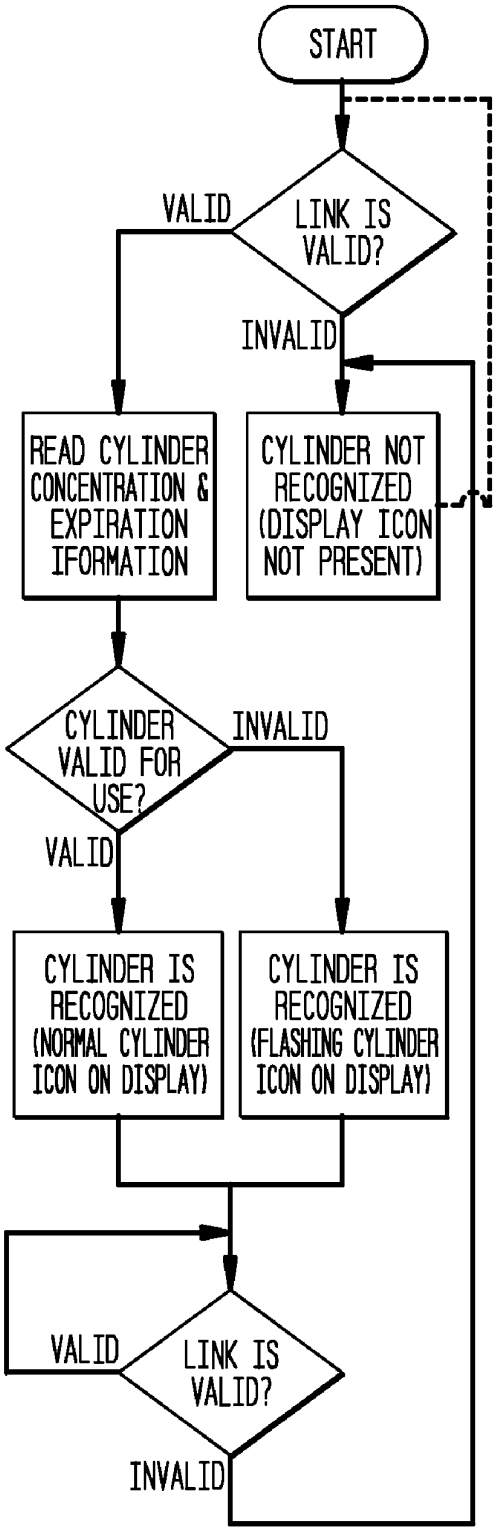
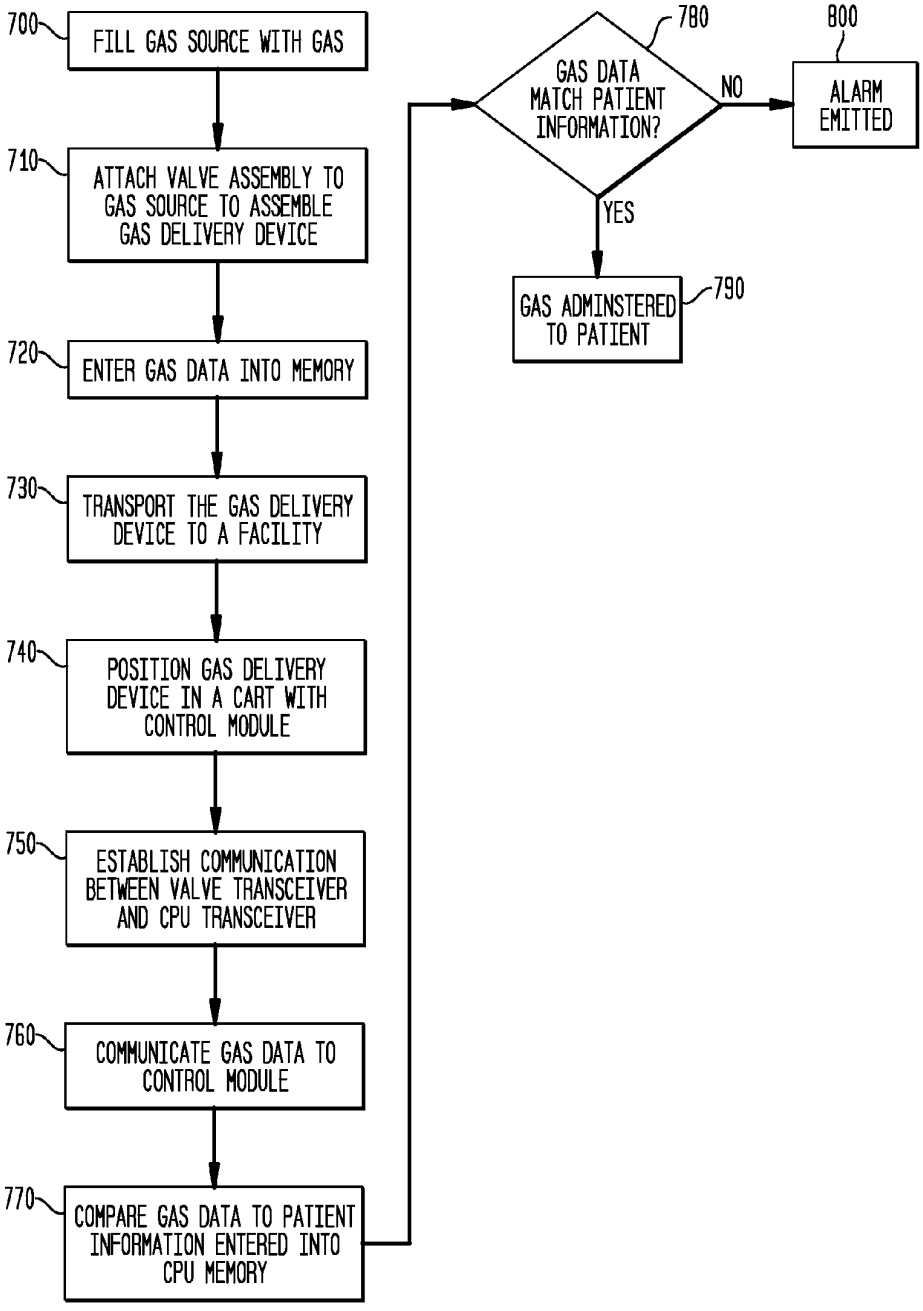

START
LINK IS VALID?
VALID
INVALID
READ CYLINDER CONCENTRATION & EXPIRATION IFORMATION
CYLINDER NOT RECOGNIZED (DISPLAY ICON NOT PRESENT)
CYLINDER VALID FOR USE?
INVALID
VALID
CYLINDER IS RECOGNIZED (NORMAL CYLINDER ICON ON DISPLAY)
CYLINDER IS RECOGNIZED (FLASHING CYLINDER ICON ON DISPLAY)
LINK IS VALID?
VALID
INVALID

FIG. 13


700
FILL GAS SOURCE WITH GAS
710
ATTACH VALVE ASSEMBLY TO GAS SOURCE TO ASSEMBLE GAS DELIVERY DEVICE
720
ENTER GAS DATA INTO MEMORY
730
TRANSPORT THE GAS DELIVERY DEVICE TO A FACILITY
740
POSITION GAS DELIVERY DEVICE IN A CART WITH CONTROL MODULE
750
ESTABLISH COMMUNICATION BETWEEN VALVE TRANSCEIVER AND CPU TRANSCEIVER
760
COMMUNICATE GAS DATA TO CONTROL MODULE
770
COMPARE GAS DATA TO PATIENT INFORMATION ENTERED INTO CPU MEMORY
780
GAS DATA MATCH PATIENT INFORMATION?
NO
800
ALARM EMITTED
YES
790
GAS ADMINSTERED TO PATIENT

GAS DELIVERY DEVICE AND SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. patent application Ser. No. 13/509,873 filed on May 15, 2012, which is the National Phase entry of PCT/US2011/020319, filed Jan. 6, 2011, the entire content of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

Embodiments of the present invention relate to gas delivery device for use in a gas delivery system for administering therapy gas and methods of administering therapy gas.

BACKGROUND

Certain medical treatments include the use of gases that are inhaled by the patient. Gas delivery devices are often utilized by hospitals to deliver the necessary gas to patients in need. It is important when administering gas therapy to these patients to verify the correct type of gas and the correct concentration are being used. It is also important to verify dosage information and administration.

Known gas delivery devices may include a computerized system for tracking patient information, including information regarding the type of gas therapy, concentration of gas to be administered and dosage information for a particular patient. However, these computerized systems often do not communicate with other components of gas delivery devices, for example, the valve that controls the flow of the gas to the computerized system and/or ventilator for administration to the patient. In addition, in known systems, the amount of gas utilized by a single patient is often difficult or impossible to discern, leading to possible overbilling for usage.

There is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is to be delivered by the gas delivery device. There is also a need for such an integrated device that does not rely on repeated manual set-ups or connections and which can also track individual patient usage accurately and simply.

SUMMARY

Aspects of the present invention pertain to a gas delivery device that may be utilized with a gas delivery system and methods for administering therapy gas to a patient. The therapy gas may comprise nitric oxide (NO). One or more embodiments of the gas delivery devices described herein may include a valve and a circuit with a valve memory in communication with a valve processor and a valve transceiver. One or more embodiments of the gas delivery systems described herein incorporate the gas delivery devices described herein with a control module including a control processing unit (CPU) in communication with a CPU memory and CPU transceiver. As will be described herein, the valve transceiver and the CPU transceiver may be in communication such that information or data from the valve memory and the CPU memory may be communicated to one another. The information communicated between the valve memory and the CPU memory may be utilized for selecting a therapy for delivery to a patient and controlling delivery of the selected therapy to the patient. The gas delivery devices and systems described herein may be utilized with medical devices such as ventilators and the like to delivery gas to a patient.

A first aspect of the present invention pertains to a gas delivery device. In one or more embodiments, the gas delivery device administers therapy gas from a gas source containing NO under the control of a control module. In one variant, the gas delivery device may include a valve attachable to the gas source and a circuit. The valve may include an inlet and an outlet in fluid communication and a valve actuator to open and close the valve to allow the gas to flow through the valve to a control module. The circuit of one or more embodiments includes a memory, a processor and a transceiver in communication with the memory to send wireless optical line-of-sight signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject. In one or more alternative embodiments, the signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject may be communicated via a wire. Examples of such wired signals may incorporate or utilize an optical cable, wired pair and/or coaxial cable. The circuit may include a memory to store gas data, which may include one or more of gas identification, gas expiration date and gas concentration. The transceiver may communicate to send the gas data to the control module via wireless optical line-of-sight signals.

In one or more embodiments, the valve may include a data input in communication with said memory, to permit a user to enter the gas data into the memory. The gas data may be provided in a bar code that may be disposed on the gas source. In such embodiments, the gas data may be entered into the data input of the valve for storage in the memory by a user-operated scanning device in communication with the data input. Specifically, the user may scan the bar code to communicate the gas data stored therein to the valve memory via the data input.

In one or more embodiments, the valve may include a power source. In such embodiments, the power source may include a battery or other portable power source. In one or more embodiments, the valve transceiver may periodically send the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent. In one or more specific embodiments, the duration of time at which no signal is sent comprises about 10 seconds.

A second aspect of the present invention pertains to a gas delivery device, as described herein, and a control module in fluid communication with the outlet of the valve of the gas delivery device and with a gas delivery mechanism, such as a ventilator. In one or more embodiments, the control module may include a CPU transceiver to receive line-of-sight signals from the transceiver and a CPU in communication with the CPU transceiver. The CPU carries out the instructions of a computer program or algorithm. As used herein the phrase "wireless optical line-of-sight signal" includes infrared signal and other signals that require a transmitter and receiver or two transceivers to be in aligned such that the signal may be transmitted in a straight line. The CPU may include a CPU memory that stores the gas data that is communicated by the valve transceiver of the gas delivery device to the CPU transceiver.

In one or more embodiments, the gas delivery system may incorporate a valve with a timer including a calendar timer and an event timer for determining or marking the date and time that the valve is opened and closed and the duration of time the valve is opened. In such embodiments, the valve

memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

In one or more variants, the gas delivery system may incorporate a control module that further includes an input means to enter patient information into the CPU memory. The control module may also have a real time clock built into the CPU module such that the control module knows what the current time and date is and can compare that to the expiration date stored in the gas delivery device. If the expiration date is passed the current date then the control module can cause an alarm and not deliver drug to the patient. When the term "patient information" is used, it is meant to include both patient information entered by the user and information that is set during manufacturing, such as the gas identification and the gas concentration that the control module is setup to deliver. The control module may also include a display. In one or more embodiments, the display incorporates an input means for entering patient information into the CPU memory. In one or more embodiments, the CPU of the control module compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver. The CPU or control module may include comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match or conflict. As used herein the phrase "do not match," includes the phrase "are not identical," "are not substantially identical," "do conflict" and/or "do substantially conflict." The CPU determines whether the patient information and additional data, or other data set matches by performing a matching algorithm which includes criteria for establishing whether one set of data (i.e. patient information) and another set of data match. The algorithm may be configured to determine a match where every parameter of the data sets match or selected parameters of the data sets match. The algorithm may be configured to include a margin of error. For example, where the patient information require a gas concentration of 800 ppm, and the additional data includes a gas concentration of 805 ppm, the algorithm may be configured to include a margin of error of ±5 ppm such it determines that the patient information and the additional data match. It will be understood that determining whether the patient information and additional data match will vary depending on the circumstances, such as variables in measuring gas concentration due to temperature and pressure considerations.

A third aspect of the present invention pertains to a control module memory comprising instructions that cause a control module processor to receive gas data from a valve via a wireless optical line-of-sight signal. The valve may be connected to a gas source containing NO and may include a memory for storing the gas data. The control module memory may include instructions that cause the control module processor to compare the gas data with user-inputted patient information. The user-inputted patient information may be stored within the control module memory. Gas data may be selected from one or more of gas identification, gas expiration date and gas concentration. In one or more embodiments, the control module memory may include instructions to cause the control module processor to coordinate delivery of therapy to the patient with a medical device, such as a ventilator and the like for delivering gas to a patient, via the wireless optical line-of-sight signal. The control module memory may also include instructions to cause the control module processor to select a therapy for delivery to a patient based on the received patient information and control delivery of the selected therapy to the patient.

In one or more embodiments, the memory may include instructions to cause the processor to detect the presence of more than one valve and whether more than one valve is open at the same time. In accordance with one or more specific embodiments, the memory includes instructions to cause the processor to receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas source, receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas source, compare the first valve status and the second valve status, and emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position. In one or more alternative embodiments, the first valve status and the second valve status may be communicated to the processor via a single wireless optical line-of-sight signal, instead of separate wireless optical line-of-sight signals. In a more specific embodiment, the memory of one or more embodiments may include instructions to cause the processor to terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

In one or more embodiments, the memory may include instructions to cause the processor to emit an alarm when a desired dose has been delivered through a valve. In such embodiments, the processor may include a memory to store the desired dose or dosage information. In such embodiments, the memory may include instructions to cause the processor to receive gas delivery information or information regarding the amount of gas delivered and compare the gas delivery information to the dosage information and emit an alarm when the gas delivery information and the dosage information match. As used herein, the term "dosage information" may be expressed in units of parts per million (ppm), milligrams of the drug per kilograms of the patient (mg/kg), millimeters per breath, and other units known for measuring and administering a dose. In one or more embodiments, the dosage information may include various dosage regimes which may include administering a standard or constant concentration of gas to the patient, administering a gas using a pulsed method. Such pulsing methods includes a method of administering a therapy gas to a patient during an inspiratory cycle of the patient, where the gas is administered over a single breath or over a plurality of breaths and is delivery independent of the respiratory pattern of the patient.

A fourth aspect of the present invention pertains to a method for administering a therapy gas to a patient. The therapy gas may comprise NO. In one or more embodiments, the method includes establishing communication between the patient and a gas delivery device via a transceiver, wherein the gas delivery device comprises a first memory including gas data, comparing the gas data with patient information stored within a second memory. The second memory may be included within a control module in communication with the gas delivery device. After comparing the gas data and the patient information, the method may further include coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal, selecting a therapy for delivery to the patient based on the comparison of the gas data and the patient information and controlling delivery of the selected therapy to the patient. In one or more

specific embodiments, the method may include entering the gas data into the first memory of the gas delivery device and/or entering the patient information into the second memory. In embodiments in which the method includes entering the patient information into the second memory, the control module may include input means by which patient information may be entered into the second memory. In one or more variants, the method includes ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information. The method may include emitting an alert based on the comparison of the gas data and the patient information.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of a gas delivery system including a gas delivery device, a gas source, a control module and a gas delivery mechanism, according to one or more embodiments;

FIG. **2** illustrates a valve assembly of the gas delivery device according to one or more embodiments attached to a gas source;

FIG. **3** illustrates a disassembled view of the valve assembly shown in FIG. **2**;

FIG. **4** is a diagram showing a circuit supported in the valve assembly shown in FIG. **2**, according to one or more embodiments;

FIG. **5** illustrates an exemplary gas source for use with the valve assembly shown in FIG. **2**;

FIG. **6** is an operational flow diagram of the communication between the circuit of the gas delivery device shown in FIG. **1** with a control module regarding the establishment of communication between the circuit and the control module

FIG. **7** illustrates a front view of an exemplary gas delivery system;

FIG. **8** illustrates a back view of the gas delivery system shown in FIG. **7**;

FIG. **9** illustrates a partial side view of the gas delivery system shown in FIG. **7**;

FIG. **10** illustrates a front view of a control module according to one or more embodiments;

FIG. **11** illustrates a back view of the control module shown in FIG. **10**;

FIG. **12** is an operational flow diagram of the communication between the circuit of the gas delivery device and the control module shown in FIG. **1** regarding the gas contained within a gas source; and

FIG. **13** is an operational flow diagram of the preparation of a gas delivery device and use within the gas delivery system according to one or more embodiments.

DETAILED DESCRIPTION

Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

A system for the administration of therapy gas is described. A first aspect of the present invention pertains to a gas delivery device. The gas delivery device may include a valve assembly including at least one valve with a circuit. The gas delivery system may include the gas delivery device (e.g. valve assembly, including a valve and a circuit) in communication with a control module to control the delivery of gas from a gas source to a ventilator or other device used to introduce the gas into the patient, for example, a nasal cannula, endotracheal tube, face mask or the like. Gas source, as used herein, may include a gas source, gas tank or other pressured vessel used to store gases at above atmospheric pressure. The gas delivery system **10** is shown in FIG. **1**. In FIG. **1**, the valve assembly **100**, including a valve **107** or valve actuator and a circuit **150**, is in communication with a control module **200** via a wireless line-of-sight connection **300**. In one or more alternative embodiments, communication between the valve assembly **100** and the control module **200** may be established via a wired signal. The gas delivery system **10** also includes a gas source **50** including a gas attached to the valve assembly **100** and a gas delivery mechanism, which includes a ventilator **400** and a breathing circuit **410**, in communication with the control module **200**.

FIGS. **2-4** illustrate the components of the valve assembly **100**. The valve assembly **100** includes a valve **107** and a circuit **150** supported in the valve assembly. FIG. **3** illustrates a disassembled view of the valve assembly **100**, showing components of the physical circuit **150** and the valve **107**. As shown in FIG. **4**, which will be described in more detail below, the circuit **150** of the gas delivery device includes a valve transceiver **120** for establishing communication with the control module **200**, which will also be discussed in greater detail below.

Referring to FIG. **2**, the valve **107** includes an attachment portion **102** for attaching the valve assembly **100** to the gas source **50**, an inlet **104** and an outlet **106** in fluid communication with the inlet **104**, as more clearly shown in FIG. **2**.

FIG. **3** illustrates a disassembled view of the valve assembly **100** and illustrates an actuator **114** is disposed on the valve **107** and is rotatable around the valve **107** for opening and closing the valve **107**. The actuator **114** includes a cap **112** mounted thereto. As shown in FIG. **3**, the circuit **150** may include a data input **108** disposed on the actuator **114**. The data input **108** may be disposed at other locations on the valve **107**. In one or more variants, the data input may include a port such as a USB port, a receiver for receiving electronic signals from a transmitted or other known input means known in the art for entering information or data into a memory.

FIG. **4** illustrates a block diagram of the circuit **150**. The circuit **150** shown in FIG. **4** includes a valve processor **122**, a valve memory **134**, a reset **128**, a valve transceiver **120** and a power source **130**. The circuit **150** may also include support circuits a timer **124**, a sensor **126** and/or other sensors. Referring to FIG. **3**, the circuit **150** is supported within the valve assembly **100**, with the physical components of the circuit **150** specifically disposed between actuator **114** and the cap **112**. As shown in FIG. **3**, the valve display **132** and the valve transceiver **120** are disposed adjacent to the cap **112**, such that the valve display **132** is visible through a window **113**. The sensor **126** and the valve processor **122** are disposed beneath the valve display **132** and the valve transceiver **120**, within the actuator **114**.

The valve processor **122** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The valve memory **134**, or computer-readable medium, may be one or more of readily available memory such as electrically erasable programmable read only memory (EEPROM), random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the valve processor **122**. The support circuits may be coupled to the valve processor **122** for supporting the circuit **150** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like.

In the embodiment shown, the valve memory **134** communicates with a data input **108** disposed on the side of the actuator **114**. The data input **108** shown in FIGS. **3-4** is used to transfer data from the valve memory **134** to other devices or to input data into the valve memory **134**. For example, gas data, which includes information regarding the gas contained within the gas source, may be entered into the valve memory **134** via the data input **108**. In one or more alternative embodiments, the gas data may be programmed or directly entered into the valve memory **134** by the gas supplier. In one or more embodiments, the gas data may be provided in the form of a bar code **610** that is disposed on a label **600** that is affixed on a to the side of the gas source, as shown in FIG. **5**. The bar code **610** may be disposed directly on the gas source. An external scanning device in communication with the electronic data input **108** may be provided and may be used to scan the bar code **610** and convey the information from the bar code **610** to the valve memory **134**. Gas data may include information regarding the gas composition (e.g., NO, O_2, NO_2, CO, etc.), concentration, expiration date, batch and lot number, date of manufacturing and other information. Gas data may be configured to include one or more types of information. The valve processor **122** may include instructions to convey all or a pre-determined portion of the gas data via the valve transceiver **120** to another transceiver.

In embodiments that utilize a timer **124**, the timer **124** may include two sub-timers, one of which is a calendar timer and the other of which is an event timer. The reset **128** may be located inside the actuator **114** and may be depressed to reset the event timer. The cap **112** also includes a window **113** that allows the user to see the valve display **132** disposed within the cap **112** that displays information regarding whether the actuator **114** is opened or closed and the duration the valve **107** was opened or closed. In one or more embodiments, the valve display **132** may alternate flashing of two different numbers, a first number may be accumulated open time, and the second number may be the time at which the valve **107** was opened for the current event. The time at which the valve **107** was opened for a current event may be preceded by other indicators.

The sensor **126** disposed within the actuator **114** may include a proximity switch model MK20-B-100-W manufactured by Meder Inc. The sensor **126** utilized in one or more embodiments may cooperate with a magnet (not shown) to sense whether the actuator **114** is turned on or turned off. Such sensors are described in U.S. Pat. No. 7,114,510, which is incorporated by reference in its entirety.

For example, the sensor **126** and a corresponding magnet (not shown) may be disposed on a stationary portion of the valve **107**. When the actuator **114** is rotated to the closed position, the sensor **126** is adjacent to the magnet that is in a fixed position on the valve **107**. When the sensor **126** is adjacent to the magnet, it sends no signal to the valve processor **122**, thereby indicating that the actuator **114** is in the "closed" position or has a valve status that includes an open position or a closed position. When the actuator **114** is rotated to open the valve **107**, the sensor **126** senses that it has been moved away from the magnet and sends a signal to the valve processor **122**, indicating an "open" position. The valve processor **122** instructs the valve memory **134** to record the event of opening the valve **107** and to record the time and date of the event as indicated by the calendar timer. The valve processor **122** instructs the valve memory **134** to continue checking the position of the valve **107** as long as the valve **107** is open. When the valve **107** is closed, the valve processor **122** uses the logged open and close times to calculate the amount of time the valve **107** was open and instructs the valve memory **134** to record that duration and the accumulated open time duration. Thus, every time the valve **107** is opened, the time and date of the event is recorded, the closing time and date is recorded, the duration of time during which the valve **107** is open is calculated and recorded, and the accumulated open time is calculated and recorded.

In one or more embodiments in which the power source **130** includes a battery, the valve transceiver **120** may be configured to communicate with the CPU transceiver **220** to preserve the life of the battery. In this embodiment the valve transceiver **120** is only turned on to receive a signal from the Control Module CPU transceiver **220** for 20 msec every second. The control module CPU transceiver **220** sends out a short transmit signal continuously and if the valve transceiver **120** is present it responds in the 20 msec interval. This conserves battery power as the valve transceiver **120** is only powered on for 20 msec every second. When the valve transceiver **120** responds it includes in its signal information regarding whether the communication from the control module CPU transceiver **220** was early or late within this 20 msec window. This ensures that once communications has been established it is synchronized with the 20 msec window that the valve transceiver **120** is powered on and able to receive communications. For example, as shown in FIG. **6**, the valve transceiver **120** sends a wireless optical line-of-sight signal during a pre-determined interval in response to a signal from the control module CPU transceiver **220**. The wireless optical line-of-sight signals sent by the valve transceiver **120** are a series of on off cycles where the transmitter is either transmitting light or is not and these correspond to digital binary signals. The mechanism by which the valve transceiver sends a wireless optical line-of-sight signal may be construed as a series of digital on off signals that correspond to data being transmitted. Once communications has been established between the control module CPU transceiver **220** and the valve transceiver **120**, the interval between communication signals may be in the range from about 20 seconds to about 5 seconds. In one or more specific embodiments, the interval or duration between transceiver signals may be about 10 seconds.

As will be described in more detail below, the control module **200** includes a CPU **210** which is connected to a CPU transceiver **220** which can send and receive wireless optical line-of-sight signals. The CPU transceiver **220** sends out a signal and waits for a response from the valve transceiver **120** when communication or more specifically, line-of-sight communication is established between the CPU transceiver **220** and the valve transceiver **120**. If no response is sent by the valve transceiver **120**, the CPU transceiver **220** sends another signal after a period of time. This configuration preserves battery life because the valve transceiver **120** does not continuously send a signal unless requested to by the CPU **210**. This is important as the gas delivery device and gas source spends most of its time in shipping and storage prior to being placed on the gas delivery system, if it was transmitting all this time trying to establish communications with the control module it would be consuming the battery life significantly.

The valve processor **122** may include link maintenance instructions to determine whether the interval should be increased or decreased. As shown in FIG. **6**, when a valid link is established between the valve transceiver **120** and CPU transceiver **121**, the valve processor **122** executes the link maintenance instructions to increase the interval or decrease the interval.

As shown more clearly in FIG. **1**, valve assembly **100** and gas source **50** is in communication with a control module **200**, which is in communication with a gas delivery mechanism.

The gas delivery mechanism shown in FIG. **1** includes a ventilator **400** with associated breathing circuit **410**. The control module **200** may include a CPU **210** and a CPU transceiver **220** in communication with the circuit **150** via the valve transceiver **120**. The control module **200** also includes a CPU memory **212** in communication with the CPU transceiver **220** to store patient information, information or data received from the valve transceiver **120** and other information. The control module **200** may also include support circuits. The CPU **210** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The CPU memory **212**, or computer-readable medium, may be one or more of readily available memory such as random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the CPU **210**. The support circuits may be coupled to the CPU **210** for supporting the control module **200** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like. The CPU **210** may also include a speaker **214** for emitting alarms. Alternatively, alarms may also be displayed visually on a display. As shown in FIG. **1**, the control module **200** may also include a regulator **110** and, optionally, pressure gauges and flow meters for determining and/or controlling the gas flow from the gas source **50**.

In one or more embodiments, the CPU transceiver **220** is disposed on a cover portion **225** (shown more clearly in FIG. **7**), that is part of a cart **500** (show more clearly in FIG. **7**) onto which the control module **200** is disposed. The cover portion **225** in one or more embodiments is in communication with the control module **200**. Communication between the cover portion **225** and the control module **200** may be established wirelessly or via a cable. As will be discussed in greater detail below, the valve assembly **100**, including the valve **107**, the circuit **150** and a gas source **50** attached to the valve **107**, are placed on the cart **500** in proximity and in a light-of-sight path with the CPU transceiver **220**. When properly configured such that communication is established between the valve transceiver **120** and the CPU transceiver **220**, the CPU transceiver **220** is positioned directly above the valve transceiver **120**, as shown more clearly in FIG. **9**. In one or more alternative embodiments, the CPU transceiver **220** may be disposed on the CPU **210**.

The CPU **210** may be in communication with a plurality of gas sensors **230** for determining the concentration of a sample of gas drawn via a sample line **232** and a sample line inlet **280** (shown more clearly in FIG. **1**) disposed on the control module **200**. As will be discussed in greater detail, the sample line **232** draws a sample of gas from a breathing circuit **410** of a ventilator **400** when the ventilator is in fluid communication with the control module **200** and gas is being delivered to the ventilator. The CPU **210** may also be in communication with a sample flow sensor **234** for sensing the flow of the sample drawn via sample line **232**, a pump **236** for drawing the sample via the sample line **232** to the flow sensor **234** and zero valve **238** controlling the flow of the sample via the sample line **232** to the sample pump **236**, sample flow sensor **234** and the plurality of CPU sensors. The sample line **232** may include a water trap **233** for collecting any water or liquid from the sample.

The control module **200** may also include a delivery module **260** for regulating the flow of gas from the gas source **50** to the ventilator **400**. The delivery module **260** may include a pressure switch **262** for determining a gas supply pressure is present, a pressure shut-off valve **264**, a proportional valve **266** and a delivery flow sensor **268**. The delivery module **260** may also include a backup on/off switch **269**. The detailed method of how the delivery module delivers the gas to the ventilator circuit is described in U.S. Pat. No. 5,558,083 which is incorporated here by reference in its entirety.

The ventilator **400** shown in FIG. **1** is in fluid communication with the control module **200** via an injector tubing **440** and in electrical communication via an injector module cable **450**. The control module **200** and more specifically, the CPU **210**, is in fluid communication with the ventilator **400** via the sample line **232**. The ventilator **400** may include a breathing circuit **410** with an inspiratory limb **412** and an expiratory limb **414** in fluid communication with the ventilator **400**. The inspiratory limb **412** may be in fluid communication with a humidifier **420**, which is in fluid communication with the ventilator **400** via an injector module **430**. The inspiratory limb **412** carries gas to the patient and the expiratory limb **414** carries gas exhaled by the patient to the ventilator **400**. The injector module **430** shown in FIG. **1** is in fluid communication with the gas source **50** via the injector tubing **440** and in electronic communication with the delivery module **260** via the injector module cable **450** such that the delivery module **260** can detect and regulate the flow of gas from the gas source **50** to the ventilator **400**. Specifically, the injector module **430** is in fluid communication with the gas source **50** via an injector tubing **440**, which is in fluid communication with one or more of the pressure switch **262**, pressure shut-off valve **246**, proportional valve **266**, flow sensor **268** and the backup switch **269** of the delivery module **260**. The injector module **430** may also be in electronic communication with the delivery module **260** via the injector module cable **450**. The inspiratory limb **412** of the ventilator **400** may include a sample tee **416** for facilitating fluid communication between the inspiratory limb **412** of the breathing circuit and the sample line **232**.

As discussed above, the control module **200** may be disposed or attached on a cart **500**, as shown in FIGS. **7-9** to facilitate movement of the gas source **50** and the gas delivery device to a patient in need of gas therapy. The gas source **50** and the valve assembly **100** attached thereto may be placed on the cart **500** in proximity to the control module **200**. More specifically, as shown in FIG. **7**, the gas source **50** is placed on the cart **500** such that the valve transceiver **120** is in proximity of the CPU transceiver **220** and a line-of-sight path is established between the valve transceiver **120** and the CPU transceiver **220**. In this configuration, the CPU **210** detects the presence of the circuit **150** and thus the gas source **50** via the CPU transceiver **220**.

As shown in FIGS. **7-9**, the gas delivery device may include more than one valve, with each valve being attached to a single gas source. In such embodiments which utilize a second gas source **60** with a second valve assembly **101**, the second valve assembly **101** is positioned in proximity and in a light-of-sight path with a second CPU transceiver as the gas source **60** is loaded onto the cart. The second CPU transceiver **222** establishes communication with the second valve assembly **101** and thus detects the presence of a second gas source **60**. In the embodiment shown in FIGS. **7-9**, the second CPU transceiver **222** may also be disposed on the cover portion **225** of a cart. In one or more alternative embodiments, the second CPU transceiver **222** may be disposed on the CPU **210**.

As shown in FIG. **8**, the cart **500** may include an optional small bin **510**, a mount **512** for supporting the control module **200** on the cart **500**, at least one a holding bracket **520**, at least one mounting strap **530**, an auxiliary bracket **540**, for holding an auxiliary gas source, a plurality of casters **550** and a caster lock lever **560** disposed on each of the plurality of casters **550**.

The cart **500** may include a mount **570** for mounting the control module **200** on to the cart.

An exemplary control module **200** is shown in FIGS. **10-12** includes a display **270** for providing visual indication to the user the components of the gas being delivered from the gas source **50** to the ventilator **400** (e.g., NO, O_2, NO_2), the concentration of each component and whether communication has been established with one or more gas sources. Other information may also be displayed to the user. In addition, visual alarms may also be displayed on the display **270**. The control module **200** may also include a main power indicator **272** indicating whether the control module is connected to a power source, such as an AC/DC power source and/or a battery. The control module **200** may also include a control wheel **274** allowing the user to navigate through various displays or information displayed on the display. An injection module tubing outlet **276** may be disposed on the control module for providing fluid communication between the delivery module **260** and the injector module **430**. An injection module cable port **278** may also be provided on the control module to provide electronic communication between the delivery module **260** and the injector module **430**. The control module **200** shown in FIGS. **10-12** also includes the sample line inlet **280** in fluid communication with the sample line **232** and the inspiratory limb **412** of the ventilator **400**. In the embodiment shown in FIGS. **10-12**, the water trap **233** is disposed on the control module, adjacent to the sample line inlet **280**.

FIG. **11** illustrates a back view of the control module **200** and shows a plurality of inlets. In the embodiment shown, two gas inlets **282**, **284** for connecting the control module **200** to the gas source **50** are provided and one auxiliary inlet **286** for connecting the control module **200** to an auxiliary gas source, which may include oxygen or other gas. A power port **288** is also provided on the back of the control module to connect the control module to an AC/DC power source.

The control module **200** may also include an input means **290** for allowing the user to enter patient information, for example the identity of the patient, the type and concentration of the gas and dose of the gas to be administered to the patient, the patient's disease or condition to be treated by the gas or reason for treatment, gestational age of the patient and patient weight. The input means **290** shown in FIG. **12** includes a keyboard integrated with the display. In one or more alternative embodiments, the input means may include a USB port or other port for the connection of an external keyboard or other input mechanism known in the art. The information entered via the input means **290** is stored within the CPU memory **212**.

The control module **200** and the valve assembly **100** may be utilized in the gas delivery system **10** to improve patient safety. Specifically, the safety benefits of the gas delivery system described herein include detecting a non-confirming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like. In addition, embodiments of the gas delivery system described herein also improve efficiency of gas therapy.

FIG. **13** is a block diagram showing the sequence of how gas delivery device, including the valve assembly **100**, may be provided and its use within the gas delivery system **10**, according to one or more embodiments. As shown in FIG. **13**, the gas delivery device **10** is prepared for use by providing a gas source **50** in the form of a gas cylinder or other container for holding a gas and filling the gas source **50** with a gas (**700**) and attaching a valve assembly **100** as described herein, to assemble the gas delivery device **10** (**710**). These steps may be performed by a gas supplier or manufacturer. The gas data regarding the gas filled within the gas source **50** is entered into the valve memory **134** as described herein (**720**). The gas data may be entered into the valve memory **134** by the gas supplier or manufacturer that provides the gas source **50** and assembles the gas delivery device **10**. Alternatively, the hospital or other medical facility may enter the gas data into the valve memory **134** after the gas delivery device has been transported to the hospital or medical facility (**730**). The gas delivery device **10** is positioned on a cart **500** (**740**) and communication between the CPU transceiver **220** and the valve transceiver **120** is established (**750**). The gas data stored within the valve memory **134** is conveyed to the control module **200** (**760**) via the wireless optical line-of-sight communication between valve transceiver **120** and the CPU transceiver **220**. The CPU **210** compares the gas data to patient information entered into the CPU memory **212** (**770**). The patient information may be entered into the CPU memory after the gas data is entered into the CPU memory **212**. The patient information may be entered into the CPU memory before the gas delivery device **10** is positioned in the cart or before communication between the CPU transceiver **220** and the valve transceiver is established. In one or more alternative embodiments, the patient information may be entered into the CPU memory **212** before the gas delivery device **10** is prepared or transported to the hospital or facility. The CPU **210** then compares whether the gas data and the patient information match (**780**). If the gas data and the patient information match, then gas is administered to the patient (**790**), for example through a ventilator or other gas delivery mechanism. If the gas data and the patient information do not match, then an alarm is emitted (**800**). As described otherwise herein, the alarm may be audible and emitted through the speaker **214** and/or may be visual and displayed on the display **270**.

The gas delivery system described herein simplifies set-up procedures by utilizing wireless line-of-sight signals to establish communication. The user does not need to ensure all the cables are correct connected and can freely load new gas sources onto a cart without disconnecting cables linking the control module **200** and the valve assembly **100** or circuit **150**. This reduces set-up time and any time spent correcting errors that may have occurred during the set-up process. The control module **200** and the circuit **150** are further designed to automatically send and detect information to establish delivery of a correct gas having the correct concentration and that is not expired. In one or more specific embodiments, such automated actions prevent the use of the gas delivery system by preventing gas flow to a patient, without user intervention.

In one or more embodiments, after communication between the valve transceiver **120** and the CPU transceiver **220** is established, the valve processor **122** includes instructions to convey the gas data stored in the valve memory **134** via the valve transceiver **120** to the CPU transceiver **220**. The CPU **210** includes instructions to store the gas data received from the CPU transceiver **220** in the CPU memory. The CPU **210** also includes an algorithm that compares the gas data with patient information that is entered into the CPU memory **212**. If the gas data and the patient information do not match, the CPU **210** includes instructions to emit an alarm, which may be audible, visual or both, alerting the user that the gas contained within the gas source is different from the gas to be administered to the patient.

For example, as illustrated in FIG. **12**, if the gas data includes gas expiration date, the CPU memory **212** includes information regarding the current date and the CPU **210** compares the gas expiration date with the current date. If the gas expiration date is earlier than the current date, the CPU **210** emits an alarm. The alarm may be emitted through one or both

the speaker **214** and display **270**. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of an expired gas by the CPU **210** may be stored within the CPU memory **212**.

If the gas data includes gas concentration information or data, the CPU memory **212** includes information regarding the desired concentration of gas to be administered to the patient. The control module **200** may be configured to alert the user that the gas contained within a gas source has incorrect concentration or a concentration that does not match the desired gas concentration. For example, a user may enter a concentration of 800 ppm into the CPU memory **212** and this concentration is compared to the gas concentration conveyed from the valve memory **134** to the CPU memory **212**. As illustrated in FIG. **12**, the CPU **210** includes instructions to compare the gas concentration of the gas with the concentration entered by the user. If the gas concentration does not match the concentration entered by the user, the CPU **210** emits an alarm, which may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of a gas with incorrect concentration may be stored within the CPU memory **212**.

In one or more embodiments, the control module **200** may be configured to detect more than one valve and to detect whether more than one valve is turned on. This configuration eliminates waste because it alerts a user that both valves are turned on and thus unnecessary gas is being delivered to via the delivery module **260**. In addition, such a configuration improves safety because it avoids the issues related to having two regulators pressurized at the same time and connected to the delivery module **260**. In one or more embodiments, the cover portion **225** of the control module **200** may include a second CPU transceiver **222** and the CPU **210** may include instructions for the second CPU transceiver **222** to detect wireless optical line-of-sight signals from a second valve assembly **101**, and more specifically, a second valve transceiver **121**. The CPU **210** may also include instructions that once a second valve assembly **101** is detected by the CPU transceiver **222**, whether both valve assemblies **100**, **101** are opened or have a valve status that includes an open position. In operation, a first valve assembly **100** includes a circuit with a valve processor with instructions to covey an open or closed position via the first valve transceiver **120**. The circuit of the second valve assembly similarly includes a valve processor with instructions to convey an open or closed position via a second valve transceiver **121**. The first CPU transceiver **220** and the second CPU transceiver **222** detect the valve statuses for each respective valve assembly from the first valve transceiver **120** and the second valve transceiver **121** via the wireless optical line-of-sight signals sent by both transceivers. The CPU **210** instructs the CPU transceivers **220**, **222** to collect the valve statuses for both valve assemblies **100**, **101** and the memory to store the valve statuses. The CPU **210** then compares the valve status information from the first valve assembly **100** and the second valve assembly **101** and, if the valve statuses both comprise an open position, the CPU **210** emits an alarm. The alarm may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas through either the first valve assembly or the second valve assembly. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas. The detection that more than one valve assembly had a valve that was turned on or had a valve status including an open position may be stored within the CPU memory.

In one or more embodiments, the control module **200** may be configured to alert a user when the desired dose has been delivered. In such embodiments, the patient information entered into the CPU memory **212** may include dosage information or the dose to be delivered to a patient. The valve processor **122** may include instructions to convey gas usage information from the valve memory **134**, including the amount of gas delivered, to the CPU memory **212** via the valve transceiver **120**. Alternatively, the valve processor **122** may include instructions to covey the duration of time the valve **170** has been turned on or has a valve status including an open position to the CPU memory **212** via the valve transceiver **120**. The CPU **210** may include instructions to compare the dosage information entered by the user and stored within the CPU memory **212** with the gas usage information. The CPU **210** may include instructions to emit an alarm when the dosage information and the gas usage information match. The CPU **210** may include instructions to emit the same or different alarm to alert the user to turn off the valve or, more specifically, the actuator **114** when the dose has been delivered. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas.

In addition, the control module **200** may be configured to alert the user that a detected valve is and remains closed and no gas is being delivered to the patient. This configuration expedites treatment time and increases efficiency for the hospital. In such embodiments, the valve processor **122** may include instructions for the valve transceiver **120** to convey the valve status to the CPU **210** via a wireless optical line-of-sight signal. The CPU **210** includes instructions to collect the valve status information and emit an alert if the dosage information is set or other input has been entered into the CPU memory **212** to commence treatment and the valve status includes a closed position.

The control module **200** may be configured to alert the user that no valve assembly or gas source has been detected. In such embodiments, the CPU **210** includes instructions to detect the presence of a wireless optical line-of-sight signal from another transceiver, for example, the valve transceiver **120**. The CPU **210** may include instructions to emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected. Similarly, the control module **200** may be configured to emit an alarm if communication between one or both of the CPU transceiver (s) **220**, **222** and one or both of the valve transceivers **120**, **121** has been lost during gas delivery. In such embodiments, the CPU **210** may include instructions to continuously detect the presence of a signal from another transceiver and emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected.

The CPU **210** may include instructions to alert a user when sensors in the control module **200** must be calibrated to ensure accurate delivery of gas to a patient. In addition, the CPU **210**

may include instructions to correlate gas usage information from the circuit **150** of the valve assembly **100** to the patient information entered into the CPU memory **212**. The CPU **210** may also have instructions to store the correlated gas usage information and the patient information in the CPU memory **212**. The valve processor **122** may also include instructions detect patient information from the CPU memory **212**. Specifically, the valve processor **122** may include instructions to collect patient information via the valve transceiver **120** from the CPU transceiver **220** and store the collected patient information in the valve memory **134**. In such embodiments in which information from the CPU **210** is collected and stored in the valve memory **134**, the CPU **210** may include instructions that the patient information and/or correlated patient information and gas usage information be conveyed from the CPU memory **212** via the CPU transceiver **220** to the valve transceiver **120**. The valve processor **122** may also include instructions to correlate gas usage information with the collected patient information and store the correlated gas usage information and collected patient information in the valve memory **134**. Alternatively, the valve processor **122** may include instructions to collect the correlated patient information and gas usage information from the CPU **210**. The correlated information may be utilized to bill the user according to patient. In addition, the correlated information may be utilized as patient demographic data, which can assist hospitals or other facilities to generate budget reports, determine usage per department, determine usage per patient diagnosis and link usage of multiple gas sources to individual patients.

A second aspect of the present invention pertains to a method for administering a therapy gas to a patient. The method includes providing a gas in a gas source. The gas source may be prepared by a supplier to contain a gas having a predetermined composition, concentration and expiration date. The method may include providing a valve assembly **100** attached to a gas source **50** to dispense the gas contained within the gas source **50** to a patient. The method may include entering gas data, which may include gas composition, gas concentration and gas expiration date, into the valve memory **134**. In one or more embodiments, the supplier may enter the gas data directly into the valve memory **134**. In another variant, the gas data is provided in the form of a bar code disposed on the gas source. In such embodiments, the method includes providing a scanner in communication with the data input **108**, scanning the bar code to collect the gas data information and conveying the gas data to the valve memory **134** via the data input **108**. These steps may be repeated for a second gas source. The gas source(s), with the valve assembly mounted thereon may be transported to a hospital or other facility for administration to a patient. The gas source(s) are then mounted onto the cart **500** and secured by the holding bracket **520** and mounting strap **530**. The method includes establishing communication between the valve transceivers disposed on each valve and the CPU transceivers **220**, **222**. Establishing communication may include positioning the valve assembly **100** in a line-of-sight path with at least one of the CPU transceivers **220**, **222**. As otherwise described herein, communication may be established by instructing the valve transceivers to send a wireless optical line-of-sight signal to the CPU transceivers **220**, **222**. The method may include instructing the valve transceiver **120** to send a wireless optical line-of-sight signal at pre-determined intervals, as otherwise described herein.

The method may include entering patient information into the CPU memory **212**. This step may be performed before or after the gas source(s) are mounted onto the cart. The method may specifically include entering patient information such as dosage information into the valve memory **134**. The method includes coordinating delivery of the gas to the patient by collecting gas data from the valve memory **134** and comparing the gas data with the patient information according to an algorithm and determining if the gas data and patient information match, according to the algorithm. Coordinating delivery of the gas may include turning on the actuator **114** of the valve **107** such that gas can flow from the inlet **104** to the outlet **106**. After the dose has been delivered, the method may include correlating the gas usage information and the patient information. The method may also include recording the patient information, gas usage information and/or the correlated patient information and gas usage information in the CPU memory **212** and/or the valve memory **134**. In one or more variants, the method may include utilizing the patient information, gas usage information and/or correlated patient information and gas usage information to generate invoices identifying the use of the gas by individual patients.

Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A valve assembly to deliver a gas comprising NO from a gas container containing the gas comprising NO, the valve assembly comprising:

a valve attachable to the gas container containing the gas comprising NO, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas comprising NO through the valve to a control module;

a circuit supported within the valve assembly and disposed between the actuator and a cap, the circuit including:

a valve memory to store gas data comprising gas concentration in the gas container and

a valve processor and a valve transceiver in communication with the valve memory to send wireless optical line-of-sight signals to communicate the gas data to the control module that controls gas delivery to a subject; and

a data input disposed on the actuator and in communication with said valve memory, to permit a user to enter the gas data into the valve memory.

2. The valve assembly of claim **1**, wherein the gas data is provided in a bar code disposed on the gas container and is entered into the data input by a user-operated scanning device in communication with the data input.

3. The valve assembly of claim 1, wherein the valve comprises a power source; and the valve transceiver periodically sends the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent.

4. The valve assembly of claim 3, wherein the duration of time at which no signal is sent comprises about 10 seconds.

5. A gas delivery system comprising:

the valve assembly of claim 1;

wherein the control module is in fluid communication with the outlet of the valve, the control module comprising:

a CPU transceiver to receive line-of-sight signals from the valve transceiver;

a CPU in communication with the CPU transceiver and including a CPU memory; and

a display to enter patient information into the CPU memory,

wherein the valve transceiver communicates the gas data comprising gas concentration to the CPU transceiver for storage in the CPU memory, and wherein the CPU compares the patient information entered into the CPU memory via the display and the gas concentration from the valve transceiver.

6. The system of claim 5, wherein the valve comprises a timer including a calendar timer and an event timer, wherein the valve memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

7. The system of claim 5, wherein the CPU comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the valve transceiver do not match.

8. The system of claim 5, wherein the CPU memory comprises instructions that cause the CPU processor to: receive gas data comprising gas concentration from the valve via a wireless optical line-of-sight signal with the valve connected to the gas container containing gas comprising NO; compare the gas data with user-inputted patient information; coordinate delivery of therapy to the patient with a medical device via the wireless optical line-of-sight signal between the CPU transceiver and the valve transceiver; select a therapy for delivery to a patient based on the received patient information; and control delivery of the selected therapy to the patient.

9. The system of claim 8, wherein the memory further comprises instructions that cause the CPU processor to:

receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas container;

receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas container;

compare the first valve status and the second valve status; and

emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position.

10. The system of claim 9, wherein the memory further comprises instructions that causes the CPU processor to:

terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

11. A method for administering a therapy gas comprising NO to a patient, the method comprising:

establishing communication via a CPU transceiver with the valve assembly of claim 1 and communicating the gas data from the valve transceiver to the CPU transceiver,

comparing the gas data communicated from the valve transceiver with patient information stored within a CPU memory;

coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal between the CPU transceiver and the valve transceiver;

selecting a therapy for delivery to the patient based on the comparison of the gas data and the patient information; and

controlling delivery of the selected therapy to the patient.

12. The method of claim 11, further comprising ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information.

13. The method of claim 11, further comprising emitting an alert based on the comparison of the gas data and the patient information.

14. The method of claim 11, further comprising entering the gas data into the valve memory.

15. The method of claim 11, further comprising entering the patient information into the CPU memory.

16. A gas delivery device comprising:

the valve assembly of claim 1; and

the gas container containing gas comprising NO attached to the valve assembly, wherein a bar code disposed on the gas container provides the gas data.

* * * * *

EXHIBIT G

US008573210B2

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Bathe et al.

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(54) **NITRIC OXIDE DELIVERY DEVICE**

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See application file for complete search history.

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(57) **ABSTRACT**

A nitric oxide delivery device including a valve assembly, a control module and a gas delivery mechanism is described. An exemplary gas delivery device includes a valve assembly with a valve and circuit including a memory, a processor and a transceiver in communication with the memory. The memory may include gas data such as gas identification, gas expiration and gas concentration. The transceiver on the circuit of the valve assembly may send wireless optical line-of-sight signals to communicate the gas data to a control module. Exemplary gas delivery mechanisms include a ventilator and a breathing circuit. Methods of administering gases containing nitric oxide are also described.

16 Claims, 12 Drawing Sheets

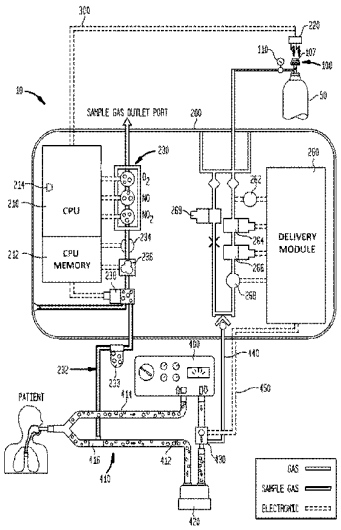

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FIG. 1

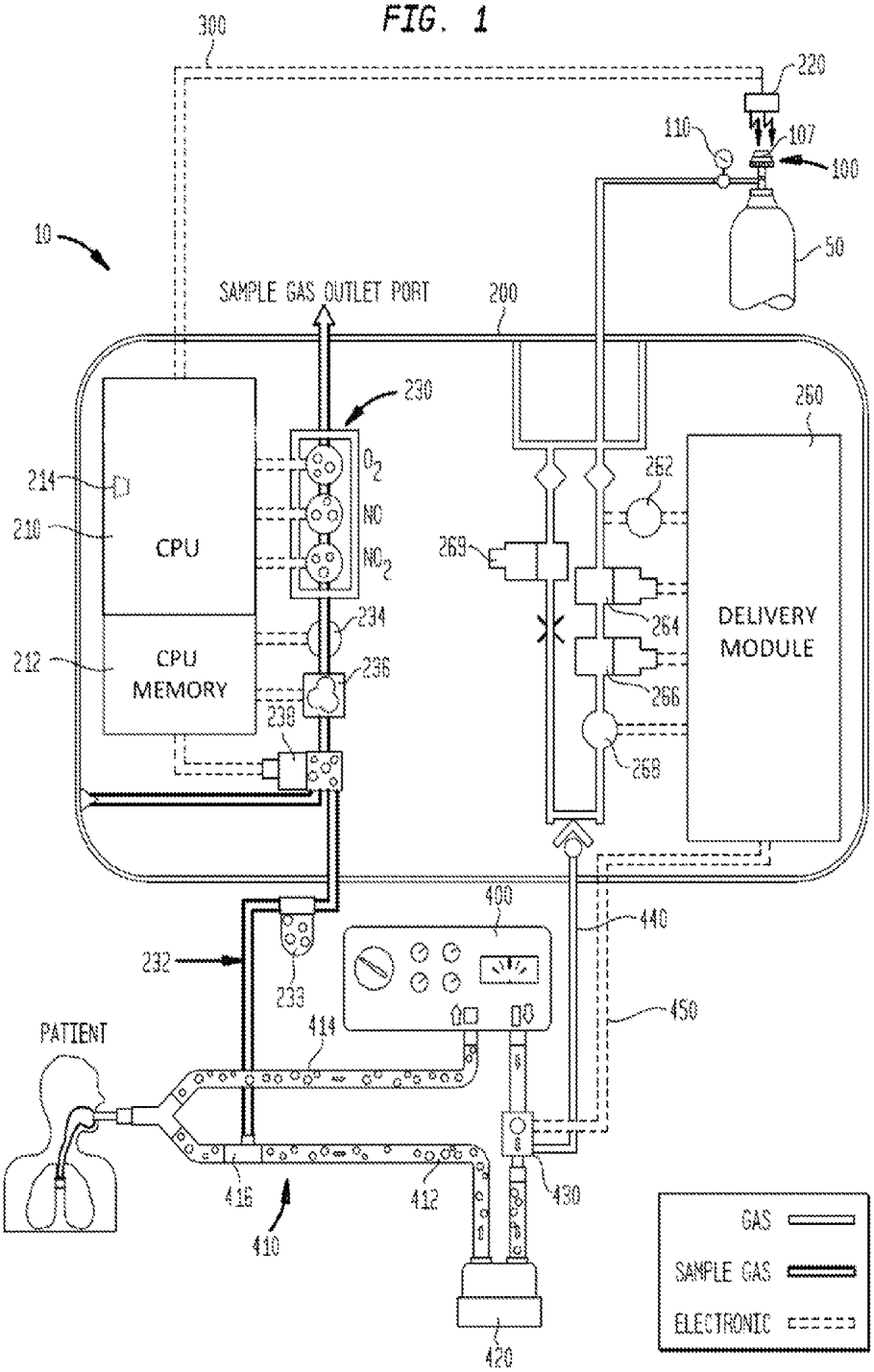

300
220
110
107
100
10
50
SAMPLE GAS OUTLET PORT
200
230
260
214
O_2
NO
NO_2
252
210
CPU
269
264
DELIVERY MODULE
234
212
CPU MEMORY
236
266
238
268
400
440
232
233
450
414
PATIENT
416
412
430
410
420
GAS
SAMPLE GAS
ELECTRONIC

FIG. 2

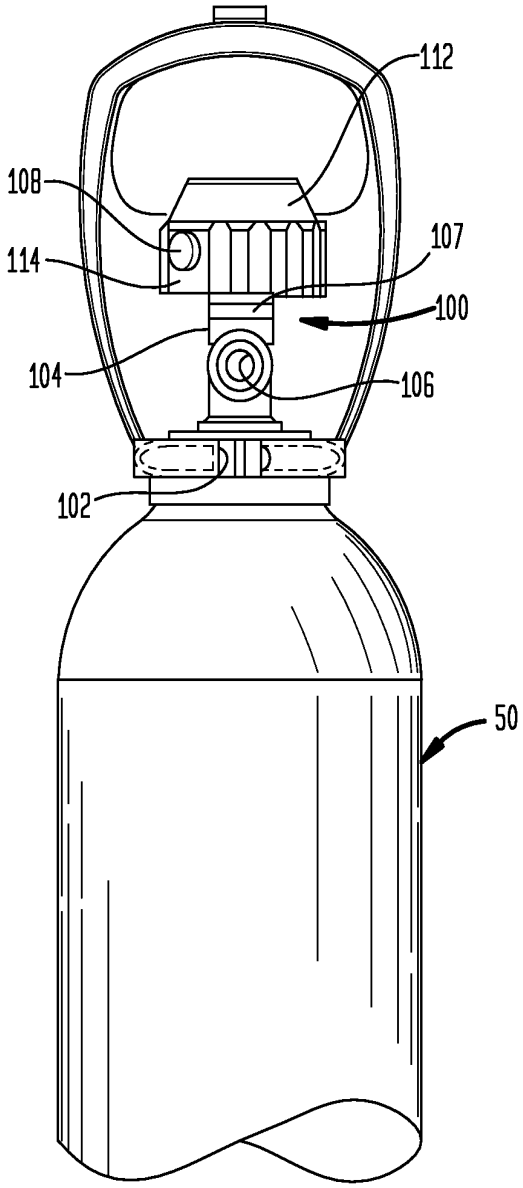


FIG. 3

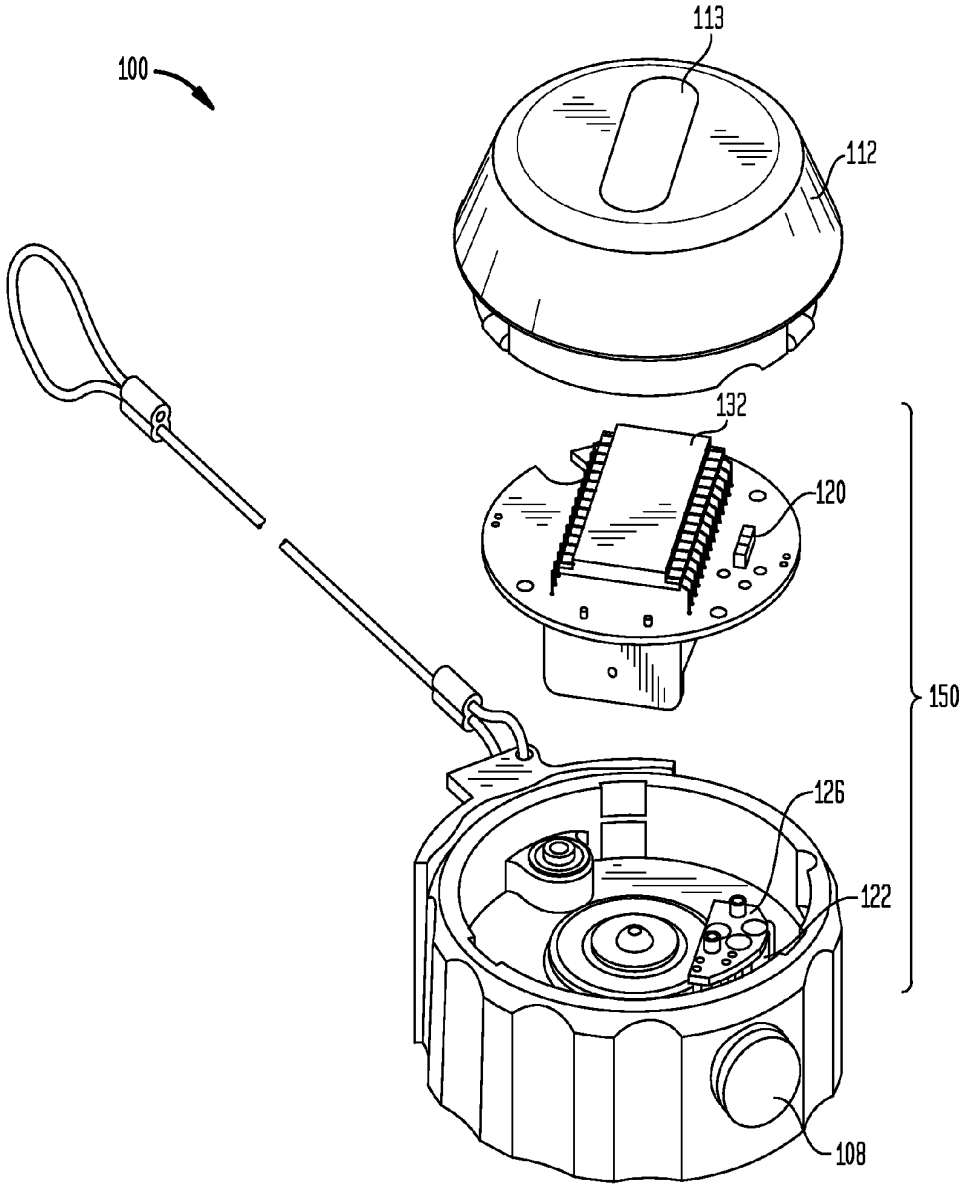


FIG. 4

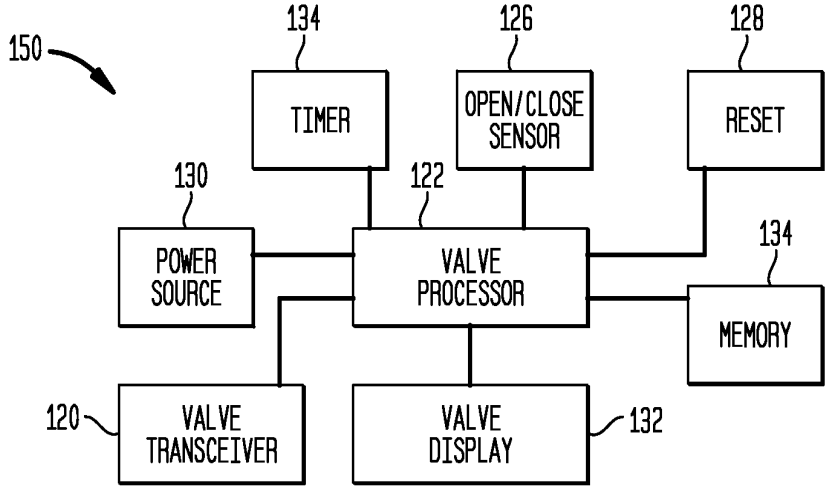

150
134
TIMER
126
OPEN/CLOSE SENSOR
128
RESET
130
POWER SOURCE
122
VALVE PROCESSOR
134
MEMORY
120
VALVE TRANSCEIVER
VALVE DISPLAY
132

FIG. 5

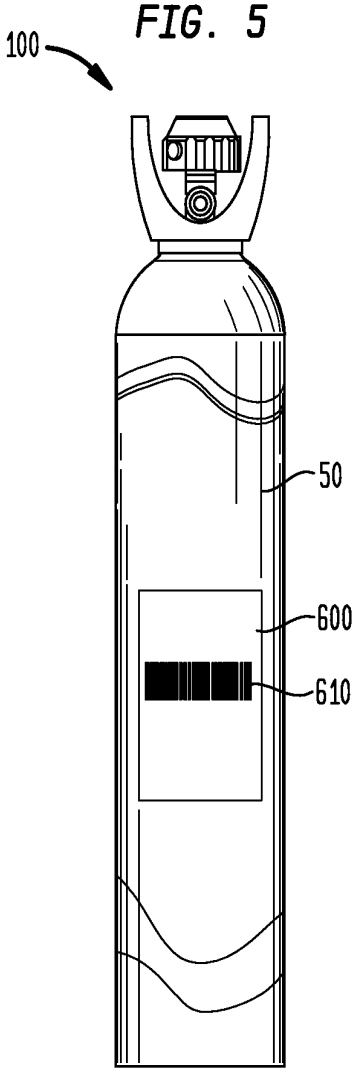

100
50
600
610

FIG. 6

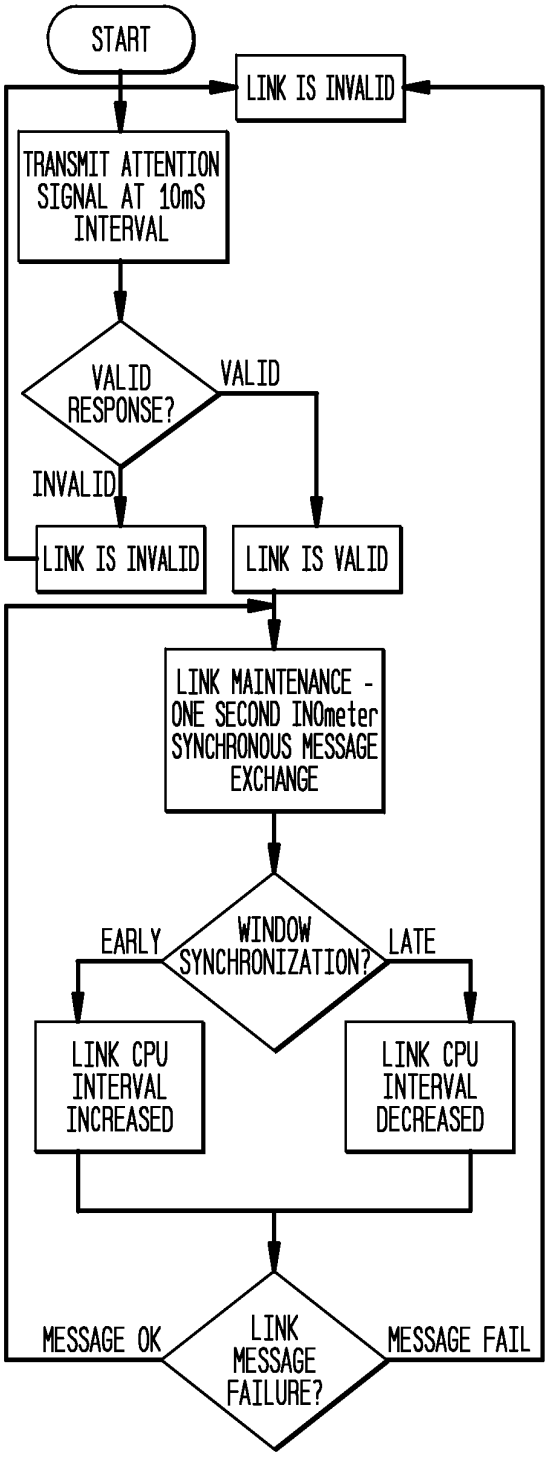

START
LINK IS INVALID
TRANSMIT ATTENTION SIGNAL AT 10mS INTERVAL
VALID RESPONSE?
VALID
INVALID
LINK IS INVALID
LINK IS VALID
LINK MAINTENANCE - ONE SECOND INOmeter SYNCHRONOUS MESSAGE EXCHANGE
WINDOW SYNCHRONIZATION?
EARLY
LATE
LINK CPU INTERVAL INCREASED
LINK CPU INTERVAL DECREASED
LINK MESSAGE FAILURE?
MESSAGE OK
MESSAGE FAIL

FIG. 7

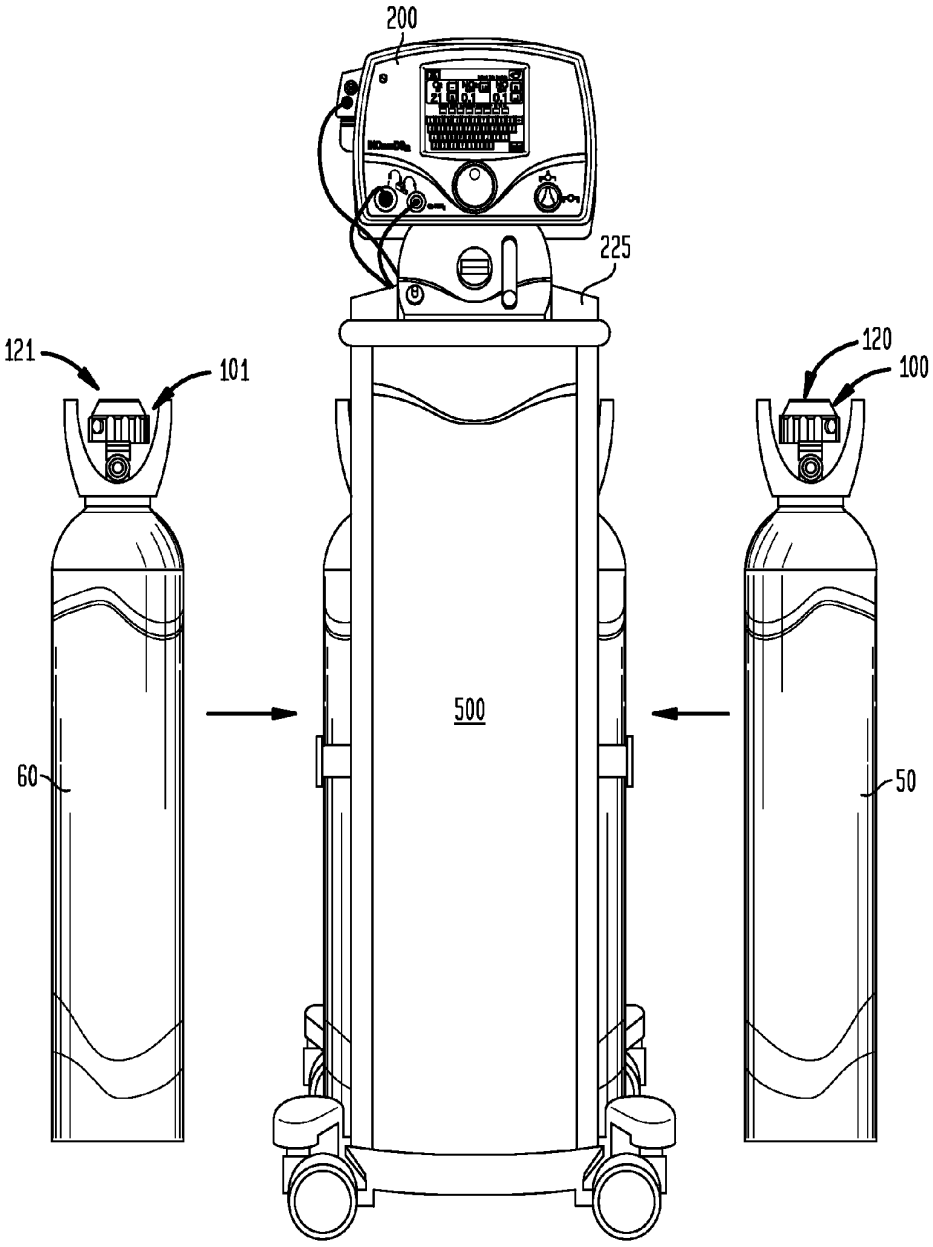


FIG. 8

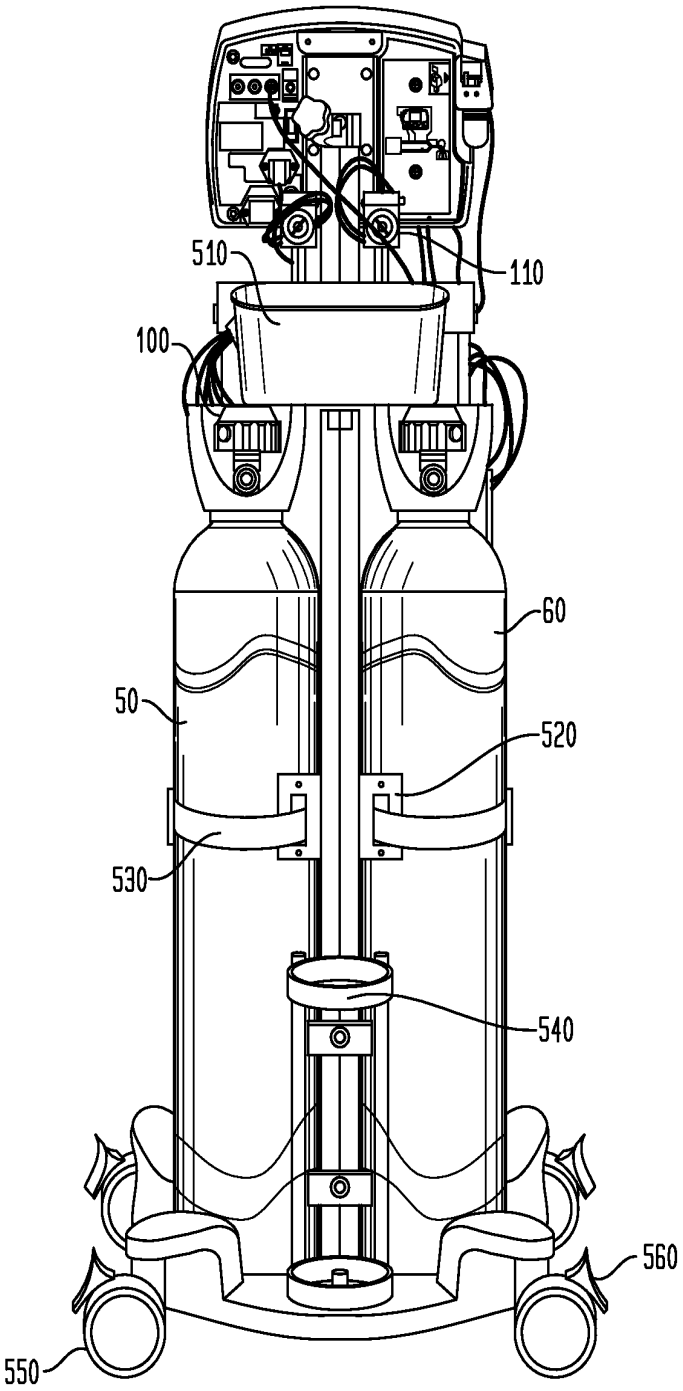


FIG. 9

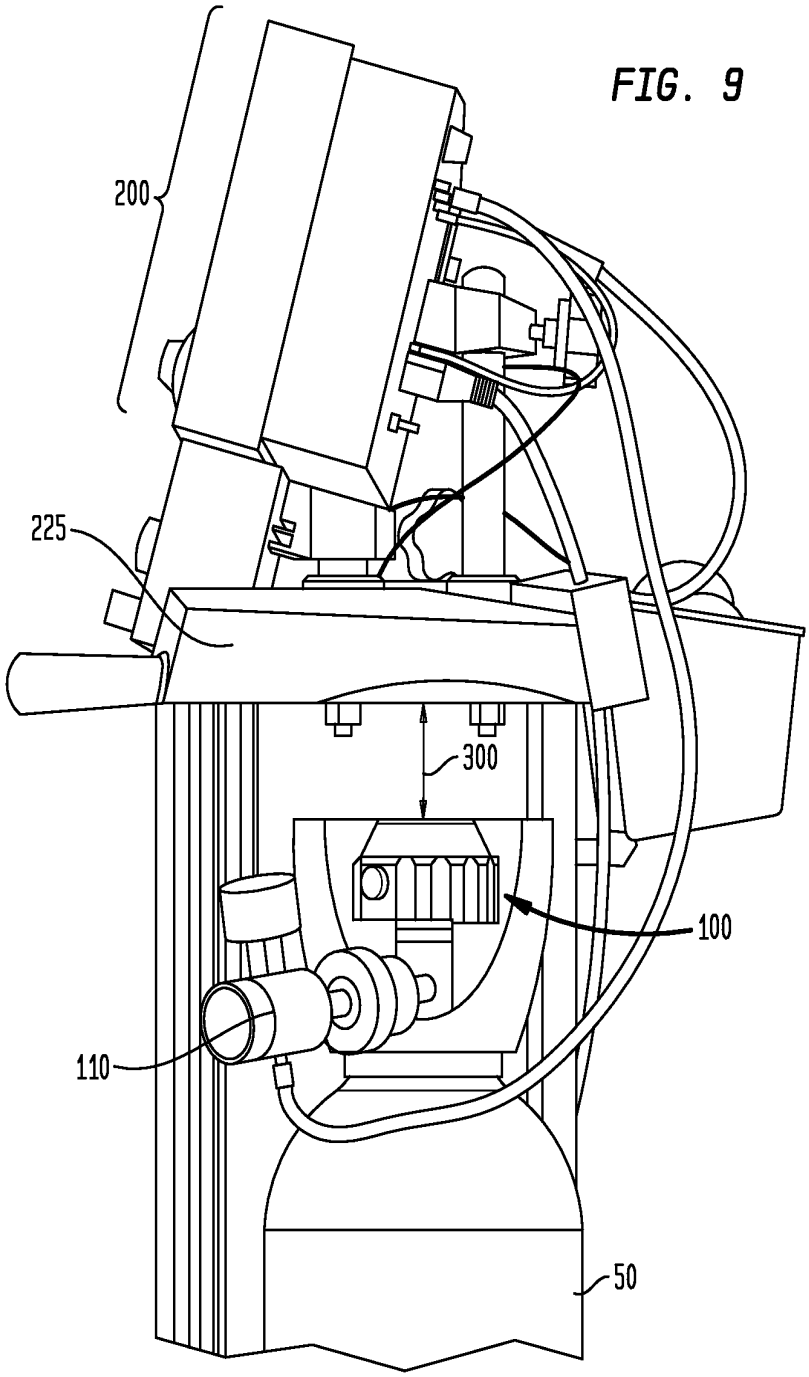


FIG. 10

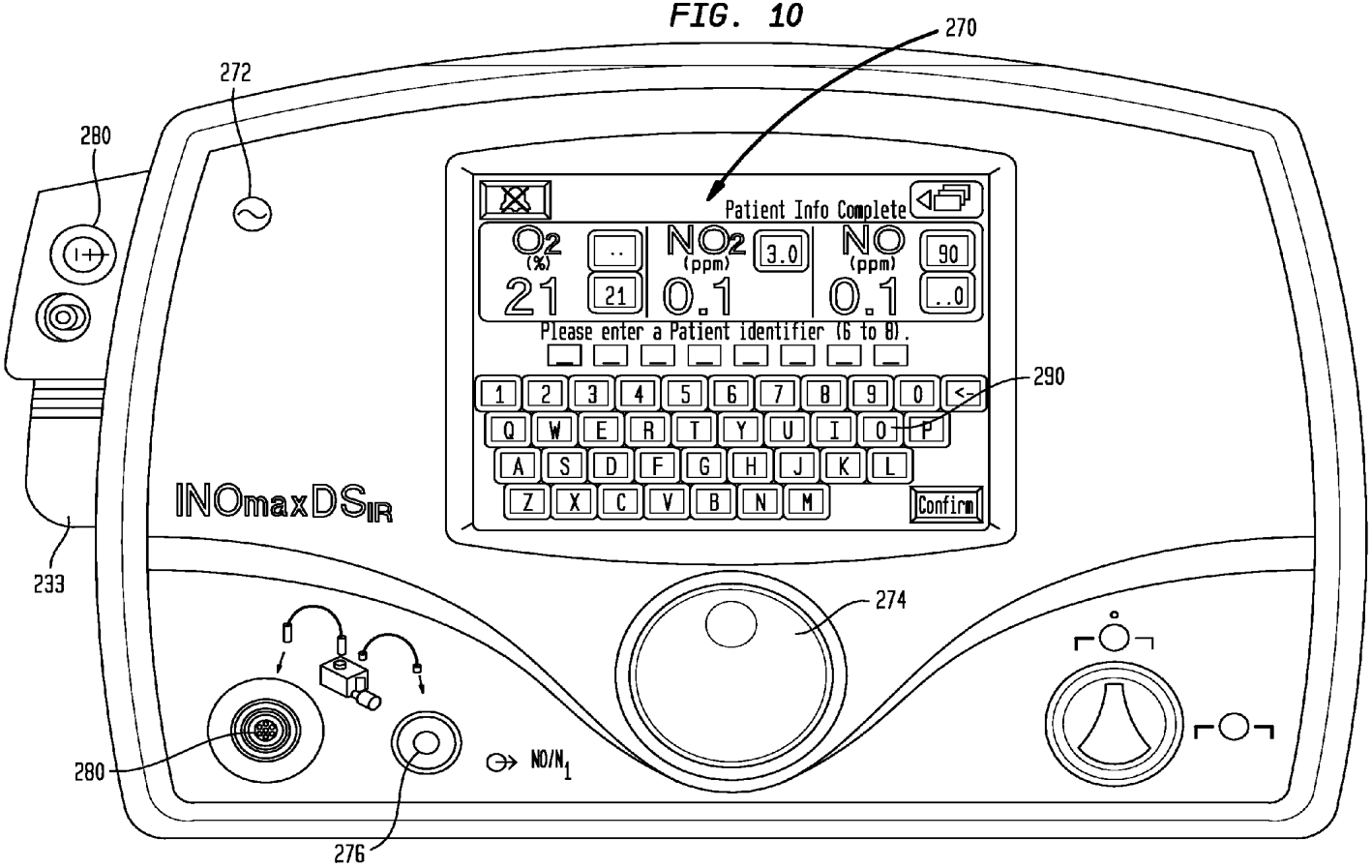

270
272
280
Patient Info Complete
O2 (%)
NO2 (ppm)
3.0
NO (ppm)
90
21
21
0.1
0.1
..0
Please enter a Patient identifier (6 to 8).
1 2 3 4 5 6 7 8 9 0 <-
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
Confirm
290
INOmaxDS IR
233
274
280
NO/N1
276

FIG. 11

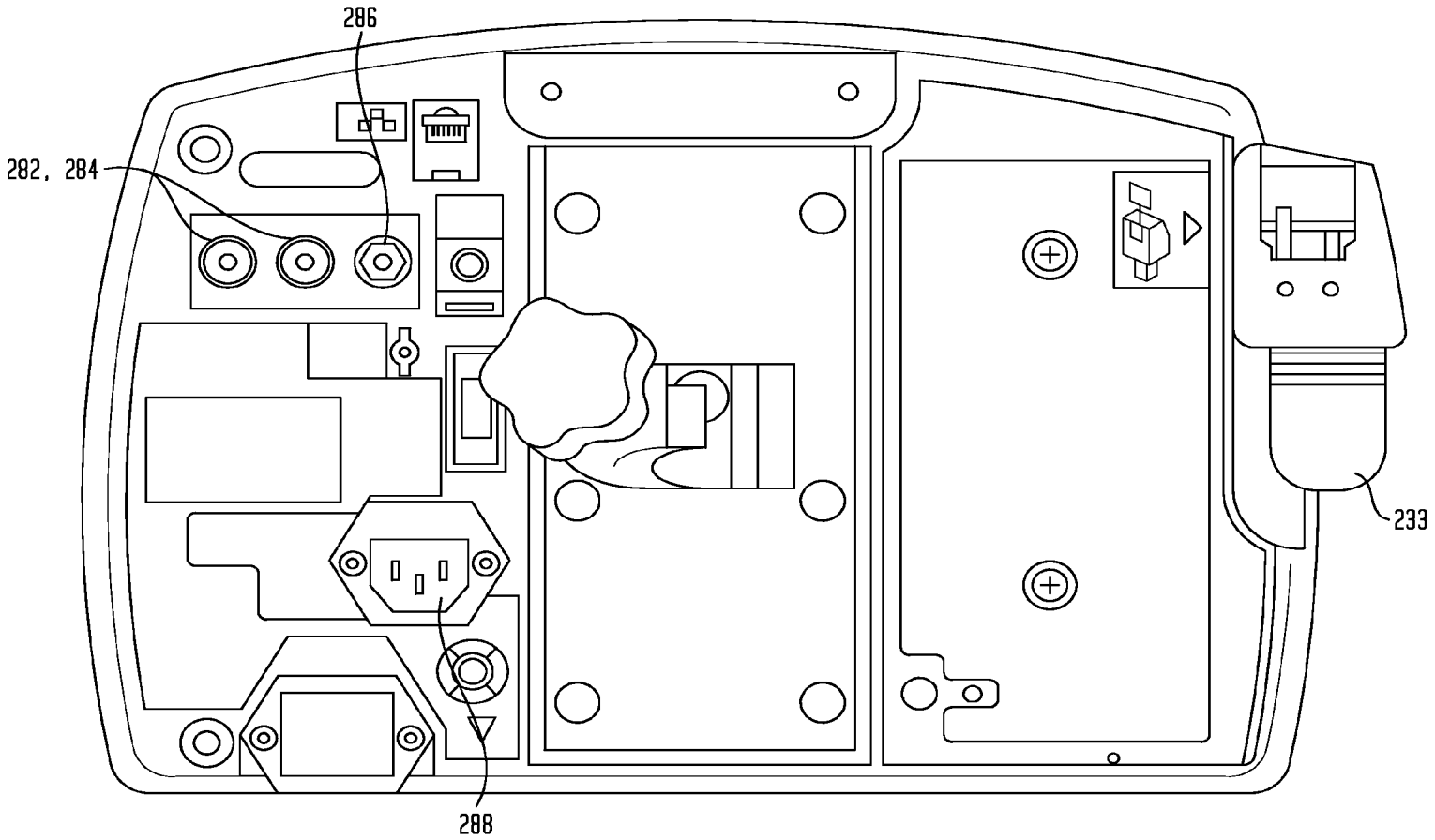


FIG. 12

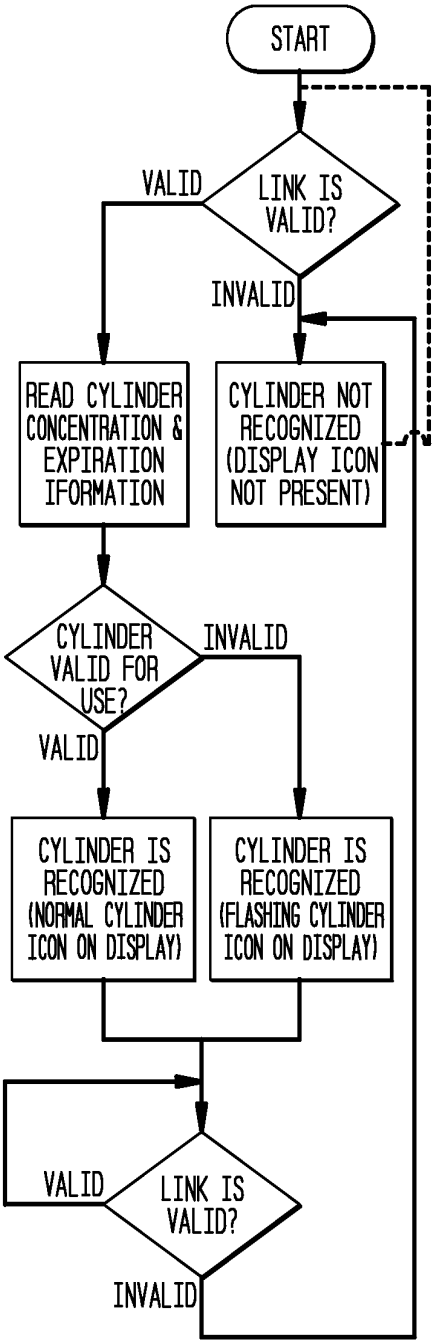
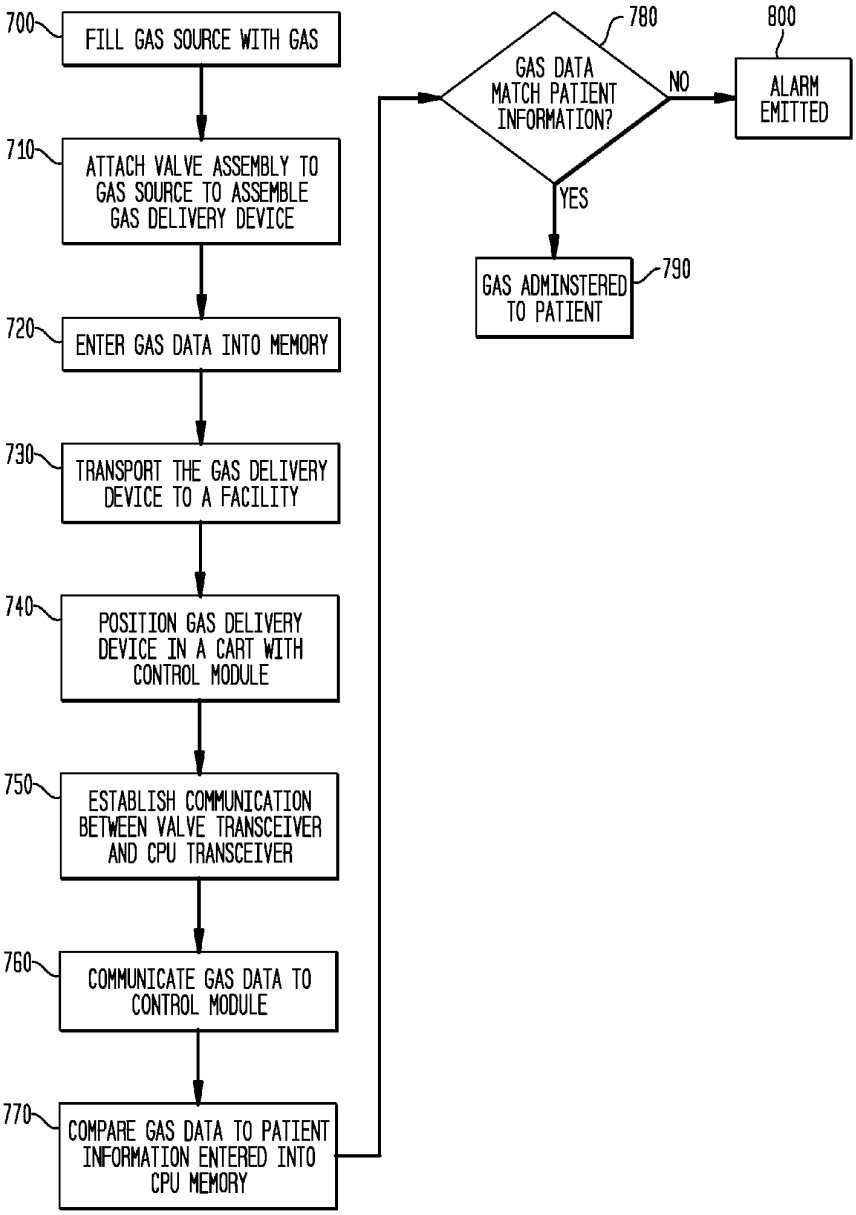

START
LINK IS VALID?
VALID
INVALID
READ CYLINDER CONCENTRATION & EXPIRATION IFORMATION
CYLINDER NOT RECOGNIZED (DISPLAY ICON NOT PRESENT)
CYLINDER VALID FOR USE?
INVALID
VALID
CYLINDER IS RECOGNIZED (NORMAL CYLINDER ICON ON DISPLAY)
CYLINDER IS RECOGNIZED (FLASHING CYLINDER ICON ON DISPLAY)
LINK IS VALID?
VALID
INVALID

FIG. 13


700
FILL GAS SOURCE WITH GAS
710
ATTACH VALVE ASSEMBLY TO GAS SOURCE TO ASSEMBLE GAS DELIVERY DEVICE
720
ENTER GAS DATA INTO MEMORY
730
TRANSPORT THE GAS DELIVERY DEVICE TO A FACILITY
740
POSITION GAS DELIVERY DEVICE IN A CART WITH CONTROL MODULE
750
ESTABLISH COMMUNICATION BETWEEN VALVE TRANSCEIVER AND CPU TRANSCEIVER
760
COMMUNICATE GAS DATA TO CONTROL MODULE
770
COMPARE GAS DATA TO PATIENT INFORMATION ENTERED INTO CPU MEMORY
780
GAS DATA MATCH PATIENT INFORMATION?
NO
800
ALARM EMITTED
YES
790
GAS ADMINSTERED TO PATIENT

NITRIC OXIDE DELIVERY DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. patent application Ser. No. 13/509,873 filed on May 15, 2012, which is the National Phase entry of PCT/US2011/020319, filed Jan. 6, 2011, the entire content of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

Embodiments of the present invention relate to gas delivery device for use in a gas delivery system for administering therapy gas and methods of administering therapy gas.

BACKGROUND

Certain medical treatments include the use of gases that are inhaled by the patient. Gas delivery devices are often utilized by hospitals to deliver the necessary gas to patients in need. It is important when administering gas therapy to these patients to verify the correct type of gas and the correct concentration are being used. It is also important to verify dosage information and administration.

Known gas delivery devices may include a computerized system for tracking patient information, including information regarding the type of gas therapy, concentration of gas to be administered and dosage information for a particular patient. However, these computerized systems often do not communicate with other components of gas delivery devices, for example, the valve that controls the flow of the gas to the computerized system and/or ventilator for administration to the patient. In addition, in known systems, the amount of gas utilized by a single patient is often difficult or impossible to discern, leading to possible overbilling for usage.

There is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is to be delivered by the gas delivery device. There is also a need for such an integrated device that does not rely on repeated manual set-ups or connections and which can also track individual patient usage accurately and simply.

SUMMARY

Aspects of the present invention pertain to a gas delivery device that may be utilized with a gas delivery system and methods for administering therapy gas to a patient. One or more embodiments of the gas delivery devices described herein may include a valve and a circuit with a valve memory in communication with a valve processor and a valve transceiver. One or more embodiments of the gas delivery systems described herein incorporate the gas delivery devices described herein with a control module including a central processing unit (CPU) in communication with a CPU memory and CPU transceiver. As will be described herein, the valve transceiver and the CPU transceiver may be in communication such that information or data from the valve memory and the CPU memory may be communicated to one another. The information communicated between the valve memory and the CPU memory may be utilized for selecting a therapy for delivery to a patient and controlling delivery of the selected therapy to the patient. The gas delivery devices and systems described herein may be utilized with medical devices such as ventilators and the like to delivery gas to a patient.

A first aspect of the present invention pertains to a gas delivery device. In one or more embodiments, the gas delivery device administers therapy gas from a gas source containing NO under the control of a control module. The control module may deliver the gas comprising NO to a patient in an amount effective to treat and/or prevent hypoxic respiratory failure and/or pulmonary hypertension. In one variant, the gas delivery device may include a valve attachable to the gas source and a circuit. The valve may include an inlet and an outlet in fluid communication and a valve actuator to open and close the valve to allow the gas to flow through the valve to a control module. The circuit of one or more embodiments includes a memory, a processor and a transceiver in communication with the memory to send wireless optical line-of-sight signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject. In one or more alternative embodiments, the signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject may be communicated via a wire. Examples of such wired signals may incorporate or utilize an optical cable, wired pair and/or coaxial cable. The circuit may include a memory to store gas data, which may include one or more of gas identification, gas expiration date and gas concentration. The transceiver may communicate to send the gas data to the control module via wireless optical line-of-sight signals.

In one or more embodiments, the valve may include a data input in communication with said memory, to permit a user to enter the gas data into the memory. The gas data may be provided in a bar code that may be disposed on the gas source. In such embodiments, the gas data may be entered into the data input of the valve for storage in the memory by a user-operated scanning device in communication with the data input. Specifically, the user may scan the bar code to communicate the gas data stored therein to the valve memory via the data input.

In one or more embodiments, the valve may include a power source. In such embodiments, the power source may include a battery or other portable power source. In one or more embodiments, the valve transceiver may periodically send the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent. In one or more specific embodiments, the duration of time at which no signal is sent comprises about 10 seconds.

A second aspect of the present invention pertains to a gas delivery device, as described herein, and a control module in fluid communication with the outlet of the valve of the gas delivery device and with a gas delivery mechanism, such as a ventilator. In one or more embodiments, the control module may include a CPU transceiver to receive line-of-sight signals from the transceiver and a CPU in communication with the CPU transceiver. The CPU carries out the instructions of a computer program or algorithm. As used herein the phrase "wireless optical line-of-sight signal" includes infrared signal and other signals that require a transmitter and receiver or two transceivers to be in aligned such that the signal may be transmitted in a straight line. The CPU may include a CPU memory that stores the gas data that is communicated by the valve transceiver of the gas delivery device to the CPU transceiver.

In one or more embodiments, the gas delivery system may incorporate a valve with a timer including a calendar timer

and an event timer for determining or marking the date and time that the valve is opened and closed and the duration of time the valve is opened. In such embodiments, the valve memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

In one or more variants, the gas delivery system may incorporate a control module that further includes an input means to enter patient information into the CPU memory. The control module may also have a real time clock built into the CPU module such that the control module knows what the current time and date is and can compare that to the expiration date stored in the gas delivery device. If the expiration date is passed the current date then the control module can cause an alarm and not deliver drug to the patient. When the term "patient information" is used, it is meant to include both patient information entered by the user and information that is set during manufacturing, such as the gas identification and the gas concentration that the control module is setup to deliver. The control module may also include a display. In one or more embodiments, the display incorporates an input means for entering patient information into the CPU memory. In one or more embodiments, the CPU of the control module compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver. The CPU or control module may include comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match or conflict. As used herein the phrase "do not match," includes the phrase "are not identical," "are not substantially identical," "do conflict" and/or "do substantially conflict." The CPU determines whether the patient information and additional data, or other data set matches by performing a matching algorithm which includes criteria for establishing whether one set of data (i.e. patient information) and another set of data match. The algorithm may be configured to determine a match where every parameter of the data sets match or selected parameters of the data sets match. The algorithm may be configured to include a margin of error. For example, where the patient information require a gas concentration of 800 ppm, and the additional data includes a gas concentration of 805 ppm, the algorithm may be configured to include a margin of error of ±5 ppm such it determines that the patient information and the additional data match. It will be understood that determining whether the patient information and additional data match will vary depending on the circumstances, such as variables in measuring gas concentration due to temperature and pressure considerations.

A third aspect of the present invention pertains to a control module memory comprising instructions that cause a control module processor to receive gas data from a valve via a wireless optical line-of-sight signal. The valve may be connected to a gas source containing NO and may include a memory for storing the gas data. The control module memory may include instructions that cause the control module processor to compare the gas data with user-inputted patient information. The user-inputted patient information may be stored within the control module memory. Gas data may be selected from one or more of gas identification, gas expiration date and gas concentration. In one or more embodiments, the control module memory may include instructions to cause the control module processor to coordinate delivery of therapy to the patient with a medical device, such as a ventilator and the like for delivering gas to a patient, via the wireless optical line-of-sight signal. The control module memory may also include instructions to cause the control module processor to select a therapy for delivery to a patient based on the received patient information and control delivery of the selected therapy to the patient.

In one or more embodiments, the memory may include instructions to cause the processor to detect the presence of more than one valve and whether more than one valve is open at the same time. In accordance with one or more specific embodiments, the memory includes instructions to cause the processor to receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas source, receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas source, compare the first valve status and the second valve status, and emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position. In one or more alternative embodiments, the first valve status and the second valve status may be communicated to the processor via a single wireless optical line-of-sight signal, instead of separate wireless optical line-of-sight signals. In a more specific embodiment, the memory of one or more embodiments may include instructions to cause the processor to terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

In one or more embodiments, the memory may include instructions to cause the processor to emit an alarm when a desired dose has been delivered through a valve. In such embodiments, the processor may include a memory to store the desired dose or dosage information. In such embodiments, the memory may include instructions to cause the processor to receive gas delivery information or information regarding the amount of gas delivered and compare the gas delivery information to the dosage information and emit an alarm when the gas delivery information and the dosage information match. As used herein, the term "dosage information" may be expressed in units of parts per million (ppm), milligrams of the drug per kilograms of the patient (mg/kg), millimeters per breath, and other units known for measuring and administering a dose. In one or more embodiments, the dosage information may include various dosage regimes which may include administering a standard or constant concentration of gas to the patient, administering a gas using a pulsed method. Such pulsing methods includes a method of administering a therapy gas to a patient during an inspiratory cycle of the patient, where the gas is administered over a single breath or over a plurality of breaths and is delivery independent of the respiratory pattern of the patient.

A fourth aspect of the present invention pertains to a method for administering a therapy gas to a patient. The therapy gas may comprise NO. In one or more embodiments, the method includes establishing communication between the patient and a gas delivery device via a transceiver, wherein the gas delivery device comprises a first memory including gas data, comparing the gas data with patient information stored within a second memory. The second memory may be included within a control module in communication with the gas delivery device. After comparing the gas data and the patient information, the method may further include coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal, selecting a therapy for delivery to the patient based on the comparison of the gas data and the patient information and controlling deliv-

ery of the selected therapy to the patient. In one or more specific embodiments, the method may include entering the gas data into the first memory of the gas delivery device and/or entering the patient information into the second memory. In embodiments in which the method includes entering the patient information into the second memory, the control module may include input means by which patient information may be entered into the second memory. In one or more variants, the method includes ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information. The method may include emitting an alert based on the comparison of the gas data and the patient information.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of a gas delivery system including a gas delivery device, a gas source, a control module and a gas delivery mechanism, according to one or more embodiments;

FIG. **2** illustrates a valve assembly of the gas delivery device according to one or more embodiments attached to a gas source;

FIG. **3** illustrates a disassembled view of the valve assembly shown in FIG. **2**;

FIG. **4** is a diagram showing a circuit supported in the valve assembly shown in FIG. **2**, according to one or more embodiments;

FIG. **5** illustrates an exemplary gas source for use with the valve assembly shown in FIG. **2**;

FIG. **6** is an operational flow diagram of the communication between the circuit of the gas delivery device shown in FIG. **1** with a control module regarding the establishment of communication between the circuit and the control module

FIG. **7** illustrates a front view of an exemplary gas delivery system;

FIG. **8** illustrates a back view of the gas delivery system shown in FIG. **7**;

FIG. **9** illustrates a partial side view of the gas delivery system shown in FIG. **7**;

FIG. **10** illustrates a front view of a control module according to one or more embodiments;

FIG. **11** illustrates a back view of the control module shown in FIG. **10**;

FIG. **12** is an operational flow diagram of the communication between the circuit of the gas delivery device and the control module shown in FIG. **1** regarding the gas contained within a gas source; and

FIG. **13** is an operational flow diagram of the preparation of a gas delivery device and use within the gas delivery system according to one or more embodiments.

DETAILED DESCRIPTION

Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

A system for the administration of therapy gas is described. A first aspect of the present invention pertains to a gas delivery device. The gas delivery device may include a valve assembly including at least one valve with a circuit. The gas delivery system may include the gas delivery device (e.g. valve assembly, including a valve and a circuit) in communication with a control module to control the delivery of gas from a gas source to a ventilator or other device used to introduce the gas into the patient, for example, a nasal cannula, endotracheal tube, face mask or the like. Gas source, as used herein, may include a gas source, gas tank or other pressured vessel used to store gases at above atmospheric pressure. The gas delivery system **10** is shown in FIG. **1**. In FIG. **1**, the valve assembly **100**, including a valve **107** or valve actuator and a circuit **150**, is in communication with a control module **200** via a wireless line-of-sight connection **300**. In one or more alternative embodiments, communication between the valve assembly **100** and the control module **200** may be established via a wired signal. The gas delivery system **10** also includes a gas source **50** including a gas attached to the valve assembly **100** and a gas delivery mechanism, which includes a ventilator **400** and a breathing circuit **410**, in communication with the control module **200**.

FIGS. **2-4** illustrate the components of the valve assembly **100**. The valve assembly **100** includes a valve **107** and a circuit **150** supported in the valve assembly. FIG. **3** illustrates a disassembled view of the valve assembly **100**, showing components of the physical circuit **150** and the valve **107**. As shown in FIG. **4**, which will be described in more detail below, the circuit **150** of the gas delivery device includes a valve transceiver **120** for establishing communication with the control module **200**, which will also be discussed in greater detail below.

Referring to FIG. **2**, the valve **107** includes an attachment portion **102** for attaching the valve assembly **100** to the gas source **50**, an inlet **104** and an outlet **106** in fluid communication with the inlet **104**, as more clearly shown in FIG. **2**.

FIG. **3** illustrates a disassembled view of the valve assembly **100** and illustrates an actuator **114** is disposed on the valve **107** and is rotatable around the valve **107** for opening and closing the valve **107**. The actuator **114** includes a cap **112** mounted thereto. As shown in FIG. **3**, the circuit **150** may include a data input **108** disposed on the actuator **114**. The data input **108** may be disposed at other locations on the valve **107**. In one or more variants, the data input may include a port such as a USB port, a receiver for receiving electronic signals from a transmitted or other known input means known in the art for entering information or data into a memory.

FIG. **4** illustrates a block diagram of the circuit **150**. The circuit **150** shown in FIG. **4** includes a valve processor **122**, a valve memory **134**, a reset **128**, a valve transceiver **120** and a power source **130**. The circuit **150** may also include support circuits a timer **124**, a sensor **126** and/or other sensors. Referring to FIG. **3**, the circuit **150** is supported within the valve assembly **100**, with the physical components of the circuit **150** specifically disposed between actuator **114** and the cap **112**. As shown in FIG. **3**, the valve display **132** and the valve transceiver **120** are disposed adjacent to the cap **112**, such that the valve display **132** is visible through a window **113**. The sensor **126** and the valve processor **122** are disposed beneath the valve display **132** and the valve transceiver **120**, within the actuator **114**.

The valve processor **122** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The valve memory **134**, or computer-readable medium, may be one or more of readily available memory such as electrically erasable programmable read only memory (EEPROM), random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the valve processor **122**. The support circuits may be coupled to the valve processor **122** for supporting the circuit **150** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like.

In the embodiment shown, the valve memory **134** communicates with a data input **108** disposed on the side of the actuator **114**. The data input **108** shown in FIGS. **3-4** is used to transfer data from the valve memory **134** to other devices or to input data into the valve memory **134**. For example, gas data, which includes information regarding the gas contained within the gas source, may be entered into the valve memory **134** via the data input **108**. In one or more alternative embodiments, the gas data may be programmed or directly entered into the valve memory **134** by the gas supplier. In one or more embodiments, the gas data may be provided in the form of a bar code **610** that is disposed on a label **600** that is affixed on a to the side of the gas source, as shown in FIG. **5**. The bar code **610** may be disposed directly on the gas source. An external scanning device in communication with the electronic data input **108** may be provided and may be used to scan the bar code **610** and convey the information from the bar code **610** to the valve memory **134**. Gas data may include information regarding the gas composition (e.g., NO, O_2, NO_2, CO, etc.), concentration, expiration date, batch and lot number, date of manufacturing and other information. Gas data may be configured to include one or more types of information. The valve processor **122** may include instructions to convey all or a pre-determined portion of the gas data via the valve transceiver **120** to another transceiver.

In embodiments that utilize a timer **124**, the timer **124** may include two sub-timers, one of which is a calendar timer and the other of which is an event timer. The reset **128** may be located inside the actuator **114** and may be depressed to reset the event timer. The cap **112** also includes a window **113** that allows the user to see the valve display **132** disposed within the cap **112** that displays information regarding whether the actuator **114** is opened or closed and the duration the valve **107** was opened or closed. In one or more embodiments, the valve display **132** may alternate flashing of two different numbers, a first number may be accumulated open time, and the second number may be the time at which the valve **107** was opened for the current event. The time at which the valve **107** was opened for a current event may be preceded by other indicators.

The sensor **126** disposed within the actuator **114** may include a proximity switch model MK20-B-100-W manufactured by Meder Inc. The sensor **126** utilized in one or more embodiments may cooperate with a magnet (not shown) to sense whether the actuator **114** is turned on or turned off. Such sensors are described in U.S. Pat. No. 7,114,510, which is incorporated by reference in its entirety.

For example, the sensor **126** and a corresponding magnet (not shown) may be disposed on a stationary portion of the valve **107**. When the actuator **114** is rotated to the closed position, the sensor **126** is adjacent to the magnet that is in a fixed position on the valve **107**. When the sensor **126** is adjacent to the magnet, it sends no signal to the valve processor **122**, thereby indicating that the actuator **114** is in the "closed" position or has a valve status that includes an open position or a closed position. When the actuator **114** is rotated to open the valve **107**, the sensor **126** senses that it has been moved away from the magnet and sends a signal to the valve processor **122**, indicating an "open" position. The valve processor **122** instructs the valve memory **134** to record the event of opening the valve **107** and to record the time and date of the event as indicated by the calendar timer. The valve processor **122** instructs the valve memory **134** to continue checking the position of the valve **107** as long as the valve **107** is open. When the valve **107** is closed, the valve processor **122** uses the logged open and close times to calculate the amount of time the valve **107** was open and instructs the valve memory **134** to record that duration and the accumulated open time duration. Thus, every time the valve **107** is opened, the time and date of the event is recorded, the closing time and date is recorded, the duration of time during which the valve **107** is open is calculated and recorded, and the accumulated open time is calculated and recorded.

In one or more embodiments in which the power source **130** includes a battery, the valve transceiver **120** may be configured to communicate with the CPU transceiver **220** to preserve the life of the battery. In this embodiment the valve transceiver **120** is only turned on to receive a signal from the Control Module CPU transceiver **220** for 20 msec every second. The control module CPU transceiver **220** sends out a short transmit signal continuously and if the valve transceiver **120** is present it responds in the 20 msec interval. This conserves battery power as the valve transceiver **120** is only powered on for 20 msec every second. When the valve transceiver **120** responds it includes in its signal information regarding whether the communication from the control module CPU transceiver **220** was early or late within this 20 msec window. This ensures that once communications has been established it is synchronized with the 20 msec window that the valve transceiver **120** is powered on and able to receive communications. For example, as shown in FIG. **6**, the valve transceiver **120** sends a wireless optical line-of-sight signal during a pre-determined interval in response to a signal from the control module CPU transceiver **220**. The wireless optical line-of-sight signals sent by the valve transceiver **120** are a series of on off cycles where the transmitter is either transmitting light or is not and these correspond to digital binary signals. The mechanism by which the valve transceiver sends a wireless optical line-of-sight signal may be construed as a series of digital on off signals that correspond to data being transmitted. Once communications has been established between the control module CPU transceiver **220** and the valve transceiver **120**, the interval between communication signals may be in the range from about 20 seconds to about 5 seconds. In one or more specific embodiments, the interval or duration between transceiver signals may be about 10 seconds.

As will be described in more detail below, the control module **200** includes a CPU **210** which is connected to a CPU transceiver **220** which can send and receive wireless optical line-of-sight signals. The CPU transceiver **220** sends out a signal and waits for a response from the valve transceiver **120** when communication or more specifically, line-of-sight communication is established between the CPU transceiver **220** and the valve transceiver **120**. If no response is sent by the valve transceiver **120**, the CPU transceiver **220** sends another signal after a period of time. This configuration preserves battery life because the valve transceiver **120** does not continuously send a signal unless requested to by the CPU **210**. This is important as the gas delivery device and gas source spends most of its time in shipping and storage prior to being placed on the gas delivery system, if it was transmitting all this time trying to establish communications with the control module it would be consuming the battery life significantly.

The valve processor **122** may include link maintenance instructions to determine whether the interval should be increased or decreased. As shown in FIG. **6**, when a valid link is established between the valve transceiver **120** and CPU transceiver **121**, the valve processor **122** executes the link maintenance instructions to increase the interval or decrease the interval.

As shown more clearly in FIG. **1**, valve assembly **100** and gas source **50** is in communication with a control module **200**, which is in communication with a gas delivery mechanism.

The gas delivery mechanism shown in FIG. **1** includes a ventilator **400** with associated breathing circuit **410**. The control module **200** may include a CPU **210** and a CPU transceiver **220** in communication with the circuit **150** via the valve transceiver **120**. The control module **200** also includes a CPU memory **212** in communication with the CPU transceiver **220** to store patient information, information or data received from the valve transceiver **120** and other information. The control module **200** may also include support circuits. The CPU **210** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The CPU memory **212**, or computer-readable medium, may be one or more of readily available memory such as random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the CPU **210**. The support circuits may be coupled to the CPU **210** for supporting the control module **200** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like. The CPU **210** may also include a speaker **214** for emitting alarms. Alternatively, alarms may also be displayed visually on a display. As shown in FIG. **1**, the control module **200** may also include a regulator **110** and, optionally, pressure gauges and flow meters for determining and/or controlling the gas flow from the gas source **50**.

In one or more embodiments, the CPU transceiver **220** is disposed on a cover portion **225** (shown more clearly in FIG. **7**), that is part of a cart **500** (show more clearly in FIG. **7**) onto which the control module **200** is disposed. The cover portion **225** in one or more embodiments is in communication with the control module **200**. Communication between the cover portion **225** and the control module **200** may be established wirelessly or via a cable. As will be discussed in greater detail below, the valve assembly **100**, including the valve **107**, the circuit **150** and a gas source **50** attached to the valve **107**, are placed on the cart **500** in proximity and in a light-of-sight path with the CPU transceiver **220**. When properly configured such that communication is established between the valve transceiver **120** and the CPU transceiver **220**, the CPU transceiver **220** is positioned directly above the valve transceiver **120**, as shown more clearly in FIG. **9**. In one or more alternative embodiments, the CPU transceiver **220** may be disposed on the CPU **210**.

The CPU **210** may be in communication with a plurality of gas sensors **230** for determining the concentration of a sample of gas drawn via a sample line **232** and a sample line inlet **280** (shown more clearly in FIG. **1**) disposed on the control module **200**. As will be discussed in greater detail, the sample line **232** draws a sample of gas from a breathing circuit **410** of a ventilator **400** when the ventilator is in fluid communication with the control module **200** and gas is being delivered to the ventilator. The CPU **210** may also be in communication with a sample flow sensor **234** for sensing the flow of the sample drawn via sample line **232**, a pump **236** for drawing the sample via the sample line **232** to the flow sensor **234** and zero valve **238** controlling the flow of the sample via the sample line **232** to the sample pump **236**, sample flow sensor **234** and the plurality of CPU sensors. The sample line **232** may include a water trap **233** for collecting any water or liquid from the sample.

The control module **200** may also include a delivery module **260** for regulating the flow of gas from the gas source **50** to the ventilator **400**. The delivery module **260** may include a pressure switch **262** for determining a gas supply pressure is present, a pressure shut-off valve **264**, a proportional valve **266** and a delivery flow sensor **268**. The delivery module **260** may also include a backup on/off switch **269**. The detailed method of how the delivery module delivers the gas to the ventilator circuit is described in U.S. Pat. No. 5,558,083 which is incorporated here by reference in its entirety.

The ventilator **400** shown in FIG. **1** is in fluid communication with the control module **200** via an injector tubing **440** and in electrical communication via an injector module cable **450**. The control module **200** and more specifically, the CPU **210**, is in fluid communication with the ventilator **400** via the sample line **232**. The ventilator **400** may include a breathing circuit **410** with an inspiratory limb **412** and an expiratory limb **414** in fluid communication with the ventilator **400**. The inspiratory limb **412** may be in fluid communication with a humidifier **420**, which is in fluid communication with the ventilator **400** via an injector module **430**. The inspiratory limb **412** carries gas to the patient and the expiratory limb **414** carries gas exhaled by the patient to the ventilator **400**. The injector module **430** shown in FIG. **1** is in fluid communication with the gas source **50** via the injector tubing **440** and in electronic communication with the delivery module **260** via the injector module cable **450** such that the delivery module **260** can detect and regulate the flow of gas from the gas source **50** to the ventilator **400**. Specifically, the injector module **430** is in fluid communication with the gas source **50** via an injector tubing **440**, which is in fluid communication with one or more of the pressure switch **262**, pressure shut-off valve **246**, proportional valve **266**, flow sensor **268** and the backup switch **269** of the delivery module **260**. The injector module **430** may also be in electronic communication with the delivery module **260** via the injector module cable **450**. The inspiratory limb **412** of the ventilator **400** may include a sample tee **416** for facilitating fluid communication between the inspiratory limb **412** of the breathing circuit and the sample line **232**.

As discussed above, the control module **200** may be disposed or attached on a cart **500**, as shown in FIGS. **7-9** to facilitate movement of the gas source **50** and the gas delivery device to a patient in need of gas therapy. The gas source **50** and the valve assembly **100** attached thereto may be placed on the cart **500** in proximity to the control module **200**. More specifically, as shown in FIG. **7**, the gas source **50** is placed on the cart **500** such that the valve transceiver **120** is in proximity of the CPU transceiver **220** and a line-of-sight path is established between the valve transceiver **120** and the CPU transceiver **220**. In this configuration, the CPU **210** detects the presence of the circuit **150** and thus the gas source **50** via the CPU transceiver **220**.

As shown in FIGS. **7-9**, the gas delivery device may include more than one valve, with each valve being attached to a single gas source. In such embodiments which utilize a second gas source **60** with a second valve assembly **101**, the second valve assembly **101** is positioned in proximity and in a light-of-sight path with a second CPU transceiver as the gas source **60** is loaded onto the cart. The second CPU transceiver **222** establishes communication with the second valve assembly **101** and thus detects the presence of a second gas source **60**. In the embodiment shown in FIGS. **7-9**, the second CPU transceiver **222** may also be disposed on the cover portion **225** of a cart. In one or more alternative embodiments, the second CPU transceiver **222** may be disposed on the CPU **210**.

As shown in FIG. **8**, the cart **500** may include an optional small bin **510**, a mount **512** for supporting the control module **200** on the cart **500**, at least one a holding bracket **520**, at least one mounting strap **530**, an auxiliary bracket **540**, for holding an auxiliary gas source, a plurality of casters **550** and a caster lock lever **560** disposed on each of the plurality of casters **550**.

The cart **500** may include a mount **570** for mounting the control module **200** on to the cart.

An exemplary control module **200** is shown in FIGS. **10-12** includes a display **270** for providing visual indication to the user the components of the gas being delivered from the gas source **50** to the ventilator **400** (e.g., NO, O_2, NO_2), the concentration of each component and whether communication has been established with one or more gas sources. Other information may also be displayed to the user. In addition, visual alarms may also be displayed on the display **270**. The control module **200** may also include a main power indicator **272** indicating whether the control module is connected to a power source, such as an AC/DC power source and/or a battery. The control module **200** may also include a control wheel **274** allowing the user to navigate through various displays or information displayed on the display. An injection module tubing outlet **276** may be disposed on the control module for providing fluid communication between the delivery module **260** and the injector module **430**. An injection module cable port **278** may also be provided on the control module to provide electronic communication between the delivery module **260** and the injector module **430**. The control module **200** shown in FIGS. **10-12** also includes the sample line inlet **280** in fluid communication with the sample line **232** and the inspiratory limb **412** of the ventilator **400**. In the embodiment shown in FIGS. **10-12**, the water trap **233** is disposed on the control module, adjacent to the sample line inlet **280**.

FIG. **11** illustrates a back view of the control module **200** and shows a plurality of inlets. In the embodiment shown, two gas inlets **282**, **284** for connecting the control module **200** to the gas source **50** are provided and one auxiliary inlet **286** for connecting the control module **200** to an auxiliary gas source, which may include oxygen or other gas. A power port **288** is also provided on the back of the control module to connect the control module to an AC/DC power source.

The control module **200** may also include an input means **290** for allowing the user to enter patient information, for example the identity of the patient, the type and concentration of the gas and dose of the gas to be administered to the patient, the patient's disease or condition to be treated by the gas or reason for treatment, gestational age of the patient and patient weight. The input means **290** shown in FIG. **12** includes a keyboard integrated with the display. In one or more alternative embodiments, the input means may include a USB port or other port for the connection of an external keyboard or other input mechanism known in the art. The information entered via the input means **290** is stored within the CPU memory **212**.

The control module **200** and the valve assembly **100** may be utilized in the gas delivery system **10** to improve patient safety. Specifically, the safety benefits of the gas delivery system described herein include detecting a non-confirming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like. In addition, embodiments of the gas delivery system described herein also improve efficiency of gas therapy.

FIG. **13** is a block diagram showing the sequence of how gas delivery device, including the valve assembly **100**, may be provided and its use within the gas delivery system **10**, according to one or more embodiments. As shown in FIG. **13**, the gas delivery device **10** is prepared for use by providing a gas source **50** in the form of a gas cylinder or other container for holding a gas and filling the gas source **50** with a gas (**700**) and attaching a valve assembly **100** as described herein, to assemble the gas delivery device **10** (**710**). These steps may be performed by a gas supplier or manufacturer. The gas data regarding the gas filled within the gas source **50** is entered into the valve memory **134** as described herein (**720**). The gas data may be entered into the valve memory **134** by the gas supplier or manufacturer that provides the gas source **50** and assembles the gas delivery device **10**. Alternatively, the hospital or other medical facility may enter the gas data into the valve memory **134** after the gas delivery device has been transported to the hospital or medical facility (**730**). The gas delivery device **10** is positioned on a cart **500** (**740**) and communication between the CPU transceiver **220** and the valve transceiver **120** is established (**750**). The gas data stored within the valve memory **134** is conveyed to the control module **200** (**760**) via the wireless optical line-of-sight communication between valve transceiver **120** and the CPU transceiver **220**. The CPU **210** compares the gas data to patient information entered into the CPU memory **212** (**770**). The patient information may be entered into the CPU memory after the gas data is entered into the CPU memory **212**. The patient information may be entered into the CPU memory before the gas delivery device **10** is positioned in the cart or before communication between the CPU transceiver **220** and the valve transceiver is established. In one or more alternative embodiments, the patient information may be entered into the CPU memory **212** before the gas delivery device **10** is prepared or transported to the hospital or facility. The CPU **210** then compares whether the gas data and the patient information match (**780**). If the gas data and the patient information match, then gas is administered to the patient (**790**), for example through a ventilator or other gas delivery mechanism. If the gas data and the patient information do not match, then an alarm is emitted (**800**). As described otherwise herein, the alarm may be audible and emitted through the speaker **214** and/or may be visual and displayed on the display **270**.

The gas delivery system described herein simplifies set-up procedures by utilizing wireless line-of-sight signals to establish communication. The user does not need to ensure all the cables are correct connected and can freely load new gas sources onto a cart without disconnecting cables linking the control module **200** and the valve assembly **100** or circuit **150**. This reduces set-up time and any time spent correcting errors that may have occurred during the set-up process. The control module **200** and the circuit **150** are further designed to automatically send and detect information to establish delivery of a correct gas having the correct concentration and that is not expired. In one or more specific embodiments, such automated actions prevent the use of the gas delivery system by preventing gas flow to a patient, without user intervention.

In one or more embodiments, after communication between the valve transceiver **120** and the CPU transceiver **220** is established, the valve processor **122** includes instructions to convey the gas data stored in the valve memory **134** via the valve transceiver **120** to the CPU transceiver **220**. The CPU **210** includes instructions to store the gas data received from the CPU transceiver **220** in the CPU memory. The CPU **210** also includes an algorithm that compares the gas data with patient information that is entered into the CPU memory **212**. If the gas data and the patient information do not match, the CPU **210** includes instructions to emit an alarm, which may be audible, visual or both, alerting the user that the gas contained within the gas source is different from the gas to be administered to the patient. For example, as illustrated in FIG. **12**, if the gas data includes gas expiration date, the CPU memory **212** includes information regarding the current date and the CPU **210** compares the gas expiration date with the current date. If the gas expiration date is earlier than the current date, the CPU **210** emits an alarm. The alarm may be emitted through one or both the speaker **214** and display **270**.

In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of an expired gas by the CPU **210** may be stored within the CPU memory **212**.

If the gas data includes gas concentration information or data, the CPU memory **212** includes information regarding the desired concentration of gas to be administered to the patient. The control module **200** may be configured to alert the user that the gas contained within a gas source has incorrect concentration or a concentration that does not match the desired gas concentration. For example, a user may enter a concentration of **800** ppm into the CPU memory **212** and this concentration is compared to the gas concentration conveyed from the valve memory **134** to the CPU memory **212**. As illustrated in FIG. **12**, the CPU **210** includes instructions to compare the gas concentration of the gas with the concentration entered by the user. If the gas concentration does not match the concentration entered by the user, the CPU **210** emits an alarm, which may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of a gas with incorrect concentration may be stored within the CPU memory **212**.

In one or more embodiments, the control module **200** may be configured to detect more than one valve and to detect whether more than one valve is turned on. This configuration eliminates waste because it alerts a user that both valves are turned on and thus unnecessary gas is being delivered to via the delivery module **260**. In addition, such a configuration improves safety because it avoids the issues related to having two regulators pressurized at the same time and connected to the delivery module **260**. In one or more embodiments, the cover portion **225** of the control module **200** may include a second CPU transceiver **222** and the CPU **210** may include instructions for the second CPU transceiver **222** to detect wireless optical line-of-sight signals from a second valve assembly **101**, and more specifically, a second valve transceiver **121**. The CPU **210** may also include instructions that once a second valve assembly **101** is detected by the CPU transceiver **222**, whether both valve assemblies **100**, **101** are opened or have a valve status that includes an open position. In operation, a first valve assembly **100** includes a circuit with a valve processor with instructions to covey an open or closed position via the first valve transceiver **120**. The circuit of the second valve assembly similarly includes a valve processor with instructions to convey an open or closed position via a second valve transceiver **121**. The first CPU transceiver **220** and the second CPU transceiver **222** detect the valve statuses for each respective valve assembly from the first valve transceiver **120** and the second valve transceiver **121** via the wireless optical line-of-sight signals sent by both transceivers. The CPU **210** instructs the CPU transceivers **220**, **222** to collect the valve statuses for both valve assemblies **100**, **101** and the memory to store the valve statuses. The CPU **210** then compares the valve status information from the first valve assembly **100** and the second valve assembly **101** and, if the valve statuses both comprise an open position, the CPU **210** emits an alarm. The alarm may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas through either the first valve assembly or the second valve assembly. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas. The detection that more than one valve assembly had a valve that was turned on or had a valve status including an open position may be stored within the CPU memory.

In one or more embodiments, the control module **200** may be configured to alert a user when the desired dose has been delivered. In such embodiments, the patient information entered into the CPU memory **212** may include dosage information or the dose to be delivered to a patient. The valve processor **122** may include instructions to convey gas usage information from the valve memory **134**, including the amount of gas delivered, to the CPU memory **212** via the valve transceiver **120**. Alternatively, the valve processor **122** may include instructions to covey the duration of time the valve **170** has been turned on or has a valve status including an open position to the CPU memory **212** via the valve transceiver **120**. The CPU **210** may include instructions to compare the dosage information entered by the user and stored within the CPU memory **212** with the gas usage information. The CPU **210** may include instructions to emit an alarm when the dosage information and the gas usage information match. The CPU **210** may include instructions to emit the same or different alarm to alert the user to turn off the valve or, more specifically, the actuator **114** when the dose has been delivered. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas.

In addition, the control module **200** may be configured to alert the user that a detected valve is and remains closed and no gas is being delivered to the patient. This configuration expedites treatment time and increases efficiency for the hospital. In such embodiments, the valve processor **122** may include instructions for the valve transceiver **120** to convey the valve status to the CPU **210** via a wireless optical line-of-sight signal. The CPU **210** includes instructions to collect the valve status information and emit an alert if the dosage information is set or other input has been entered into the CPU memory **212** to commence treatment and the valve status includes a closed position.

The control module **200** may be configured to alert the user that no valve assembly or gas source has been detected. In such embodiments, the CPU **210** includes instructions to detect the presence of a wireless optical line-of-sight signal from another transceiver, for example, the valve transceiver **120**. The CPU **210** may include instructions to emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected. Similarly, the control module **200** may be configured to emit an alarm if communication between one or both of the CPU transceiver (s) **220**, **222** and one or both of the valve transceivers **120**, **121** has been lost during gas delivery. In such embodiments, the CPU **210** may include instructions to continuously detect the presence of a signal from another transceiver and emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected.

The CPU **210** may include instructions to alert a user when sensors in the control module **200** must be calibrated to ensure accurate delivery of gas to a patient. In addition, the CPU **210** may include instructions to correlate gas usage information

from the circuit **150** of the valve assembly **100** to the patient information entered into the CPU memory **212**. The CPU **210** may also have instructions to store the correlated gas usage information and the patient information in the CPU memory **212**. The valve processor **122** may also include instructions detect patient information from the CPU memory **212**. Specifically, the valve processor **122** may include instructions to collect patient information via the valve transceiver **120** from the CPU transceiver **220** and store the collected patient information in the valve memory **134**. In such embodiments in which information from the CPU **210** is collected and stored in the valve memory **134**, the CPU **210** may include instructions that the patient information and/or correlated patient information and gas usage information be conveyed from the CPU memory **212** via the CPU transceiver **220** to the valve transceiver **120**. The valve processor **122** may also include instructions to correlate gas usage information with the collected patient information and store the correlated gas usage information and collected patient information in the valve memory **134**. Alternatively, the valve processor **122** may include instructions to collect the correlated patient information and gas usage information from the CPU **210**. The correlated information may be utilized to bill the user according to patient. In addition, the correlated information may be utilized as patient demographic data, which can assist hospitals or other facilities to generate budget reports, determine usage per department, determine usage per patient diagnosis and link usage of multiple gas sources to individual patients.

In one or more embodiments, the gas used for treatment comprises nitric oxide. Nitric oxide relaxes vascular smooth muscle and when inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature. Accordingly, nitric oxide may be used to treat or prevent pulmonary hypertension and/or hypoxic respiratory failure in a patient by administering an effective amount of a gas comprising nitric oxide. As used herein, a patient refers to a mammal at risk for developing or diagnosed with the referenced disorder. According to one or more embodiments, the patient is a human. In some embodiments, the patient may be term or near-term neonate (i.e. >34 weeks).

Nitric oxide is commercially available as INOmax® from Ikaria, Inc. INOmax® is currently indicated for the treatment of term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiological evidence of pulmonary hypertension.

The gas source may comprise a container having a gas comprising nitric oxide. The nitric oxide may be stored in a carrier gas, such as nitrogen, with a known concentration of nitric oxide. In some embodiments, the nitric concentration in the container may be in the range from 20 ppm to 10,000 ppm or from 100 ppm to 5000 ppm. Exemplary nitric oxide storage concentrations include 100 ppm, 800 pm, 2440 ppm and 4880 ppm. The concentration of nitric oxide delivered to the patient's lungs may vary depending on the patient or the condition treated, but generally may be in the range from 5 ppm to 100 ppm for preventing or treating various forms of pulmonary hypertension and/or hypoxic respiratory failure. In one or more embodiments, the nitric oxide is delivered at a concentration of about 20 ppm. In some embodiments where the condition being treated or prevented is hypoxic respiratory failure, the nitric oxide concentration may be delivered at a dose of about 20 ppm.

A second aspect of the present invention pertains to a method for administering a therapy gas to a patient. The method includes providing a gas in a gas source. The gas source may be prepared by a supplier to contain a gas having a predetermined composition, concentration and expiration date. The method may include providing a valve assembly **100** attached to a gas source **50** to dispense the gas contained within the gas source **50** to a patient. The method may include entering gas data, which may include gas composition, gas concentration and gas expiration date, into the valve memory **134**. In one or more embodiments, the supplier may enter the gas data directly into the valve memory **134**. In another variant, the gas data is provided in the form of a bar code disposed on the gas source. In such embodiments, the method includes providing a scanner in communication with the data input **108**, scanning the bar code to collect the gas data information and conveying the gas data to the valve memory **134** via the data input **108**. These steps may be repeated for a second gas source. The gas source(s), with the valve assembly mounted thereon may be transported to a hospital or other facility for administration to a patient. The gas source(s) are then mounted onto the cart **500** and secured by the holding bracket **520** and mounting strap **530**. The method includes establishing communication between the valve transceivers disposed on each valve and the CPU transceivers **220**, **222**. Establishing communication may include positioning the valve assembly **100** in a line-of-sight path with at least one of the CPU transceivers **220**, **222**. As otherwise described herein, communication may be established by instructing the valve transceivers to send a wireless optical line-of-sight signal to the CPU transceivers **220**, **222**. The method may include instructing the valve transceiver **120** to send a wireless optical line-of-sight signal at pre-determined intervals, as otherwise described herein.

The method may include entering patient information into the CPU memory **212**. This step may be performed before or after the gas source(s) are mounted onto the cart. The method may specifically include entering patient information such as dosage information into the valve memory **134**. The method includes coordinating delivery of the gas to the patient by collecting gas data from the valve memory **134** and comparing the gas data with the patient information according to an algorithm and determining if the gas data and patient information match, according to the algorithm. Coordinating delivery of the gas may include turning on the actuator **114** of the valve **107** such that gas can flow from the inlet **104** to the outlet **106**. After the dose has been delivered, the method may include correlating the gas usage information and the patient information. The method may also include recording the patient information, gas usage information and/or the correlated patient information and gas usage information in the CPU memory **212** and/or the valve memory **134**. In one or more variants, the method may include utilizing the patient information, gas usage information and/or correlated patient information and gas usage information to generate invoices identifying the use of the gas by individual patients.

Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

Although the invention herein has been described with reference to particular embodiments, it is to be understood

that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A nitric oxide delivery device comprising:

a control module to deliver a gas comprising NO to a patient in an amount effective to treat or prevent hypoxic respiratory failure; and

a valve assembly to deliver the gas comprising NO from a gas container containing the gas comprising NO to the control module, the valve assembly comprising:

a valve attachable to the gas container containing the gas comprising NO, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas comprising NO through the valve to the control module; and

a circuit supported within the valve assembly and disposed between the actuator and a cap, the circuit including:

a valve memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration in the gas container and

a valve processor and a valve transceiver in communication with the valve memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired.

2. The nitric oxide delivery device of claim **1**, where in the valve assembly further comprises a data input disposed on the actuator and in communication with said valve memory, to permit a user to enter the gas data into the valve memory.

3. The nitric oxide delivery device of claim **2**, wherein the gas data is provided in a bar code disposed on the gas container and is entered into the data input by a user-operated scanning device in communication with the data input.

4. The nitric oxide delivery device of claim **1**, wherein the valve comprises a power source; and the valve transceiver periodically sends the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent.

5. The nitric oxide delivery device of claim **4**, wherein the duration of time at which no signal is sent comprises about 10 seconds.

6. The nitric oxide delivery device of claim **1**, wherein the control module comprises:

a CPU transceiver to receive line-of-sight signals from the valve transceiver;

a central processing unit (CPU) in communication with the CPU transceiver and including a CPU memory; and

a display to enter patient information into the CPU memory,

wherein the valve transceiver communicates the gas data to the CPU transceiver for storage in the CPU memory, and wherein the CPU compares the patient information entered into the CPU memory via the display and the gas data from the valve transceiver.

7. The nitric oxide delivery device of claim **6**, wherein the valve comprises a timer including a calendar timer and an event timer, wherein the valve memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

8. The nitric oxide delivery device of claim **6**, wherein the CPU comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the valve transceiver do not match.

9. The nitric oxide delivery device of claim **6**, wherein the CPU memory comprises instructions that cause the CPU processor to: receive gas data from the valve via a wireless optical line-of-sight signal with the valve connected to the gas container containing gas comprising NO; compare the gas data with user-inputted patient information; coordinate delivery of therapy to the patient with a medical device via the wireless optical line-of-sight signal between the CPU transceiver and the valve transceiver; select a therapy for delivery to a patient based on the received patient information; and control delivery of the selected therapy to the patient.

10. The nitric oxide delivery device of claim **9**, wherein the CPU memory further comprises instructions that cause the CPU processor to:

receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas container;

receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas container;

compare the first valve status and the second valve status; and

emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position.

11. The nitric oxide delivery device of claim **10**, wherein the memory further comprises instructions that causes the CPU processor to:

terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

12. A method for treating or preventing hypoxic respiratory failure in a patient, the method comprising:

providing the nitric oxide delivery device of claim **6**;

establishing communication between the valve transceiver and the CPU transceiver and communicating the gas data from the valve transceiver to the CPU;

comparing the gas data communicated from the valve transceiver with patient information stored within the CPU memory; and

delivering the gas comprising NO to the patient in an amount effective to treat or prevent hypoxic respiratory failure.

13. The method of claim **12**, further comprising ceasing delivery of the gas comprising NO to the patient based on the comparison of the gas data and the patient information.

14. The method of claim **12**, further comprising emitting an alert based on the comparison of the gas data and the patient information.

15. The method of claim **12**, further comprising entering the gas data into the valve memory.

16. The method of claim **12**, further comprising entering the patient information into the CPU memory.

* * * * *

EXHIBIT H

US008573209B2

(12) **United States Patent**
Bathe et al.

(10) **Patent No.: US 8,573,209 B2**
(45) **Date of Patent: *Nov. 5, 2013**

(54) **GAS DELIVERY DEVICE AND SYSTEM**

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(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(86) PCT No.: **PCT/US2011/020319**

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(2), (4) Date: **Jun. 11, 2012**

(87) PCT Pub. No.: **WO2012/094008**

PCT Pub. Date: **Jul. 12, 2012**

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A62B 9/02 (2006.01)
F16K 31/02 (2006.01)

(52) **U.S. Cl.**
USPC **128/205.24**; 128/203.14; 128/204.21

(58) **Field of Classification Search**
USPC 128/203.12, 203.14, 204.18, 128/204.21–201.23, 205.24
See application file for complete search history.

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Primary Examiner — Justine Yu
Assistant Examiner — Michael Tsai
(74) *Attorney, Agent, or Firm* — Servilla Whitney LLC

(57) **ABSTRACT**

A gas delivery system including a gas delivery device (**100**), a control module (**200**) and a gas delivery mechanism is described. An exemplary gas delivery device includes a valve (**107**) assembly with a valve and circuit including a memory (**134**), a processor (**122**) and a transceiver (**120**) in communication with the memory. The memory may include gas data such as gas identification, gas expiration and gas concentration. The transceiver on the circuit of the valve assembly may send wireless optical line-of-sight signals to communicate the gas data to a control module. Exemplary gas delivery mechanisms include a ventilator (**400**) and a breathing circuit (**410**). Methods of administering gas are also described.

7 Claims, 12 Drawing Sheets

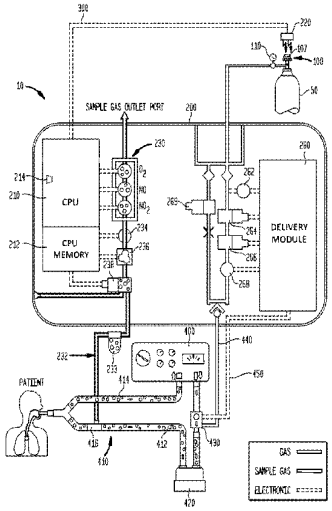

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FIG. 1

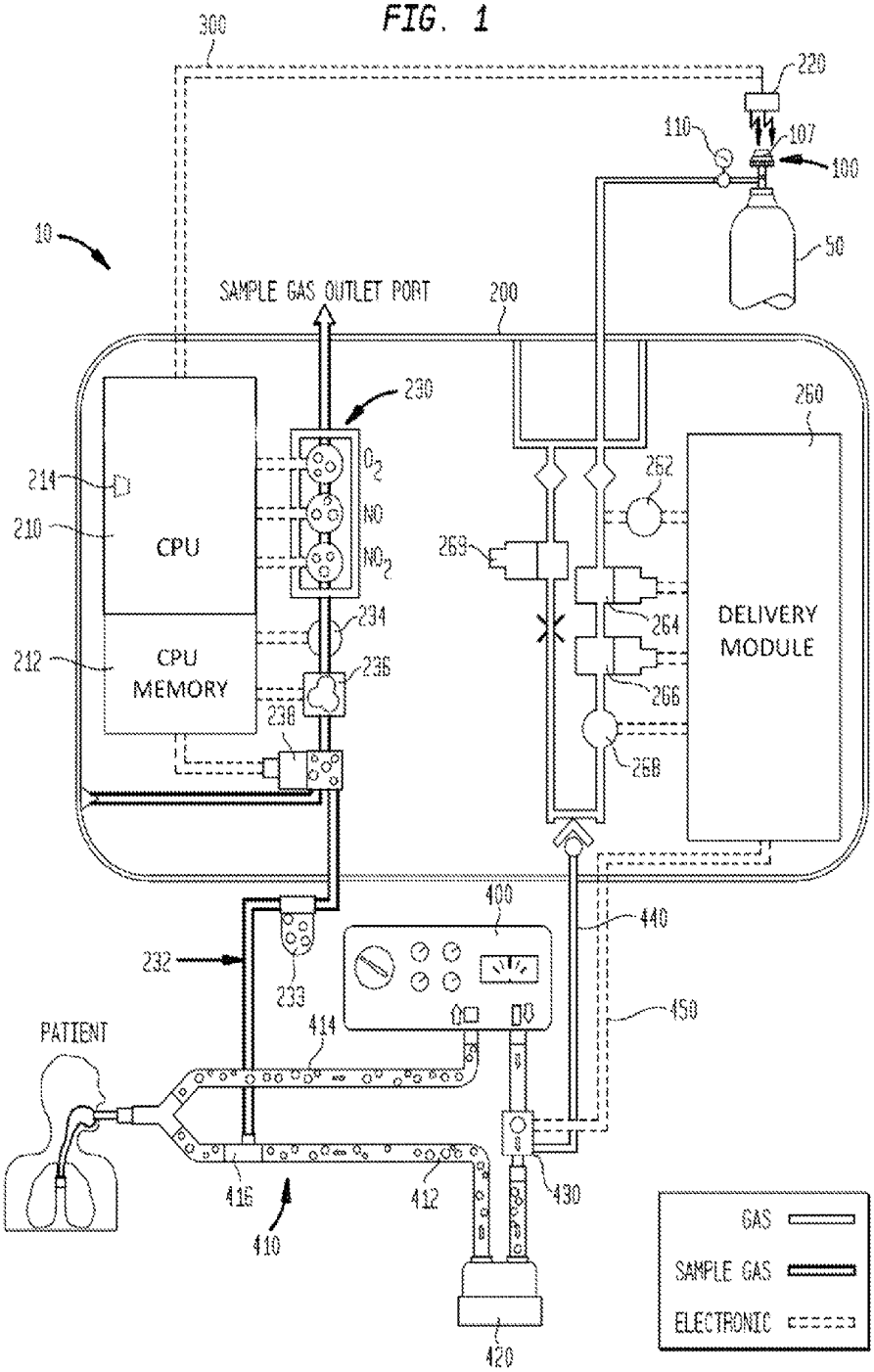

300
220
110
107
100
10
50
SAMPLE GAS OUTLET PORT
200
230
260
214
210
CPU
O_2
NO
NO_2
262
268
264
DELIVERY MODULE
212
CPU MEMORY
234
236
238
266
268
400
440
232
233
450
414
PATIENT
416
412
430
410
420
GAS
SAMPLE GAS
ELECTRONIC

FIG. 2

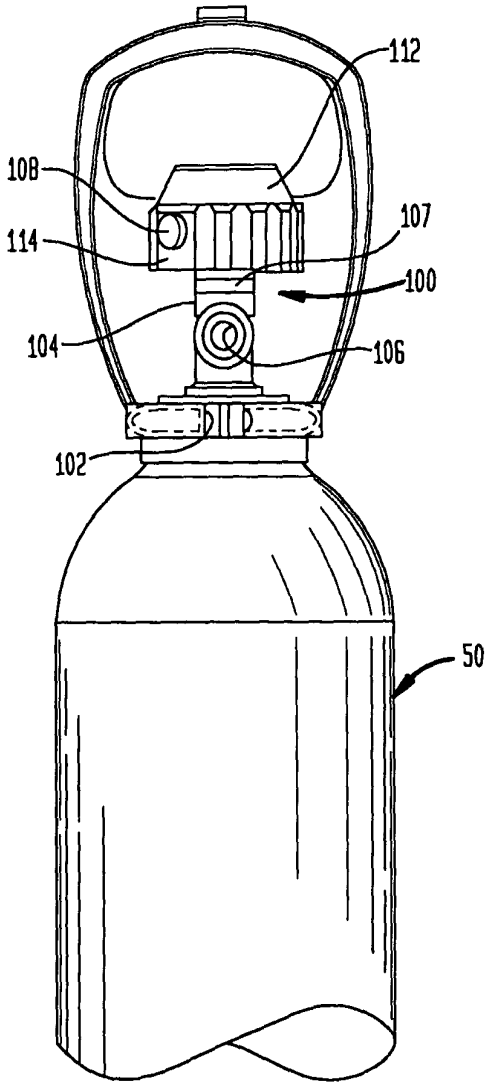


FIG. 3

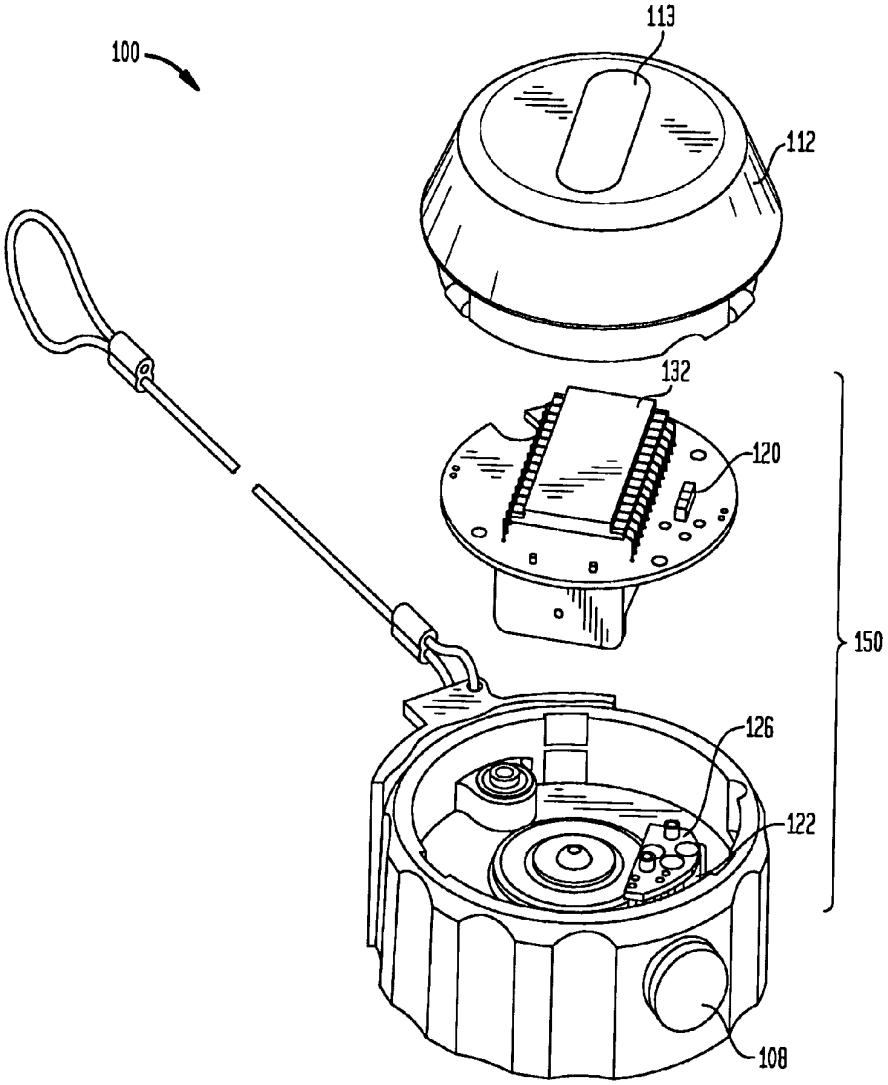


FIG. 4

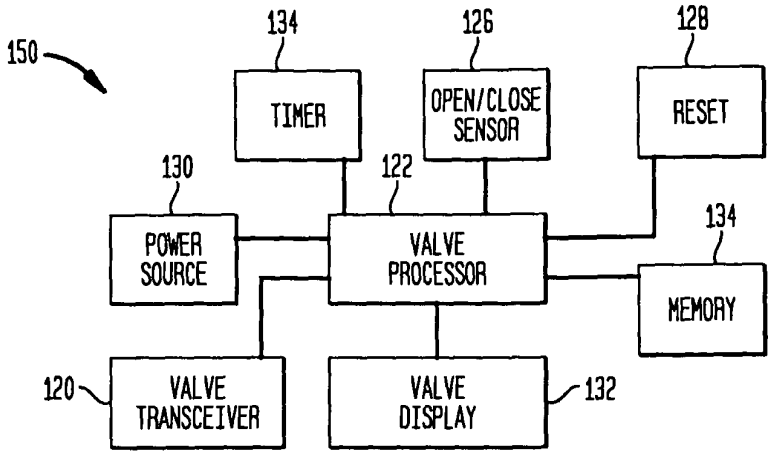

150
134
126
128
TIMER
OPEN/CLOSE SENSOR
RESET
130
122
134
POWER SOURCE
VALVE PROCESSOR
MEMORY
120
VALVE TRANSCEIVER
VALVE DISPLAY
132

FIG. 5

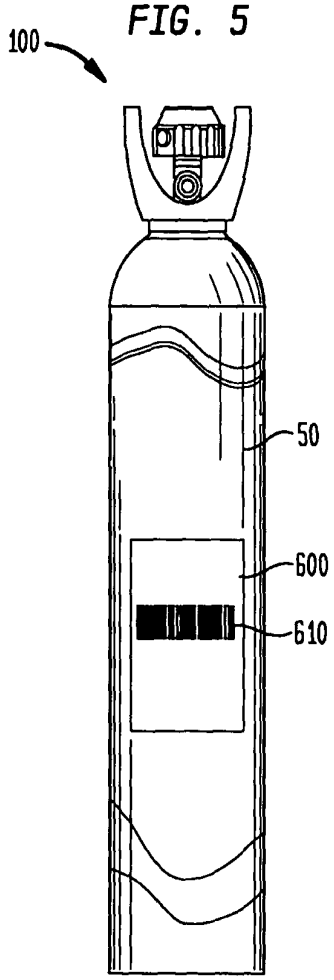

100
50
600
610

FIG. 6

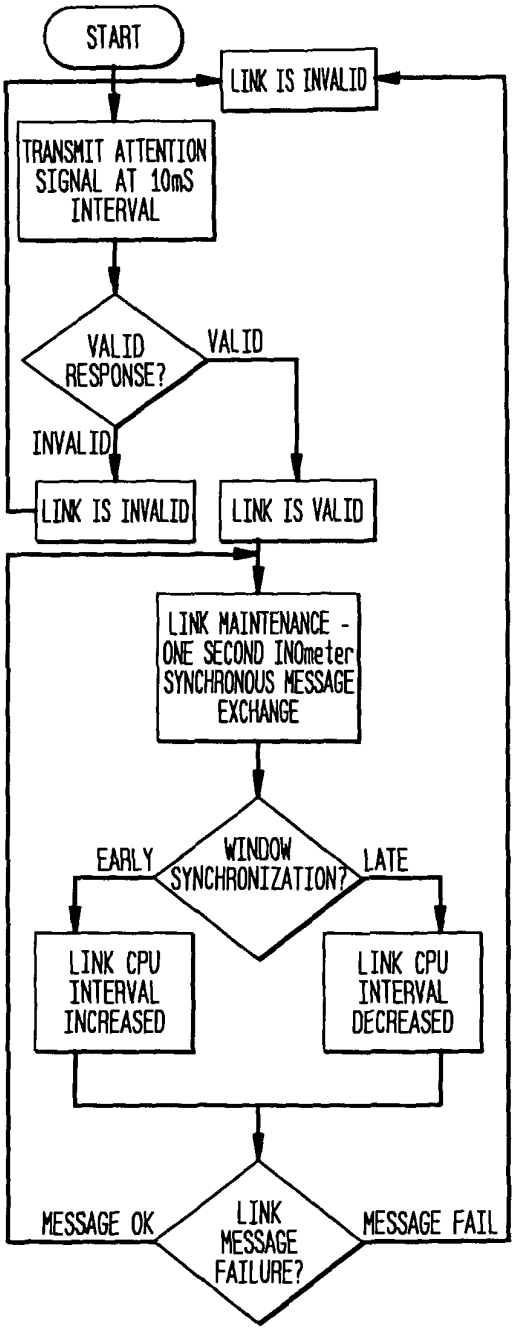

START
LINK IS INVALID
TRANSMIT ATTENTION SIGNAL AT 10mS INTERVAL
VALID RESPONSE?
VALID
INVALID
LINK IS INVALID
LINK IS VALID
LINK MAINTENANCE - ONE SECOND INOmeter SYNCHRONOUS MESSAGE EXCHANGE
WINDOW SYNCHRONIZATION?
EARLY
LATE
LINK CPU INTERVAL INCREASED
LINK CPU INTERVAL DECREASED
LINK MESSAGE FAILURE?
MESSAGE OK
MESSAGE FAIL

FIG. 7

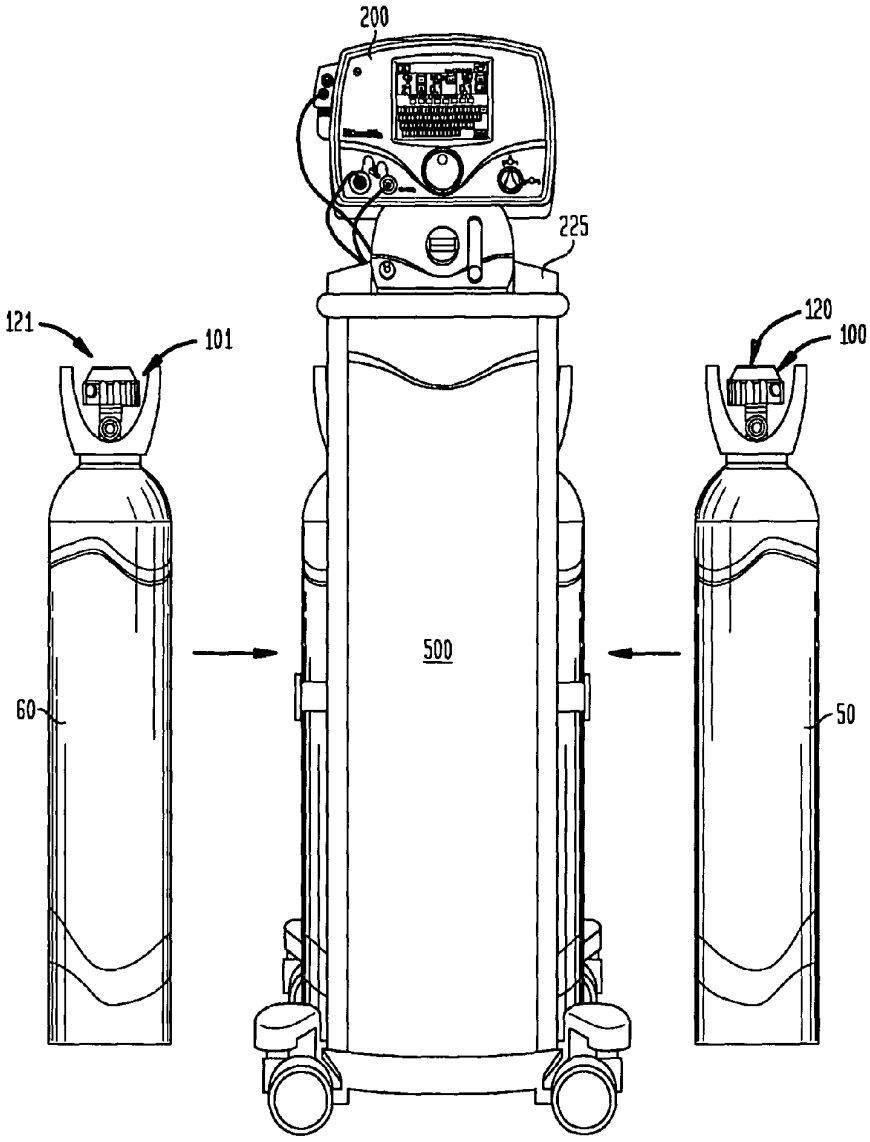


FIG. 8

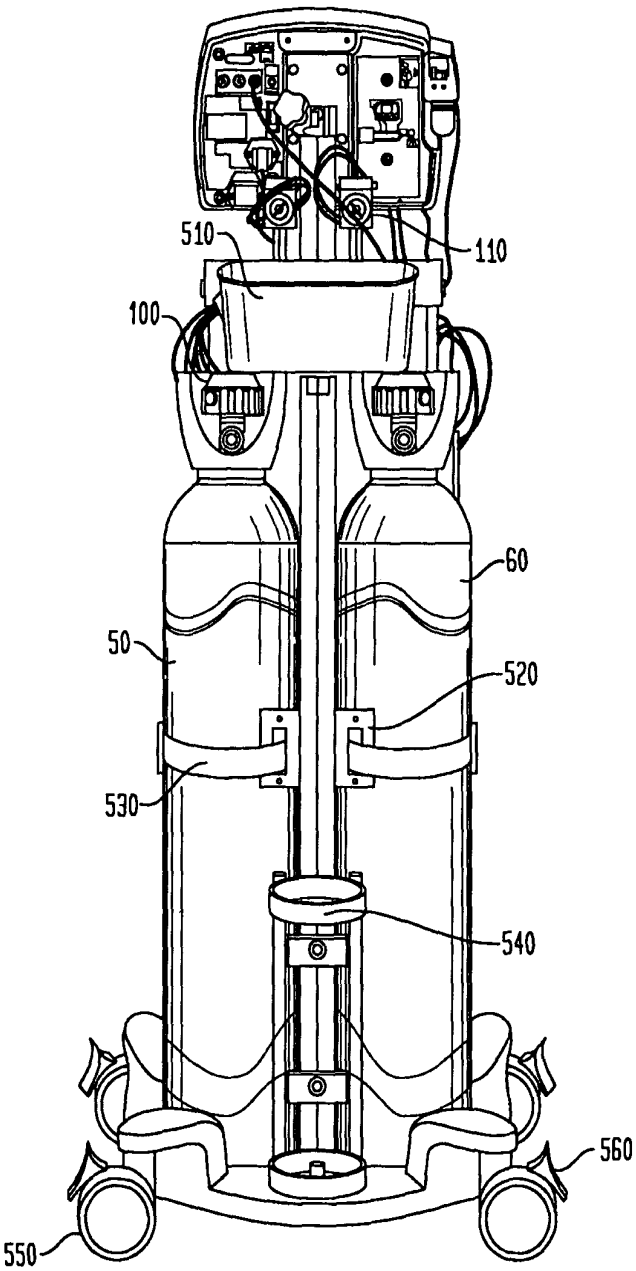


FIG. 9

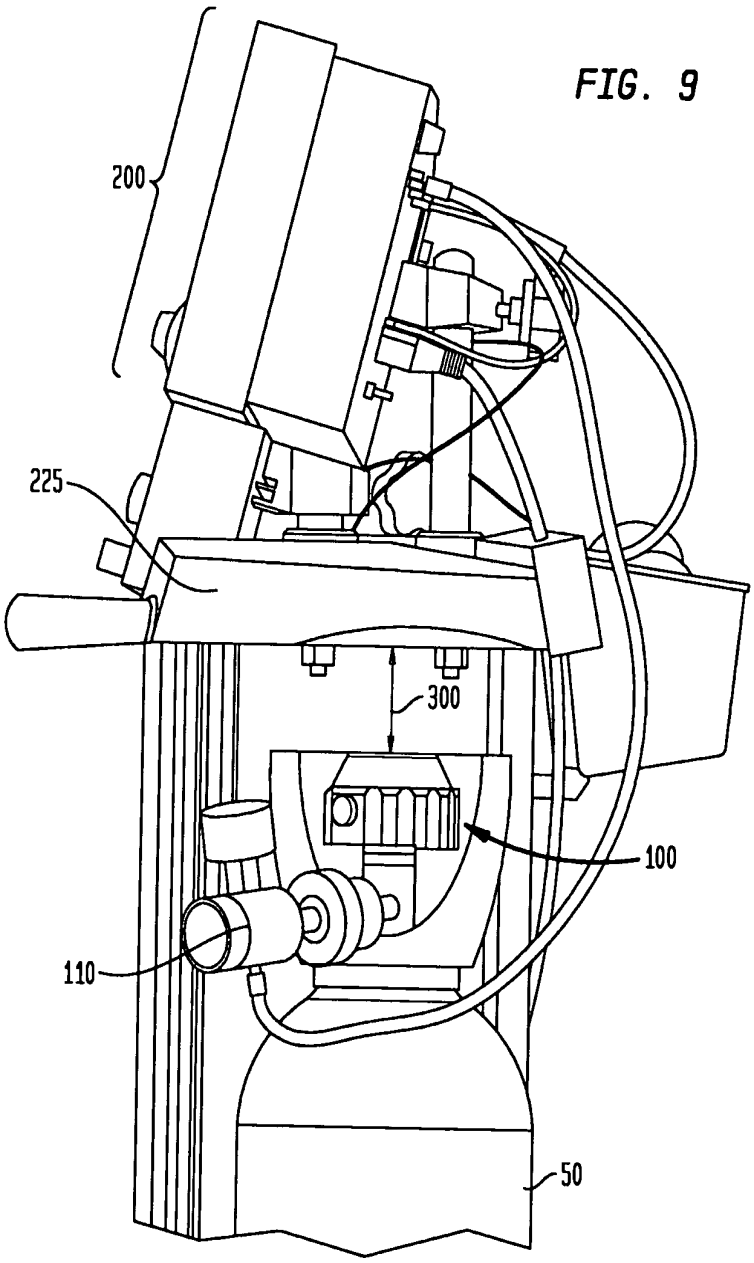


FIG. 10

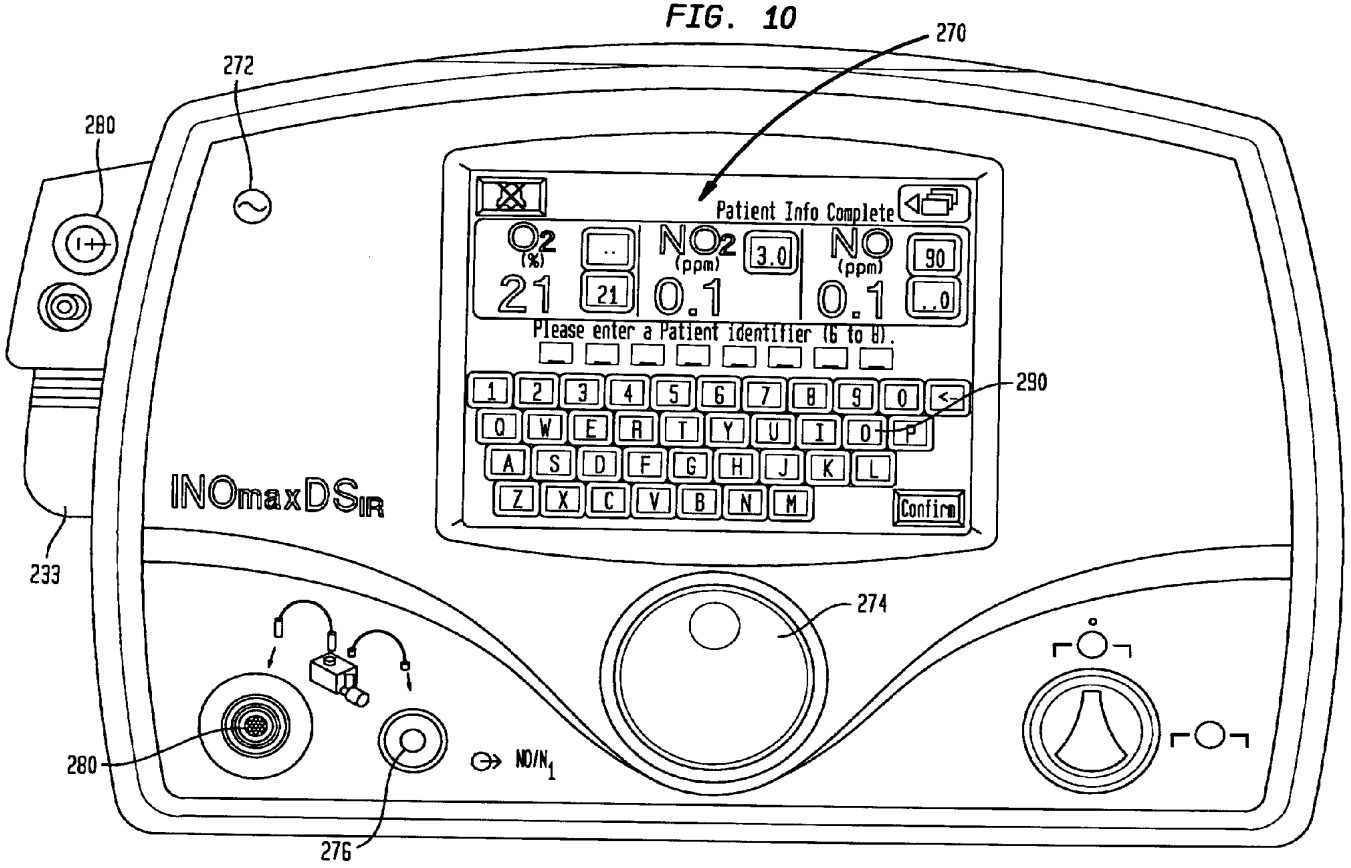

270
272
280
Patient Info Complete
O2 (%)
NO2 (ppm)
3.0
NO (ppm)
90
21
21
0.1
0.1
.0
Please enter a Patient identifier (6 to 8).
290
INOmaxDS IR
Confirm
233
274
280
NO/N1
276

FIG. 11

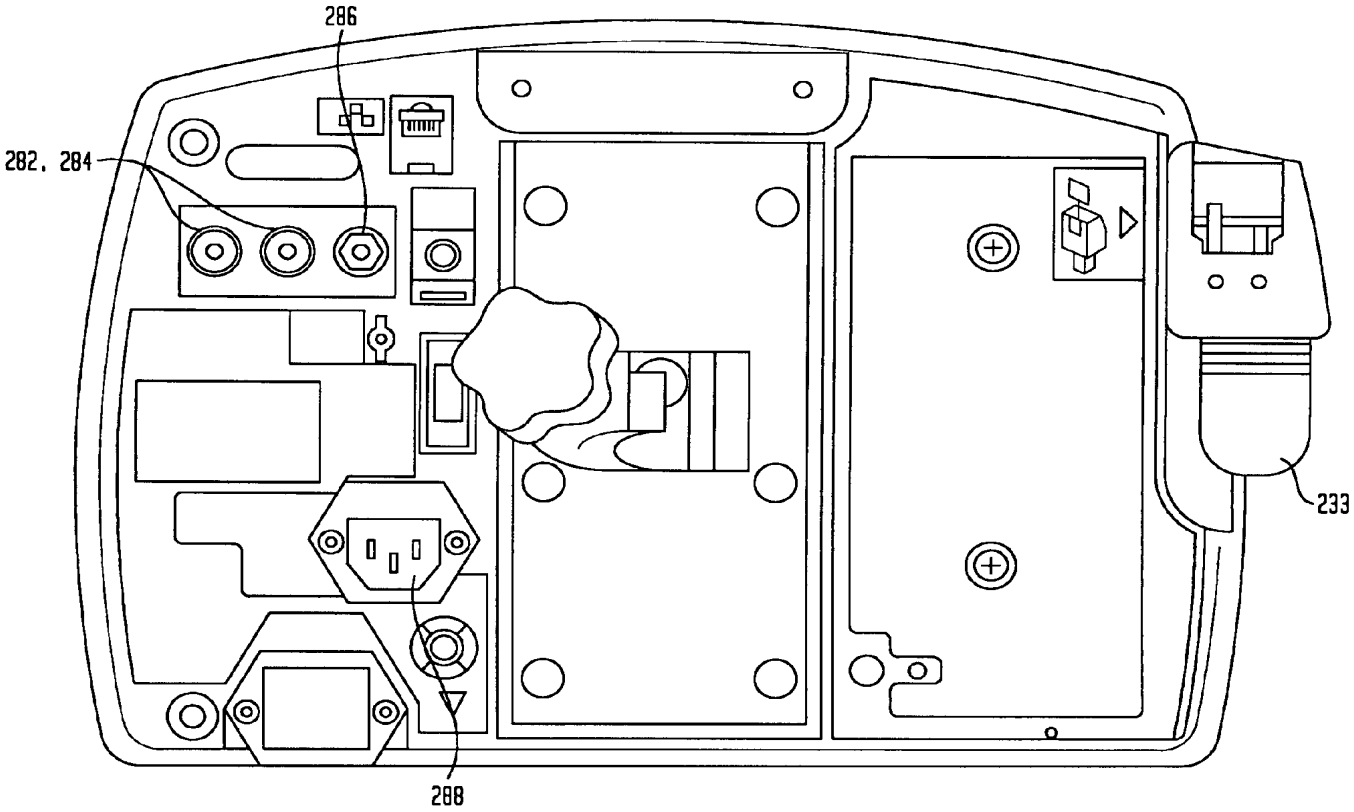


FIG. 12

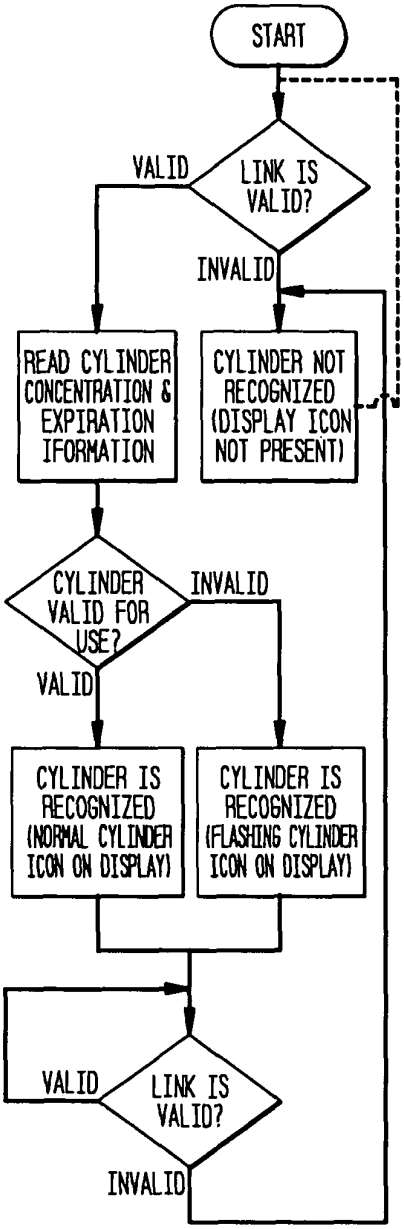
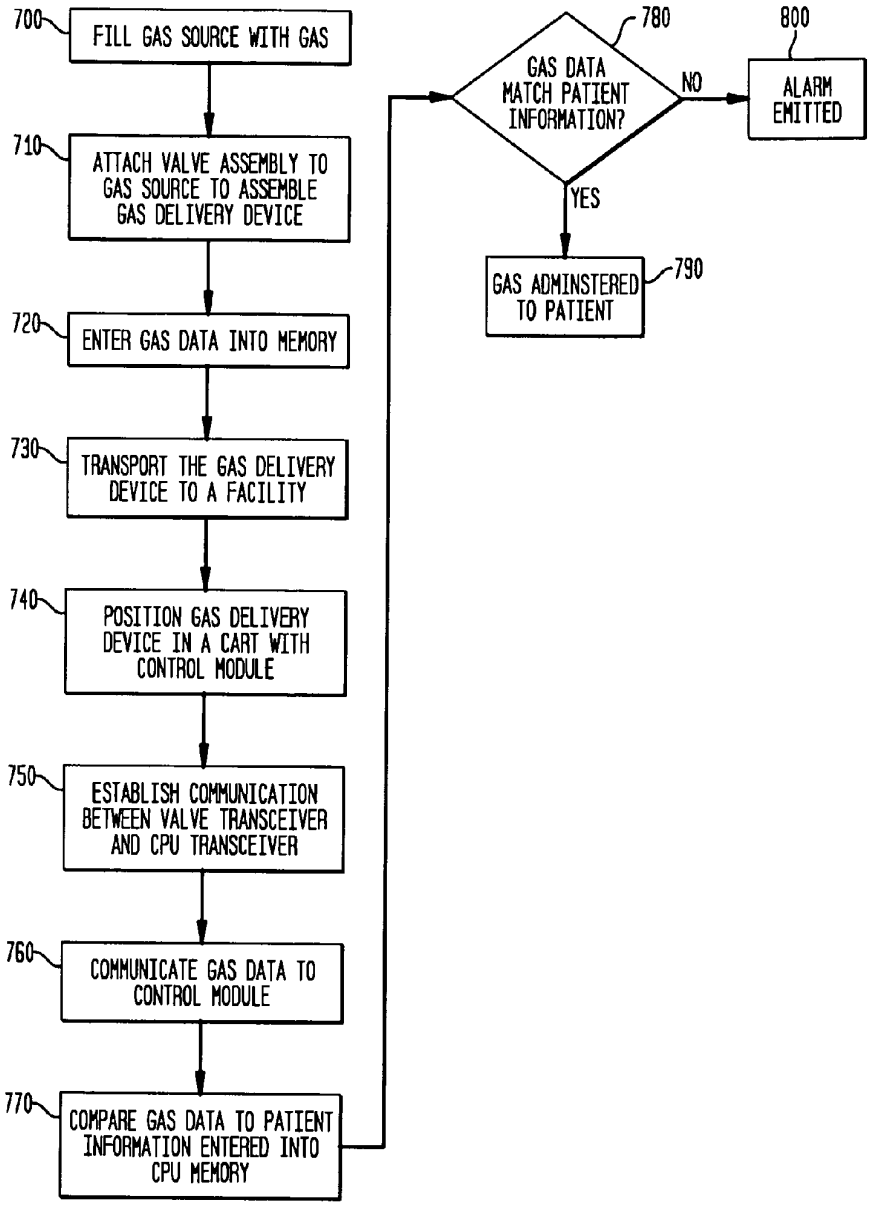

START
LINK IS VALID?
VALID
INVALID
READ CYLINDER CONCENTRATION & EXPIRATION IFORMATION
CYLINDER NOT RECOGNIZED (DISPLAY ICON NOT PRESENT)
CYLINDER VALID FOR USE?
INVALID
VALID
CYLINDER IS RECOGNIZED (NORMAL CYLINDER ICON ON DISPLAY)
CYLINDER IS RECOGNIZED (FLASHING CYLINDER ICON ON DISPLAY)
LINK IS VALID?
VALID
INVALID

FIG. 13


700
FILL GAS SOURCE WITH GAS
710
ATTACH VALVE ASSEMBLY TO GAS SOURCE TO ASSEMBLE GAS DELIVERY DEVICE
720
ENTER GAS DATA INTO MEMORY
730
TRANSPORT THE GAS DELIVERY DEVICE TO A FACILITY
740
POSITION GAS DELIVERY DEVICE IN A CART WITH CONTROL MODULE
750
ESTABLISH COMMUNICATION BETWEEN VALVE TRANSCEIVER AND CPU TRANSCEIVER
760
COMMUNICATE GAS DATA TO CONTROL MODULE
770
COMPARE GAS DATA TO PATIENT INFORMATION ENTERED INTO CPU MEMORY
780
GAS DATA MATCH PATIENT INFORMATION?
NO
800
ALARM EMITTED
YES
790
GAS ADMINSTERED TO PATIENT

GAS DELIVERY DEVICE AND SYSTEM

TECHNICAL FIELD

Embodiments of the present invention relate to gas delivery device for use in a gas delivery system for administering therapy gas and methods of administering therapy gas.

BACKGROUND

Certain medical treatments include the use of gases that are inhaled by the patient. Gas delivery devices are often utilized by hospitals to deliver the necessary gas to patients in need. It is important when administering gas therapy to these patients to verify the correct type of gas and the correct concentration are being used. It is also important to verify dosage information and administration.

Known gas delivery devices may include a computerized system for tracking patient information, including information regarding the type of gas therapy, concentration of gas to be administered and dosage information for a particular patient. However, these computerized systems often do not communicate with other components of gas delivery devices, for example, the valve that controls the flow of the gas to the computerized system and/or ventilator for administration to the patient. In addition, in known systems, the amount of gas utilized by a single patient is often difficult or impossible to discern, leading to possible overbilling for usage.

There is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is to be delivered by the gas delivery device. There is also a need for such an integrated device that does not rely on repeated manual set-ups or connections and which can also track individual patient usage accurately and simply.

SUMMARY

Aspects of the present invention pertain to a gas delivery device that may be utilized with a gas delivery system and methods for administering therapy gas to a patient. One or more embodiments of the gas delivery devices described herein may include a valve and a circuit with a valve memory in communication with a valve processor and a valve transceiver. One or more embodiments of the gas delivery systems described herein incorporate the gas delivery devices described herein with a control module including a central processing unit (CPU) in communication with a CPU memory and CPU transceiver. As will be described herein, the valve transceiver and the CPU transceiver may be in communication such that information or data from the valve memory and the CPU memory may be communicated to one another. The information communicated between the valve memory and the CPU memory may be utilized for selecting a therapy for delivery to a patient and controlling delivery of the selected therapy to the patient. The gas delivery devices and systems described herein may be utilized with medical devices such as ventilators and the like to delivery gas to a patient.

A first aspect of the present invention pertains to a gas delivery device. In one or more embodiments, the gas delivery device administers therapy gas from a gas source under the control of a control module. In one variant, the gas delivery device may include a valve attachable to the gas source and a circuit. The valve may include an inlet and an outlet in fluid communication and a valve actuator to open and close the valve to allow the gas to flow through the valve to a control module. The circuit of one or more embodiments includes a memory, a processor and a transceiver in communication with the memory to send wireless optical line-of-sight signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject. In one or more alternative embodiments, the signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject may be communicated via a wire. Examples of such wired signals may incorporate or utilize an optical cable, wired pair and/or coaxial cable. The circuit may include a memory to store gas data, which may include one or more of gas identification, gas expiration date and gas concentration. The transceiver may communicate to send the gas data to the control module via wireless optical line-of-sight signals.

In one or more embodiments, the valve may include a data input in communication with said memory, to permit a user to enter the gas data into the memory. The gas data may be provided in a bar code that may be disposed on the gas source. In such embodiments, the gas data may be entered into the data input of the valve for storage in the memory by a user-operated scanning device in communication with the data input. Specifically, the user may scan the bar code to communicate the gas data stored therein to the valve memory via the data input.

In one or more embodiments, the valve may include a power source. In such embodiments, the power source may include a battery or other portable power source. In one or more embodiments, the valve transceiver may periodically send the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent. In one or more specific embodiments, the duration of time at which no signal is sent comprises about 10 seconds.

A second aspect of the present invention pertains to a gas delivery device, as described herein, and a control module in fluid communication with the outlet of the valve of the gas delivery device and with a gas delivery mechanism, such as a ventilator. In one or more embodiments, the control module may include a CPU transceiver to receive line-of-sight signals from the transceiver and a CPU in communication with the CPU transceiver. The CPU carries out the instructions of a computer program or algorithm. As used herein the phrase "wireless optical line-of-sight signal" includes infrared signal and other signals that require a transmitter and receiver or two transceivers to be in aligned such that the signal may be transmitted in a straight line. The CPU may include a CPU memory that stores the gas data that is communicated by the valve transceiver of the gas delivery device to the CPU transceiver.

In one or more embodiments, the gas delivery system may incorporate a valve with a timer including a calendar timer and an event timer for determining or marking the date and time that the valve is opened and closed and the duration of time the valve is opened. In such embodiments, the valve memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

In one or more variants, the gas delivery system may incorporate a control module that further includes an input means to enter patient information into the CPU memory. The control module may also have a real time clock built into the CPU module such that the control module knows what the current time and date is and can compare that to the expiration date stored in the gas delivery device. If the expiration date is

passed the current date then the control module can cause an alarm and not deliver drug to the patient. When the term "patient information" is used, it is meant to include both patient information entered by the user and information that is set during manufacturing, such as the gas identification and the gas concentration that the control module is setup to deliver. The control module may also include a display. In one or more embodiments, the display incorporates an input means for entering patient information into the CPU memory. In one or more embodiments, the CPU of the control module compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver. The CPU or control module may include comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match or conflict. As used herein the phrase "do not match," includes the phrase "are not identical," "are not substantially identical," "do conflict" and/or "do substantially conflict." The CPU determines whether the patient information and additional data, or other data set matches by performing a matching algorithm which includes criteria for establishing whether one set of data (i.e. patient information) and another set of data match. The algorithm may be configured to determine a match where every parameter of the data sets match or selected parameters of the data sets match. The algorithm may be configured-to include a margin of error. For example, where the patient information require a gas concentration of 800 ppm, and the additional data includes a gas concentration of 805 ppm, the algorithm may be configured to include a margin of error of ±5 ppm such it determines that the patient information and the additional data match. It will be understood that determining whether the patient information and additional data match will vary depending on the circumstances, such as variables in measuring gas concentration due to temperature and pressure considerations.

A third aspect of the present invention pertains to a control module memory comprising instructions that cause a control module processor to receive gas data from a valve via a wireless optical line-of-sight signal. The valve may be connected to a gas source and may include a memory for storing the gas data. The control module memory may include instructions that cause the control module processor to compare the gas data with user-inputted patient information. The user-inputted patient information may be stored within the control module memory. Gas data may be selected from one or more of gas identification, gas expiration date and gas concentration. In one or more embodiments, the control module memory may include instructions to cause the control module processor to coordinate delivery of therapy to the patient with a medical device, such as a ventilator and the like for delivering gas to a patient, via the wireless optical line-of-sight signal. The control module memory may also include instructions to cause the control module processor to select a therapy for delivery to a patient based on the received patient information and control delivery of the selected therapy to the patient.

In one or more embodiments, the memory may include instructions to cause the processor to detect the presence of more than one valve and whether more than one valve is open at the same time. In accordance with one or more specific embodiments, the memory includes instructions to cause the processor to receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas source, receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas source, compare the first valve status and the second valve status, and emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position. In one or more alternative embodiments, the first valve status and the second valve status may be communicated to the processor via a single wireless optical line-of-sight signal, instead of separate wireless optical line-of-sight signals. In a more specific embodiment, the memory of one or more embodiments may include instructions to cause the processor to terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

In one or more embodiments, the memory may include instructions to cause the processor to emit an alarm when a desired dose has been delivered through a valve. In such embodiments, the processor may include a memory to store the desired dose or dosage information. In such embodiments, the memory may include instructions to cause the processor to receive gas delivery information or information regarding the amount of gas delivered and compare the gas delivery information to the dosage information and emit an alarm when the gas delivery information and the dosage information match. As used herein, the term "dosage information" may be expressed in units of parts per million (ppm), milligrams of the drug per kilograms of the patient (mg/kg), millimeters per breath, and other units known for measuring and administering a dose. In one or more embodiments, the dosage information may include various dosage regimes which may include administering a standard or constant concentration of gas to the patient, administering a gas using a pulsed method. Such pulsing methods includes a method of administering a therapy gas to a patient during an inspiratory cycle of the patient, where the gas is administered over a single breath or over a plurality of breaths and is delivery independent of the respiratory pattern of the patient.

A fourth aspect of the present invention pertains to a method for administering a therapy gas to a patient. In one or more embodiments, the method includes establishing communication between the patient and a gas delivery device via a transceiver, wherein the gas delivery device comprises a first memory including gas data, comparing the gas data with patient information stored within a second memory. The second memory may be included within a control module in communication with the gas delivery device. After comparing the gas data and the patient information, the method may further include coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal, selecting a therapy for delivery to the patient based on the comparison of the gas data and the patient information and controlling delivery of the selected therapy to the patient. In one or more specific embodiments, the method may include entering the gas data into the first memory of the gas delivery device and/or entering the patient information into the second memory. In embodiments in which the method includes entering the patient information into the second memory, the control module may include input means by which patient information may be entered into the second memory. In one or more variants, the method includes ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information. The method may include emitting an alert based on the comparison of the gas data and the patient information.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of a gas delivery system including a gas delivery device, a gas source, a control module and a gas delivery mechanism, according to one or more embodiments;

FIG. **2** illustrates a valve assembly of the gas delivery device according to one or more embodiments attached to a gas source;

FIG. **3** illustrates a disassembled view of the valve assembly shown in FIG. **2**;

FIG. **4** is a diagram showing a circuit supported in the valve assembly shown in FIG. **2**, according to one or more embodiments;

FIG. **5** illustrates an exemplary gas source for use with the valve assembly shown in FIG. **2**;

FIG. **6** is an operational flow diagram of the communication between the circuit of the gas delivery device shown in FIG. **1** with a control module regarding the establishment of communication between the circuit and the control module

FIG. **7** illustrates a front view of an exemplary gas delivery system;

FIG. **8** illustrates a back view of the gas delivery system shown in FIG. **7**;

FIG. **9** illustrates a partial side view of the gas delivery system shown in FIG. **7**;

FIG. **10** illustrates a front view of a control module according to one or more embodiments;

FIG. **11** illustrates a back view of the control module shown in FIG. **10**;

FIG. **12** is an operational flow diagram of the communication between the circuit of the gas delivery device and the control module shown in FIG. **1** regarding the gas contained within a gas source; and

FIG. **13** is an operational flow diagram of the preparation of a gas delivery device and use within the gas delivery system according to one or more embodiments.

DETAILED DESCRIPTION

Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

A system for the administration of therapy gas is described. A first aspect of the present invention pertains to a gas delivery device. The gas delivery device may include a valve assembly including at least one valve with a circuit. The gas delivery system may include the gas delivery device (e.g. valve assembly, including a valve and a circuit) in communication with a control module to control the delivery of gas from a gas source to a ventilator or other device used to introduce the gas into the patient, for example, a nasal cannula, endotracheal tube, face mask or the like. Gas source, as used herein, may include a gas source, gas tank or other pressured vessel used to store gases at above atmospheric pressure. The gas delivery system **10** is shown in FIG. **1**. In FIG. **1**, the valve assembly **100**, including a valve **107** or valve actuator and a circuit **150**, is in communication with a control module **200** via a wireless line-of-sight connection **300**. In one or more alternative embodiments, communication between the valve assembly **100** and the control module **200** may be established via a wired signal. The gas delivery system **10** also includes a gas source **50** including a gas attached to the valve assembly **100** and a gas delivery mechanism, which includes a ventilator **400** and a breathing circuit **410**, in communication with the control module **200**.

FIGS. **2-4** illustrate the components of the valve assembly **100**. The valve assembly **100** includes a valve **107** and a circuit **150** supported in the valve assembly. FIG. **3** illustrates a disassembled view of the valve assembly **100**, showing components of the physical circuit **150** and the valve **107**. As shown in FIG. **4**, which will be described in more detail below, the circuit **150** of the gas delivery device includes a valve transceiver **120** for establishing communication with the control module **200**, which will also be discussed in greater detail below.

Referring to FIG. **2**, the valve **107** includes an attachment portion **102** for attaching the valve assembly **100** to the gas source **50**, an inlet **104** and an outlet **106** in fluid communication with the inlet **104**, as more clearly shown in FIG. **2**.

FIG. **3** illustrates a disassembled view of the valve assembly **100** and illustrates an actuator **114** is disposed on the valve **107** and is rotatable around the valve **107** for opening and closing the valve **107**. The actuator **114** includes a cap **112** mounted thereto. As shown in FIG. **3**, the circuit **150** may include a data input **108** disposed on the actuator **114**. The data input **108** may be disposed at other locations on the valve **107**. In one or more variants, the data input may include a port such as a USB port, a receiver for receiving electronic signals from a transmitted or other known input means known in the art for entering information or data into a memory.

FIG. **4** illustrates a block diagram of the circuit **150**. The circuit **150** shown in FIG. **4** includes a valve processor **122**, a valve memory **134**, a reset **128**, a valve transceiver **120** and a power source **130**. The circuit **150** may also include support circuits a timer **124**, a sensor **126** and/or other sensors. Referring to FIG. **3**, the circuit **150** is supported within the valve assembly **100**, with the physical components of the circuit **150** specifically disposed between actuator **114** and the cap **112**. As shown in FIG. **3**, the valve display **132** and the valve transceiver **120** are disposed adjacent to the cap **112**, such that the valve display **132** is visible through a window **113**. The sensor **126** and the valve processor **122** are disposed beneath the valve display **132** and the valve transceiver **120**, within the actuator **114**.

The valve processor **122** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The valve memory **134**, or computer-readable medium, may be one or more of readily available memory such as electrically erasable programmable read only memory (EEPROM), random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the valve processor **122**. The support circuits may be coupled to the valve processor **122** for supporting the circuit **150** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like.

In the embodiment shown, the valve memory **134** communicates with a data input **108** disposed on the side of the actuator **114**. The data input **108** shown in FIGS. **3-4** is used to transfer data from the valve memory **134** to other devices or to input data into the valve memory **134**. For example, gas data, which includes information regarding the gas contained within the gas source, may be entered into the valve memory **134** via the data input **108**. In one or more alternative embodiments, the gas data may be programmed or directly entered into the valve memory **134** by the gas supplier. In one or more embodiments, the gas data may be provided in the form of a bar code **610** that is disposed on a label **600** that is affixed on a to the side of the gas source, as shown in FIG. **5**. The bar code **610** may be disposed directly on the gas source. An external scanning device in communication with the electronic data input **108** may be provided and may be used to scan the bar code **610** and convey the information from the bar code **610** to the valve memory **134**. Gas data may include information regarding the gas composition (e.g., NO, O_2,

NO_2, CO, etc.), concentration, expiration date, batch and lot number, date of manufacturing and other information. Gas data may be configured to include one or more types of information. The valve processor **122** may include instructions to convey all or a pre-determined portion of the gas data via the valve transceiver **120** to another transceiver.

In embodiments that utilize a timer **124**, the timer **124** may include two sub-timers, one of which is a calendar timer and the other of which is an event timer. The reset **128** may be located inside the actuator **114** and may be depressed to reset the event timer. The cap **112** also includes a window **113** that allows the user to see the valve display **132** disposed within the cap **112** that displays information regarding whether the actuator **114** is opened or closed and the duration the valve **107** was opened or closed. In one or more embodiments, the valve display **132** may alternate flashing of two different numbers, a first number may be accumulated open time, and the second number may be the time at which the valve **107** was opened for the current event. The time at which the valve **107** was opened for a current event may be preceded by other indicators.

The sensor **126** disposed within the actuator **114** may include a proximity switch model MK20-B-100-W manufactured by Meder Inc. The sensor **126** utilized in one or more embodiments may cooperate with a magnet (not shown) to sense whether the actuator **114** is turned on or turned off. Such sensors are described in U.S. Pat. No. 7,114,510, which is incorporated by reference in its entirety.

For example, the sensor **126** and a corresponding magnet (not shown) may be disposed on a stationary portion of the valve **107**. When the actuator **114** is rotated to the closed position, the sensor **126** is adjacent to the magnet that is in a fixed position on the valve **107**. When the sensor **126** is adjacent to the magnet, it sends no signal to the valve processor **122**, thereby indicating that the actuator **114** is in the "closed" position or has a valve status that includes an open position or a closed position. When the actuator **114** is rotated to open the valve **107**, the sensor **126** senses that it has been moved away from the magnet and sends a signal to the valve processor **122**, indicating an "open" position. The valve processor **122** instructs the valve memory **134** to record the event of opening the valve **107** and to record the time and date of the event as indicated by the calendar timer. The valve processor **122** instructs the valve memory **134** to continue checking the position of the valve **107** as long as the valve **107** is open. When the valve **107** is closed, the valve processor **122** uses the logged open and close times to calculate the amount of time the valve **107** was open and instructs the valve memory **134** to record that duration and the accumulated open time duration. Thus, every time the valve **107** is opened, the time and date of the event is recorded, the closing time and date is recorded, the duration of time during which the valve **107** is open is calculated and recorded, and the accumulated open time is calculated and recorded.

In one or more embodiments in which the power source **130** includes a battery, the valve transceiver **120** may be configured to communicate with the CPU transceiver **220** to preserve the life of the battery. In this embodiment the valve transceiver **120** is only turned on to receive a signal from the Control Module CPU transceiver **220** for 20 msec every second. The control module CPU transceiver **220** sends out a short transmit signal continuously and if the valve transceiver **120** is present it responds in the 20 msec interval. This conserves battery power as the valve transceiver **120** is only powered on for 20 msec every second. When the valve transceiver **120** responds it includes in its signal information regarding whether the communication from the control module CPU transceiver **220** was early or late within this 20 msec window. This ensures that once communications has been established it is synchronized with the 20 msec window that the valve transceiver **120** is powered on and able to receive communications. For example, as shown in FIG. **6**, the valve transceiver **120** sends a wireless optical line-of-sight signal during a pre-determined interval in response to a signal from the control module CPU transceiver **220**. The wireless optical line-of-sight signals sent by the valve transceiver **120** are a series of on off cycles where the transmitter is either transmitting light or is not and these correspond to digital binary signals. The mechanism by which the valve transceiver sends a wireless optical line-of-sight signal may be construed as a series of digital on off signals that correspond to data being transmitted. Once communications has been established between the control module CPU transceiver **220** and the valve transceiver **120**, the interval between communication signals may be in the range from about 20 seconds to about 5 seconds. In one or more specific embodiments, the interval or duration between transceiver signals may be about 10 seconds.

As will be described in more detail below, the control module **200** includes a CPU **210** which is connected to a CPU transceiver **220** which can send and receive wireless optical line-of-sight signals. The CPU transceiver **220** sends out a signal and waits for a response from the valve transceiver **120** when communication or more specifically, line-of-sight communication is established between the CPU transceiver **220** and the valve transceiver **120**. If no response is sent by the valve transceiver **120**, the CPU transceiver **220** sends another signal after a period of time. This configuration preserves battery life because the valve transceiver **120** does not continuously send a signal unless requested to by the CPU **210**. This is important as the gas delivery device and gas source spends most of its time in shipping and storage prior to being placed on the gas delivery system, if it was transmitting all this time trying to establish communications with the control module it would be consuming the battery life significantly.

The valve processor **122** may include link maintenance instructions to determine whether the interval should be increased or decreased. As shown in FIG. **6**, when a valid link is established between the valve transceiver **120** and CPU transceiver **121**, the valve processor **122** executes the link maintenance instructions to increase the interval or decrease the interval.

As shown more clearly in FIG. **1**, valve assembly **100** and gas source **50** is in communication with a control module **200**, which is in communication with a gas delivery mechanism. The gas delivery mechanism shown in FIG. **1** includes a ventilator **400** with associated breathing circuit **410**. The control module **200** may include a CPU **210** and a CPU transceiver **220** in communication with the circuit **150** via the valve transceiver **120**. The control module **200** also includes a CPU memory **212** in communication with the CPU transceiver **220** to store patient information, information or data received from the valve transceiver **120** and other information. The control module **200** may also include support circuits. The CPU **210** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The CPU memory **212**, or computer-readable medium, may be one or more of readily available memory such as random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the CPU **210**. The support circuits may be coupled to the CPU **210** for supporting the control module **200** in a conventional manner. These circuits include cache,

power supplies, clock circuits, input/output circuitry, subsystems, and the like. The CPU **210** may also include a speaker **214** for emitting alarms. Alternatively, alarms may also be displayed visually on a display. As shown in FIG. **1**, the control module **200** may also include a regulator **110** and, optionally, pressure gauges and flow meters for determining and/or controlling the gas flow from the gas source **50**.

In one or more embodiments, the CPU transceiver **220** is disposed on a cover portion **225** (shown more clearly in FIG. **7**), that is part of a cart **500** (show more clearly in FIG. **7**) onto which the control module **200** is disposed. The cover portion **225** in one or more embodiments is in communication with the control module **200**. Communication between the cover portion **225** and the control module **200** may be established wirelessly or via a cable. As will be discussed in greater detail below, the valve assembly **100**, including the valve **107**, the circuit **150** and a gas source **50** attached to the valve **107**, are placed on the cart **500** in proximity and in a light-of-sight path with the CPU transceiver **220**. When properly configured such that communication is established between the valve transceiver **120** and the CPU transceiver **220**, the CPU transceiver **220** is positioned directly above the valve transceiver **120**, as shown more clearly in FIG. **9**. In one or more alternative embodiments, the CPU transceiver **220** may be disposed on the CPU **210**.

The CPU **210** may be in communication with a plurality of gas sensors **230** for determining the concentration of a sample of gas drawn via a sample line **232** and a sample line inlet **280** (shown more clearly in FIG. **1**) disposed on the control module **200**. As will be discussed in greater detail, the sample line **232** draws a sample of gas from a breathing circuit **410** of a ventilator **400** when the ventilator is in fluid communication with the control module **200** and gas is being delivered to the ventilator. The CPU **210** may also be in communication with a sample flow sensor **234** for sensing the flow of the sample drawn via sample line **232**, a pump **236** for drawing the sample via the sample line **232** to the flow sensor **234** and zero valve **238** controlling the flow of the sample via the sample line **232** to the sample pump **236**, sample flow sensor **234** and the plurality of CPU sensors. The sample line **232** may include a water trap **233** for collecting any water or liquid from the sample.

The control module **200** may also include a delivery module **260** for regulating the flow of gas from the gas source **50** to the ventilator **400**. The delivery module **260** may include a pressure switch **262** for determining a gas supply pressure is present, a pressure shut-off valve **264**, a proportional valve **266** and a delivery flow sensor **268**. The delivery module **260** may also include a backup on/off switch **269**. The detailed method of how the delivery module delivers the gas to the ventilator circuit is described in U.S. Pat. No. 5,558,083 which is incorporated here by reference in its entirety.

The ventilator **400** shown in FIG. **1** is in fluid communication with the control module **200** via an injector tubing **440** and in electrical communication via an injector module cable **450**. The control module **200** and more specifically, the CPU **210**, is in fluid communication with the ventilator **400** via the sample line **232**. The ventilator **400** may include a breathing circuit **410** with an inspiratory limb **412** and an expiratory limb **414** in fluid communication with the ventilator **400**. The inspiratory limb **412** may be in fluid communication with a humidifier **420**, which is in fluid communication with the ventilator **400** via an injector module **430**. The inspiratory limb **412** carries gas to the patient and the expiratory limb **414** carries gas exhaled by the patient to the ventilator **400**. The injector module **430** shown in FIG. **1** is in fluid communication with the gas source **50** via the injector tubing **440** and in electronic communication with the delivery module **260** via the injector module cable **450** such that the delivery module **260** can detect and regulate the flow of gas from the gas source **50** to the ventilator **400**. Specifically, the injector module **430** is in fluid communication with the gas source **50** via an injector tubing **440**, which is in fluid communication with one or more of the pressure switch **262**, pressure shut-off valve **246**, proportional valve **266**, flow sensor **268** and the backup switch **269** of the delivery module **260**. The injector module **430** may also be in electronic communication with the delivery module **260** via the injector module cable **450**. The inspiratory limb **412** of the ventilator **400** may include a sample tee **416** for facilitating fluid communication between the inspiratory limb **412** of the breathing circuit and the sample line **232**.

As discussed above, the control module **200** may be disposed or attached on a cart **500**, as shown in FIGS. **7-9** to facilitate movement of the gas source **50** and the gas delivery device to a patient in need of gas therapy. The gas source **50** and the valve assembly **100** attached thereto may be placed on the cart **500** in proximity to the control module **200**. More specifically, as shown in FIG. **7**, the gas source **50** is placed on the cart **500** such that the valve transceiver **120** is in proximity of the CPU transceiver **220** and a line-of-sight path is established between the valve transceiver **120** and the CPU transceiver **220**. In this configuration, the CPU **210** detects the presence of the circuit **150** and thus the gas source **50** via the CPU transceiver **220**.

As shown in FIGS. **7-9**, the gas delivery device may include more than one valve, with each valve being attached to a single gas source. In such embodiments which utilize a second gas source **60** with a second valve assembly **101**, the second valve assembly **101** is positioned in proximity and in a light-of-sight path with a second CPU transceiver as the gas source **60** is loaded onto the cart. The second CPU transceiver **222** establishes communication with the second valve assembly **101** and thus detects the presence of a second gas source **60**. In the embodiment shown in FIGS. **7-9**, the second CPU transceiver **222** may also be disposed on the cover portion **225** of a cart. In one or more alternative embodiments, the second CPU transceiver **222** may be disposed on the CPU **210**.

As shown in FIG. **8**, the cart **500** may include an optional small bin **510**, a mount **512** for supporting the control module **200** on the cart **500**, at least one a holding bracket **520**, at least one mounting strap **530**, an auxiliary bracket **540**, for holding an auxiliary gas source, a plurality of casters **550** and a caster lock lever **560** disposed on each of the plurality of casters **550**. The cart **500** may include a mount **570** for mounting the control module **200** on to the cart.

An exemplary control module **200** is shown in FIGS. **10-12** includes a display **270** for providing visual indication to the user the components of the gas being delivered from the gas source **50** to the ventilator **400** (e.g., NO, O_2, NO_2), the concentration of each component and whether communication has been established with one or more gas sources. Other information may also be displayed to the user. In addition, visual alarms may also be displayed on the display **270**. The control module **200** may also include a main power indicator **272** indicating whether the control module is connected to a power source, such as an AC/DC power source and/or a battery. The control module **200** may also include a control wheel **274** allowing the user to navigate through various displays or information displayed on the display. An injection module tubing outlet **276** may be disposed on the control module for providing fluid communication between the delivery module **260** and the injector module **430**. An injection module cable port **278** may also be provided on the

control module to provide electronic communication between the delivery module **260** and the injector module **430**. The control module **200** shown in FIGS. **10-12** also includes the sample line inlet **280** in fluid communication with the sample line **232** and the inspiratory limb **412** of the ventilator **400**. In the embodiment shown in FIGS. **10-12**, the water trap **233** is disposed on the control module, adjacent to the sample line inlet **280**.

FIG. **11** illustrates a back view of the control module **200** and shows a plurality of inlets. In the embodiment shown, two gas inlets **282**, **284** for connecting the control module **200** to the gas source **50** are provided and one auxiliary inlet **286** for connecting the control module **200** to an auxiliary gas source, which may include oxygen or other gas. A power port **288** is also provided on the back of the control module to connect the control module to an AC/DC power source.

The control module **200** may also include an input means **290** for allowing the user to enter patient information, for example the identity of the patient, the type and concentration of the gas and dose of the gas to be administered to the patient, the patient's disease or condition to be treated by the gas or reason for treatment, gestational age of the patient and patient weight. The input means **290** shown in FIG. **12** includes a keyboard integrated with the display. In one or more alternative embodiments, the input means may include a USB port or other port for the connection of an external keyboard or other input mechanism known in the art. The information entered via the input means **290** is stored within the CPU memory **212**.

The control module **200** and the valve assembly **100** may be utilized in the gas delivery system **10** to improve patient safety. Specifically, the safety benefits of the gas delivery system described herein include detecting a non-confirming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like. In addition, embodiments of the gas delivery system described herein also improve efficiency of gas therapy.

FIG. **13** is a block diagram showing the sequence of how gas delivery device, including the valve assembly **100**, may be provided and its use within the gas delivery system **10**, according to one or more embodiments. As shown in FIG. **13**, the gas delivery device **10** is prepared for use by providing a gas source **50** in the form of a gas cylinder or other container for holding a gas and filling the gas source **50** with a gas (**700**) and attaching a valve assembly **100** as described herein, to assemble the gas delivery device **10** (**710**). These steps may be performed by a gas supplier or manufacturer. The gas data regarding the gas filled within the gas source **50** is entered into the valve memory **134** as described herein (**720**). The gas data may be entered into the valve memory **134** by the gas supplier or manufacturer that provides the gas source **50** and assembles the gas delivery device **10**. Alternatively, the hospital or other medical facility may enter the gas data into the valve memory **134** after the gas delivery device has been transported to the hospital or medical facility (**730**). The gas delivery device **10** is positioned on a cart **500** (**740**) and communication between the CPU transceiver **220** and the valve transceiver **120** is established (**750**). The gas data stored within the valve memory **134** is conveyed to the control module **200** (**760**) via the wireless optical line-of-sight communication between valve transceiver **120** and the CPU transceiver **220**. The CPU **210** compares the gas data to patient information entered into the CPU memory **212** (**770**). The patient information may be entered into the CPU memory after the gas data is entered into the CPU memory **212**. The patient information may be entered into the CPU memory before the gas delivery device **10** is positioned in the cart or before communication between the CPU transceiver **220** and the valve transceiver is established. In one or more alternative embodiments, the patient information may be entered into the CPU memory **212** before the gas delivery device **10** is prepared or transported to the hospital or facility. The CPU **210** then compares whether the gas data and the patient information match (**780**). If the gas data and the patient information match, then gas is administered to the patient (**790**), for example through a ventilator or other gas delivery mechanism. If the gas data and the patient information do not match, then an alarm is emitted (**800**). As described otherwise herein, the alarm may be audible and emitted through the speaker **214** and/or may be visual and displayed on the display **270**.

The gas delivery system described herein simplifies set-up procedures by utilizing wireless line-of-sight signals to establish communication. The user does not need to ensure all the cables are correct connected and can freely load new gas sources onto a cart without disconnecting cables linking the control module **200** and the valve assembly **100** or circuit **150**. This reduces set-up time and any time spent correcting errors that may have occurred during the set-up process. The control module **200** and the circuit **150** are further designed to automatically send and detect information to establish delivery of a correct gas having the correct concentration and that is not expired. In one or more specific embodiments, such automated actions prevent the use of the gas delivery system by preventing gas flow to a patient, without user intervention.

In one or more embodiments, after communication between the valve transceiver **120** and the CPU transceiver **220** is established, the valve processor **122** includes instructions to convey the gas data stored in the valve memory **134** via the valve transceiver **120** to the CPU transceiver **220**. The CPU **210** includes instructions to store the gas data received from the CPU transceiver **220** in the CPU memory. The CPU **210** also includes an algorithm that compares the gas data with patient information that is entered into the CPU memory **212**. If the gas data and the patient information do not match, the CPU **210** includes instructions to emit an alarm, which may be audible, visual or both, alerting the user that the gas contained within the gas source is different from the gas to be administered to the patient. For example, as illustrated in FIG. **12**, if the gas data includes gas expiration date, the CPU memory **212** includes information regarding the current date and the CPU **210** compares the gas expiration date with the current date. If the gas expiration date is earlier than the current date, the CPU **210** emits an alarm. The alarm may be emitted through one or both the speaker **214** and display **270**. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of an expired gas by the CPU **210** may be stored within the CPU memory **212**.

If the gas data includes gas concentration information or data, the CPU memory **212** includes information regarding the desired concentration of gas to be administered to the patient. The control module **200** may be configured to alert the user that the gas contained within a gas source has incorrect concentration or a concentration that does not match the desired gas concentration. For example, a user may enter a concentration of 800 ppm into the CPU memory **212** and this concentration is compared to the gas concentration conveyed from the valve memory **134** to the CPU memory **212**. As illustrated in FIG. **12**, the CPU **210** includes instructions to compare the gas concentration of the gas with the concentration entered by the user. If the gas concentration does not

match the concentration entered by the user, the CPU **210** emits an alarm, which may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of a gas with incorrect concentration may be stored within the CPU memory **212**.

In one or more embodiments, the control module **200** may be configured to detect more than one valve and to detect whether more than one valve is turned on. This configuration eliminates waste because it alerts a user that both valves are turned on and thus unnecessary gas is being delivered to via the delivery module **260**. In addition, such a configuration improves safety because it avoids the issues related to having two regulators pressurized at the same time and connected to the delivery module **260**. In one or more embodiments, the cover portion **225** of the control module **200** may include a second CPU transceiver **222** and the CPU **210** may include instructions for the second CPU transceiver **222** to detect wireless optical line-of-sight signals from a second valve assembly **101**, and more specifically, a second valve transceiver **121**. The CPU **210** may also include instructions that once a second valve assembly **101** is detected by the CPU transceiver **222**, whether both valve assemblies **100**, **101** are opened or have a valve status that includes an open position. In operation, a first valve assembly **100** includes a circuit with a valve processor with instructions to covey an open or closed position via the first valve transceiver **120**. The circuit of the second valve assembly similarly includes a valve processor with instructions to convey an open or closed position via a second valve transceiver **121**. The first CPU transceiver **220** and the second CPU transceiver **222** detect the valve statuses for each respective valve assembly from the first valve transceiver **120** and the second valve transceiver **121** via the wireless optical line-of-sight signals sent by both transceivers. The CPU **210** instructs the CPU transceivers **220**, **222** to collect the valve statuses for both valve assemblies **100**, **101** and the memory to store the valve statuses. The CPU **210** then compares the valve status information from the first valve assembly **100** and the second valve assembly **101** and, if the valve statuses both comprise an open position, the CPU **210** emits an alarm. The alarm may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas through either the first valve assembly or the second valve assembly. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas. The detection that more than one valve assembly had a valve that was turned on or had a valve status including an open position may be stored within the CPU memory.

In one or more embodiments, the control module **200** may be configured to alert a user when the desired dose has been delivered. In such embodiments, the patient information entered into the CPU memory **212** may include dosage information or the dose to be delivered to a patient. The valve processor **122** may include instructions to convey gas usage information from the valve memory **134**, including the amount of gas delivered, to the CPU memory **212** via the valve transceiver **120**. Alternatively, the valve processor **122** may include instructions to covey the duration of time the valve **170** has been turned on or has a valve status including an open position to the CPU memory **212** via the valve transceiver **120**. The CPU **210** may include instructions to compare the dosage information entered by the user and stored within the CPU memory **212** with the gas usage information. The CPU **210** may include instructions to emit an alarm when the dosage information and the gas usage information match. The CPU **210** may include instructions to emit the same or different alarm to alert the user to turn off the valve or, more specifically, the actuator **114** when the dose has been delivered. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas.

In addition, the control module **200** may be configured to alert the user that a detected valve is and remains closed and no gas is being delivered to the patient. This configuration expedites treatment time and increases efficiency for the hospital. In such embodiments, the valve processor **122** may include instructions for the valve transceiver **120** to convey the valve status to the CPU **210** via a wireless optical line-of-sight signal. The CPU **210** includes instructions to collect the valve status information and emit an alert if the dosage information is set or other input has been entered into the CPU memory **212** to commence treatment and the valve status includes a closed position.

The control module **200** may be configured to alert the user that no valve assembly or gas source has been detected. In such embodiments, the CPU **210** includes instructions to detect the presence of a wireless optical line-of-sight signal from another transceiver, for example, the valve transceiver **120**. The CPU **210** may include instructions to emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected. Similarly, the control module **200** may be configured to emit an alarm if communication between one or both of the CPU transceiver (s) **220**, **222** and one or both of the valve transceivers **120**, **121** has been lost during gas delivery. In such embodiments, the CPU **210** may include instructions to continuously detect the presence of a signal from another transceiver and emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected.

The CPU **210** may include instructions to alert a user when sensors in the control module **200** must be calibrated to ensure accurate delivery of gas to a patient. In addition, the CPU **210** may include instructions to correlate gas usage information from the circuit **150** of the valve assembly **100** to the patient information entered into the CPU memory **212**. The CPU **210** may also have instructions to store the correlated gas usage information and the patient information in the CPU memory **212**. The valve processor **122** may also include instructions detect patient information from the CPU memory **212**. Specifically, the valve processor **122** may include instructions to collect patient information via the valve transceiver **120** from the CPU transceiver **220** and store the collected patient information in the valve memory **134**. In such embodiments in which information from the CPU **210** is collected and stored in the valve memory **134**, the CPU **210** may include instructions that the patient information and/or correlated patient information and gas usage information be conveyed from the CPU memory **212** via the CPU transceiver **220** to the valve transceiver **120**. The valve processor **122** may also include instructions to correlate gas usage information with the collected patient information and store the correlated gas usage information and collected patient information in the valve memory **134**. Alternatively, the valve processor **122** may

include instructions to collect the correlated patient information and gas usage information from the CPU **210**. The correlated information may be utilized to bill the user according to patient. In addition, the correlated information may be utilized as patient demographic data, which can assist hospitals or other facilities to generate budget reports, determine usage per department, determine usage per patient diagnosis and link usage of multiple gas sources to individual patients.

A second aspect of the present invention pertains to a method for administering a therapy gas to a patient. The method includes providing a gas in a gas source. The gas source may be prepared by a supplier to contain a gas having a predetermined composition, concentration and expiration date. The method may include providing a valve assembly **100** attached to a gas source **50** to dispense the gas contained within the gas source **50** to a patient. The method may include entering gas data, which may include gas composition, gas concentration and gas expiration date, into the valve memory **134**. In one or more embodiments, the supplier may enter the gas data directly into the valve memory **134**. In another variant, the gas data is provided in the form of a bar code disposed on the gas source. In such embodiments, the method includes providing a scanner in communication with the data input **108**, scanning the bar code to collect the gas data information and conveying the gas data to the valve memory **134** via the data input **108**. These steps may be repeated for a second gas source. The gas source(s), with the valve assembly mounted thereon may be transported to a hospital or other facility for administration to a patient. The gas source(s) are then mounted onto the cart **500** and secured by the holding bracket **520** and mounting strap **530**. The method includes establishing communication between the valve transceivers disposed on each valve and the CPU transceivers **220**, **222**. Establishing communication may include positioning the valve assembly **100** in a line-of-sight path with at least one of the CPU transceivers **220**, **222**. As otherwise described herein, communication may be established by instructing the valve transceivers to send a wireless optical line-of-sight signal to the CPU transceivers **220**, **222**. The method may include instructing the valve transceiver **120** to send a wireless optical line-of-sight signal at pre-determined intervals, as otherwise described herein.

The method may include entering patient information into the CPU memory **212**. This step may be performed before or after the gas source(s) are mounted onto the cart. The method may specifically include entering patient information such as dosage information into the valve memory **134**. The method includes coordinating delivery of the gas to the patient by collecting gas data from the valve memory **134** and comparing the gas data with the patient information according to an algorithm and determining if the gas data and patient information match, according to the algorithm. Coordinating delivery of the gas may include turning on the actuator **114** of the valve **107** such that gas can flow from the inlet **104** to the outlet **106**. After the dose has been delivered, the method may include correlating the gas usage information and the patient information. The method may also include recording the patient information, gas usage information and/or the correlated patient information and gas usage information in the CPU memory **212** and/or the valve memory **134**. In one or more variants, the method may include utilizing the patient information, gas usage information and/or correlated patient information and gas usage information to generate invoices identifying the use of the gas by individual patients.

Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising:

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module; and

a circuit including:

memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration and

a processor and a transceiver in communication with the memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module that controls gas delivery to a subject and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired,

wherein the valve further comprises a data input in communication with said memory, to permit a user to enter the gas data into the memory.

2. The device of claim **1**, wherein the gas data is provided in a bar code disposed on the gas source and is entered into the data input by a user-operated scanning device in communication with the data input.

3. A gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising:

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module; and

a circuit including:

memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration and

a processor and a transceiver in communication with the memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module that controls gas delivery to a subject and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired,

wherein the valve comprises a power source; and the transceiver periodically sends the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent.

4. The device of claim **3**, wherein the duration of time at which no signal is sent comprises about 10 seconds.

5. A gas delivery system comprising:

a gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising:

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that controls gas delivery to a subject; and

a circuit including:

memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration and

a processor and a transceiver in communication with the memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired; and

the control module, wherein the control module is in fluid communication with the outlet of the valve and a ventilator and the control module comprises:

a CPU transceiver to receive line-of-sight signals from the transceiver; and

a central processing unit (CPUC in communication with the CPU transceiver and including a CPU memory,

wherein the transceiver communicates the gas data to the CPU transceiver for storage in the CPU memory, and

wherein the valve comprises a timer including a calendar timer and an event timer, wherein the memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

6. A gas delivery system comprising:

a gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising:

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that control gas delivery to a subject; and

a circuit including:

memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration and

a processor and a transceiver in communication with the memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired; and

the control module, wherein the control module is in fluid communication with the outlet of the valve and a ventilator and the control module comprises:

a CPU transceiver to receive line-of-sight signals from the transceiver; and

a central processing unit (CPU) in communication with the CPU transceiver and including a CPU memory,

wherein the transceiver communicates the gas data to the CPU transceiver for storage in the CPU memory,

wherein the control module further comprises an input means to enter patient information into the CPU memory; and a display, and

wherein the CPU compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver.

7. The system of claim 6, wherein the CPU comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match.

* * * * *

EXHIBIT I

US008776794B2

(12) **United States Patent**
Bathe et al.

(10) **Patent No.: US 8,776,794 B2**
(45) **Date of Patent: *Jul. 15, 2014**

(54) **NITRIC OXIDE DELIVERY DEVICE**

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(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(65) **Prior Publication Data**

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Related U.S. Application Data

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A62B 9/02 (2006.01)
F16K 31/02 (2006.01)

(52) **U.S. Cl.**
USPC **128/205.24**; 128/203.14; 128/204.21

(58) **Field of Classification Search**
CPC . A61M 5/168; A61M 5/16831; A61M 5/172; A61M 16/10; A61M 16/20; A61M 16/00; A61M 2205/14; A61M 2205/276; A61M 2205/3546; A61M 2205/3553; A61M 2205/3561; A61M 2205/3569; A61M 2205/60; A61M 2205/0072; A61M 2205/6081; A61M 2016/122; A61M 2016/1005; A61M 2016/102; A61M 2016/1025; A61M 2016/103; A61M 2016/1035; A61M 2016/20; A61M 2016/201; A61M 2016/202; A61M 2016/203; A61M 2016/204; A61M 2016/205; A62B 9/00; A62B 18/00
USPC 128/203.12, 203.14, 204.18, 128/204.21–204.23, 205.24, 898
See application file for complete search history.

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Primary Examiner — Justine Yu
Assistant Examiner — Michael Tsai
(74) *Attorney, Agent, or Firm* — Servilla Whitney LLC

(57) **ABSTRACT**

A nitric oxide delivery device including a valve assembly, a control module and a gas delivery mechanism is described. An exemplary gas delivery device includes a valve assembly with a valve and circuit including a memory, a processor and a transceiver in communication with the memory. The memory may include gas data such as gas identification, gas expiration and gas concentration. The transceiver on the circuit of the valve assembly may send wireless optical line-of-sight signals to communicate the gas data to a control module. Exemplary gas delivery mechanisms include a ventilator and a breathing circuit. Methods of administering gases containing nitric oxide are also described.

20 Claims, 12 Drawing Sheets

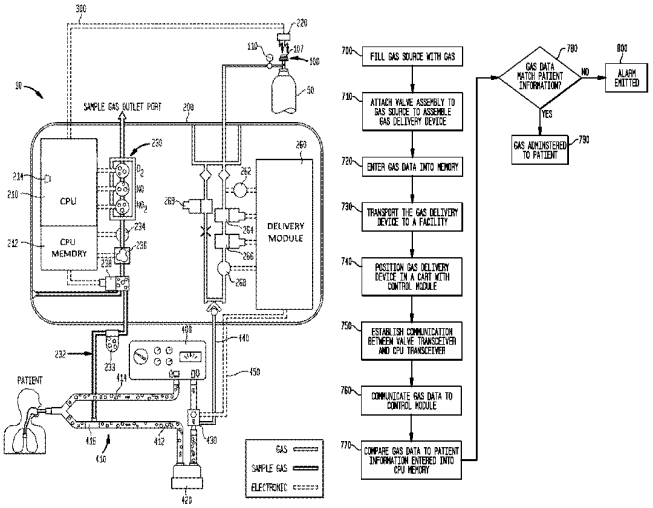

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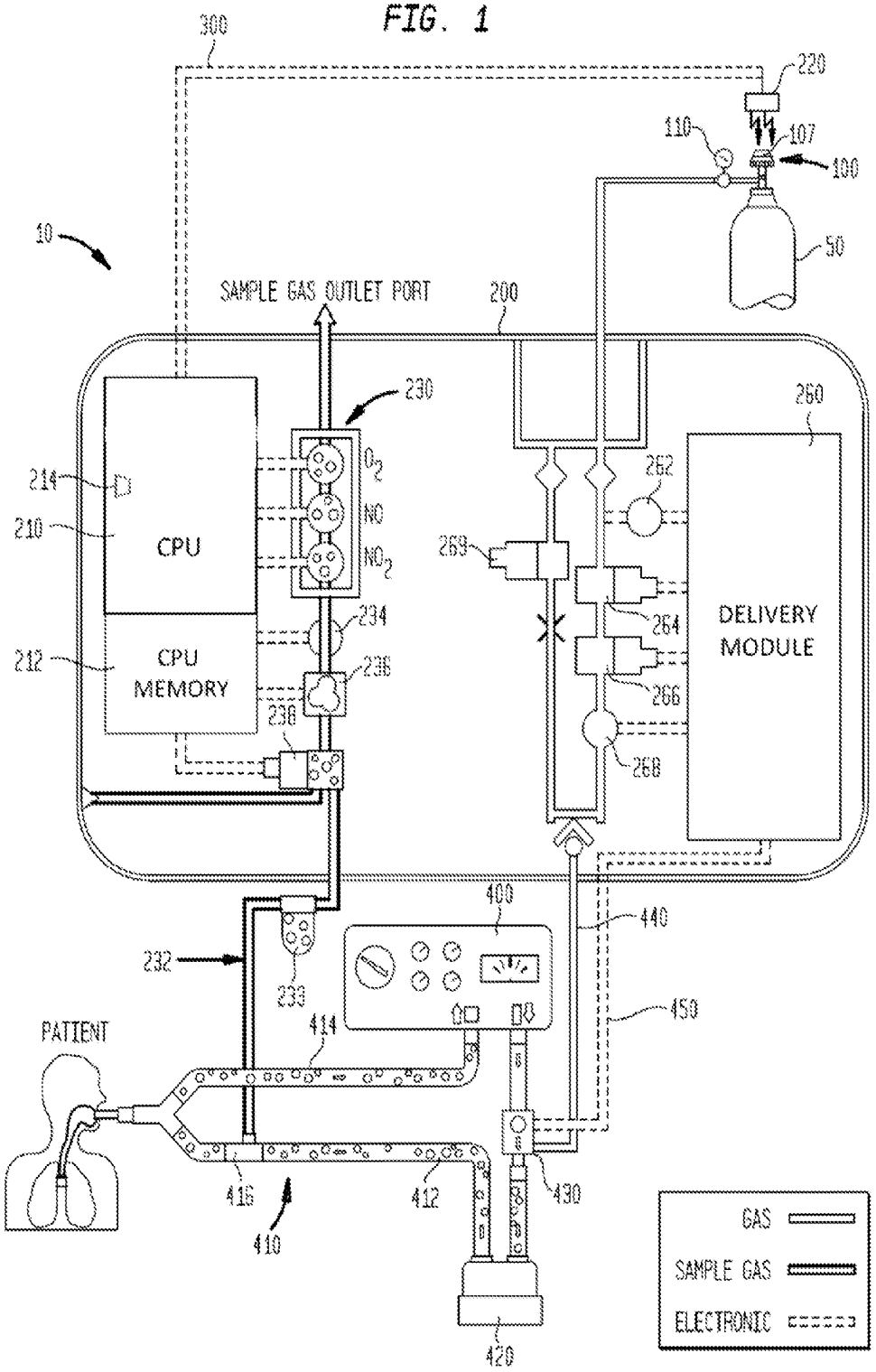
FIG. 1


300
220
110
107
100
10
50
SAMPLE GAS OUTLET PORT
200
230
260
214
210
CPU
O_2
NO
NO_2
262
269
212
CPU MEMORY
234
236
238
264
DELIVERY MODULE
266
268
400
440
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233
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450
PATIENT
416
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420
GAS
SAMPLE GAS
ELECTRONIC

FIG. 2

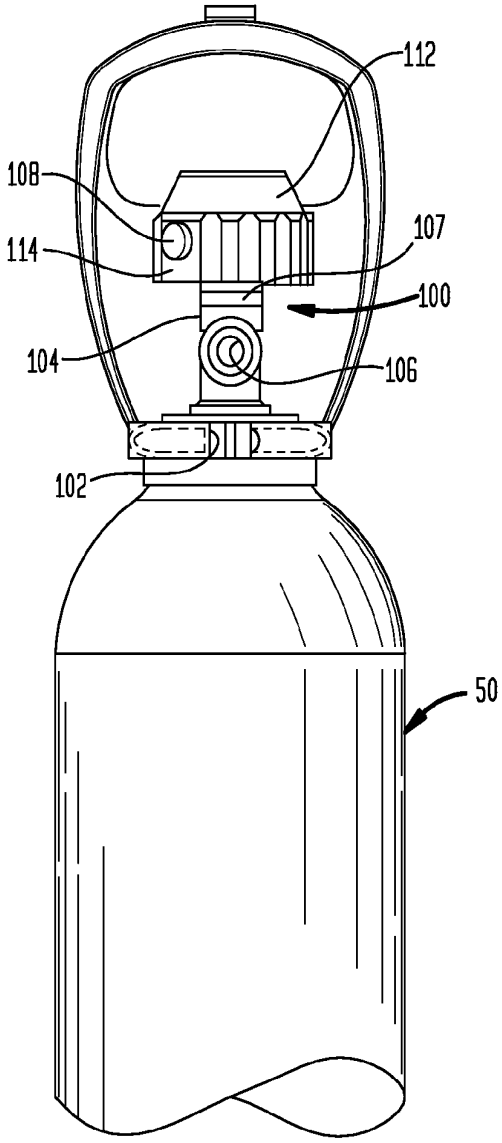


FIG. 3

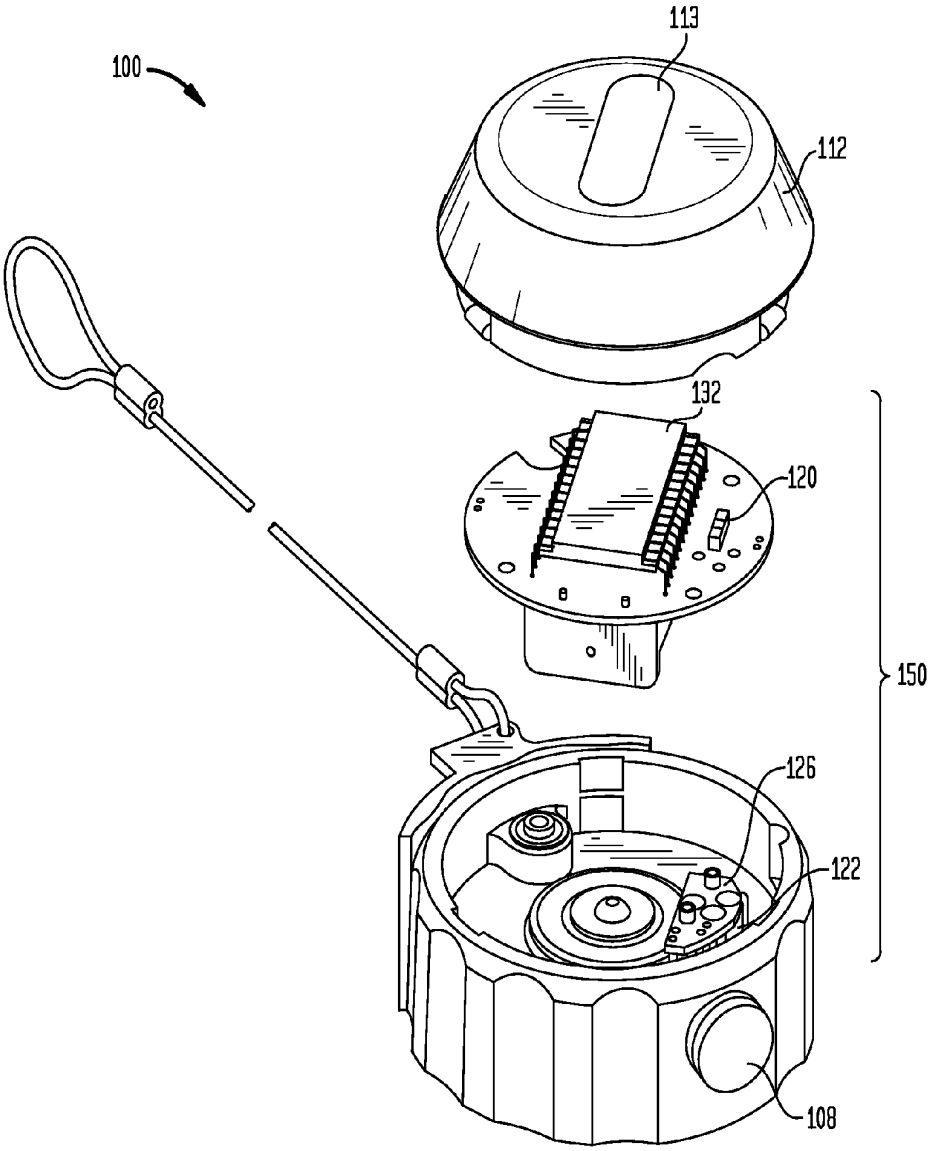


FIG. 4

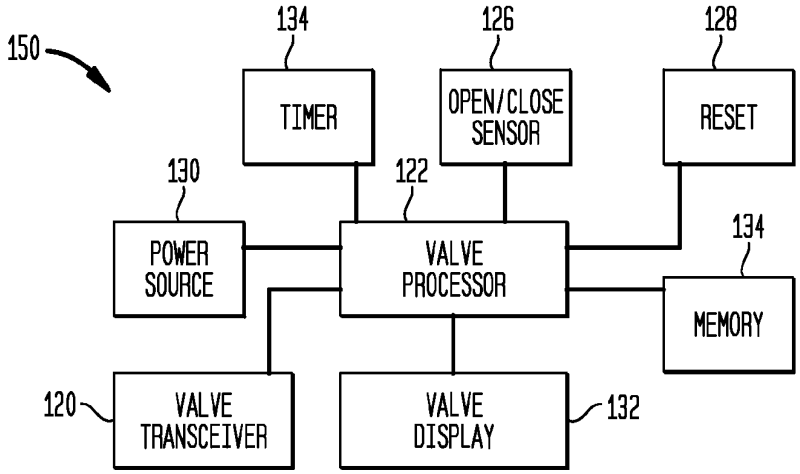

150
134
TIMER
126
OPEN/CLOSE SENSOR
128
RESET
130
POWER SOURCE
122
VALVE PROCESSOR
134
MEMORY
120
VALVE TRANSCEIVER
VALVE DISPLAY
132

FIG. 5

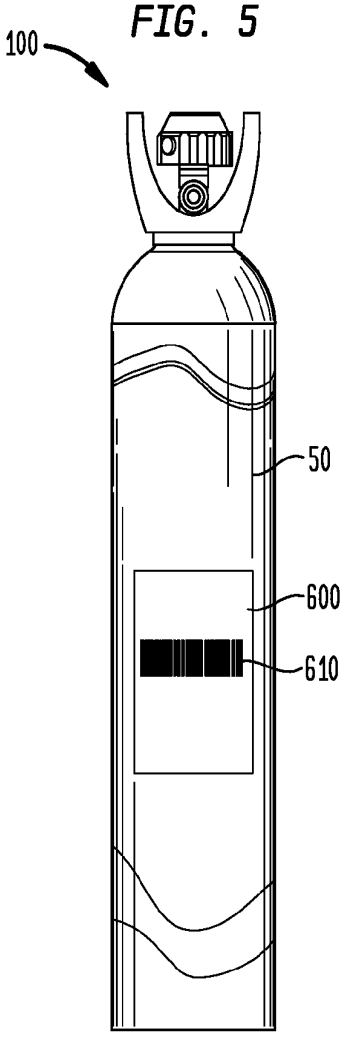

100
50
600
610

FIG. 6

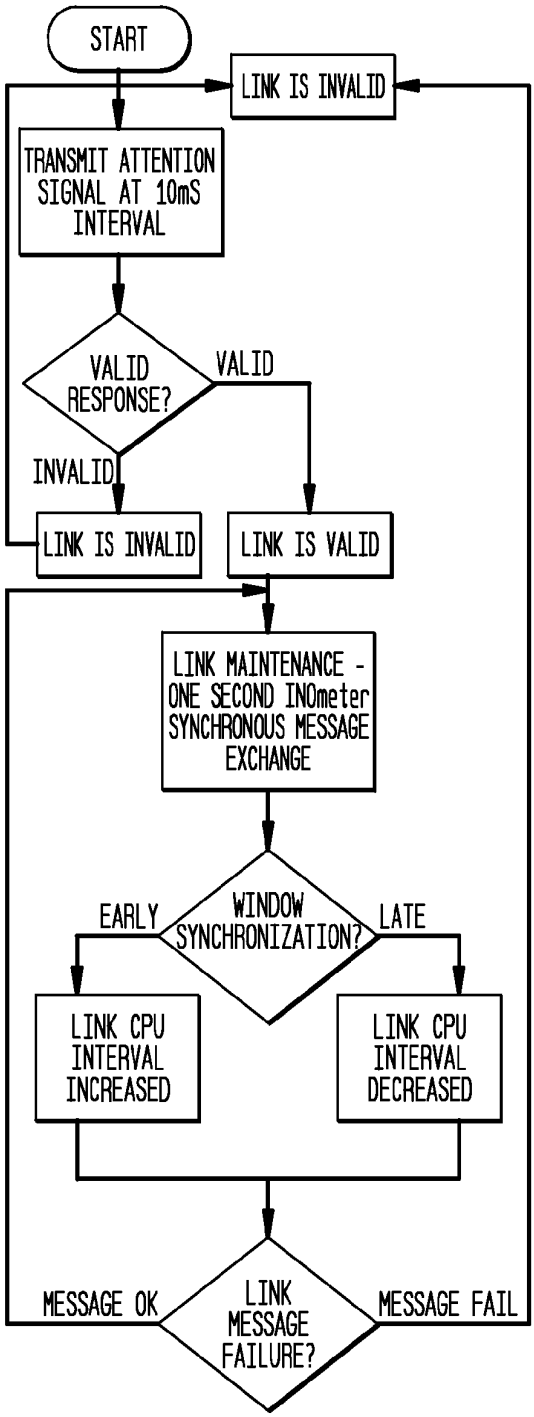

START
LINK IS INVALID
TRANSMIT ATTENTION SIGNAL AT 10mS INTERVAL
VALID RESPONSE?
VALID
INVALID
LINK IS INVALID
LINK IS VALID
LINK MAINTENANCE - ONE SECOND INOmeter SYNCHRONOUS MESSAGE EXCHANGE
WINDOW SYNCHRONIZATION?
EARLY
LATE
LINK CPU INTERVAL INCREASED
LINK CPU INTERVAL DECREASED
LINK MESSAGE FAILURE?
MESSAGE OK
MESSAGE FAIL

FIG. 7

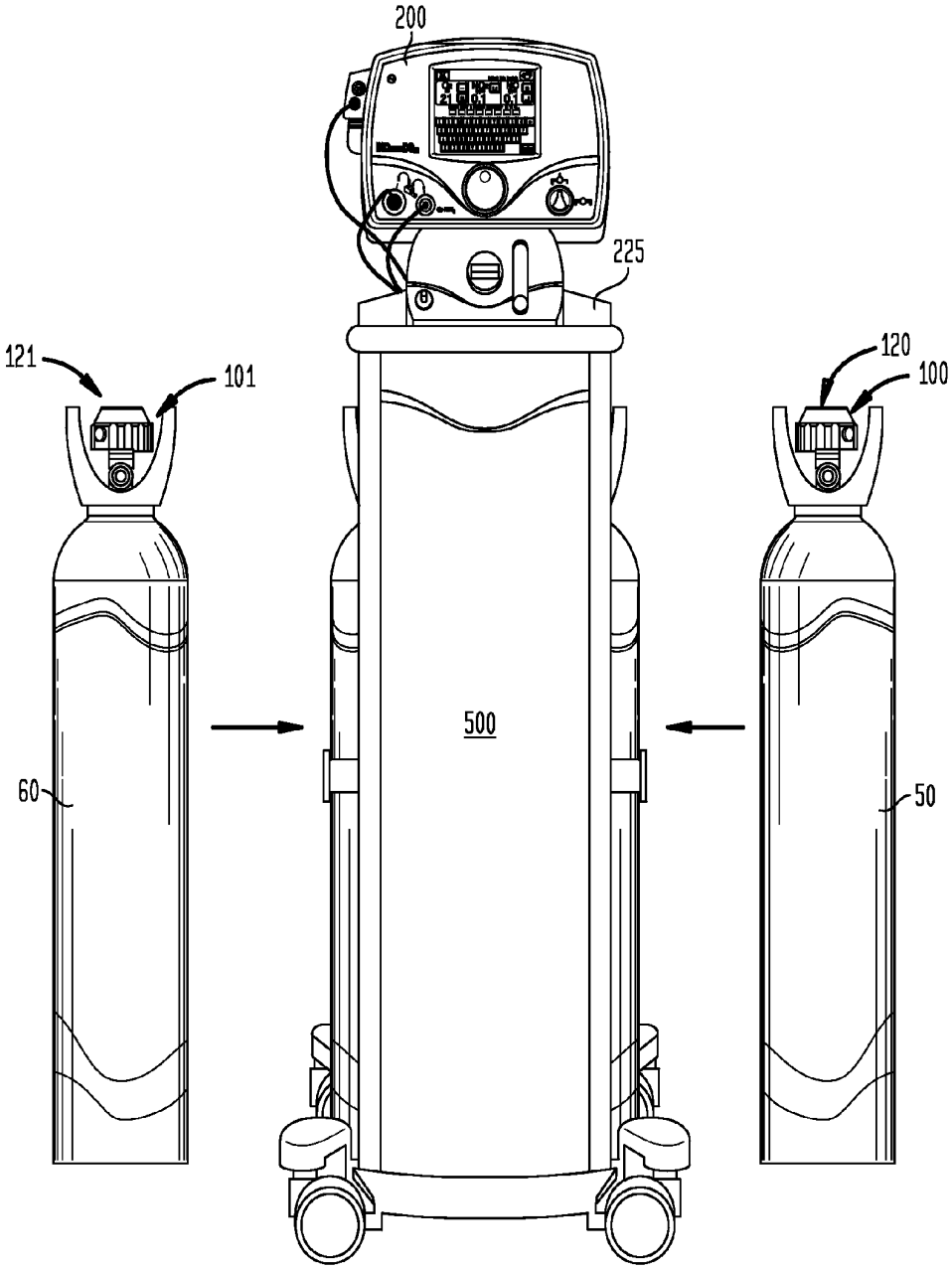


FIG. 8

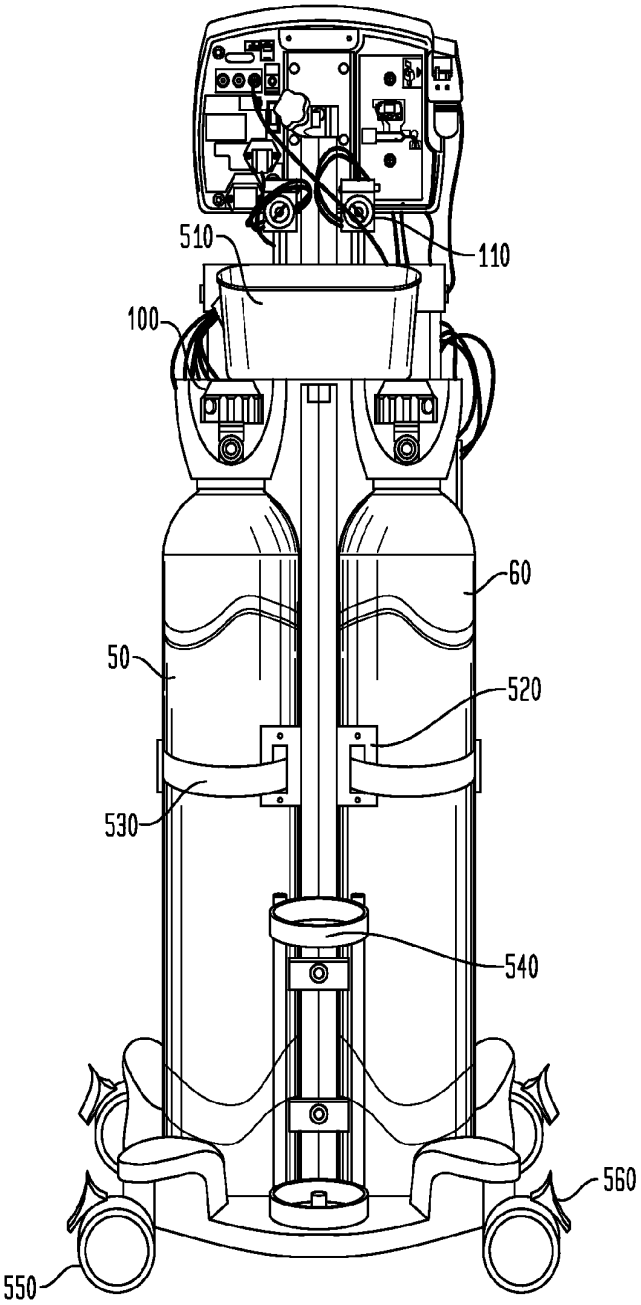


FIG. 9

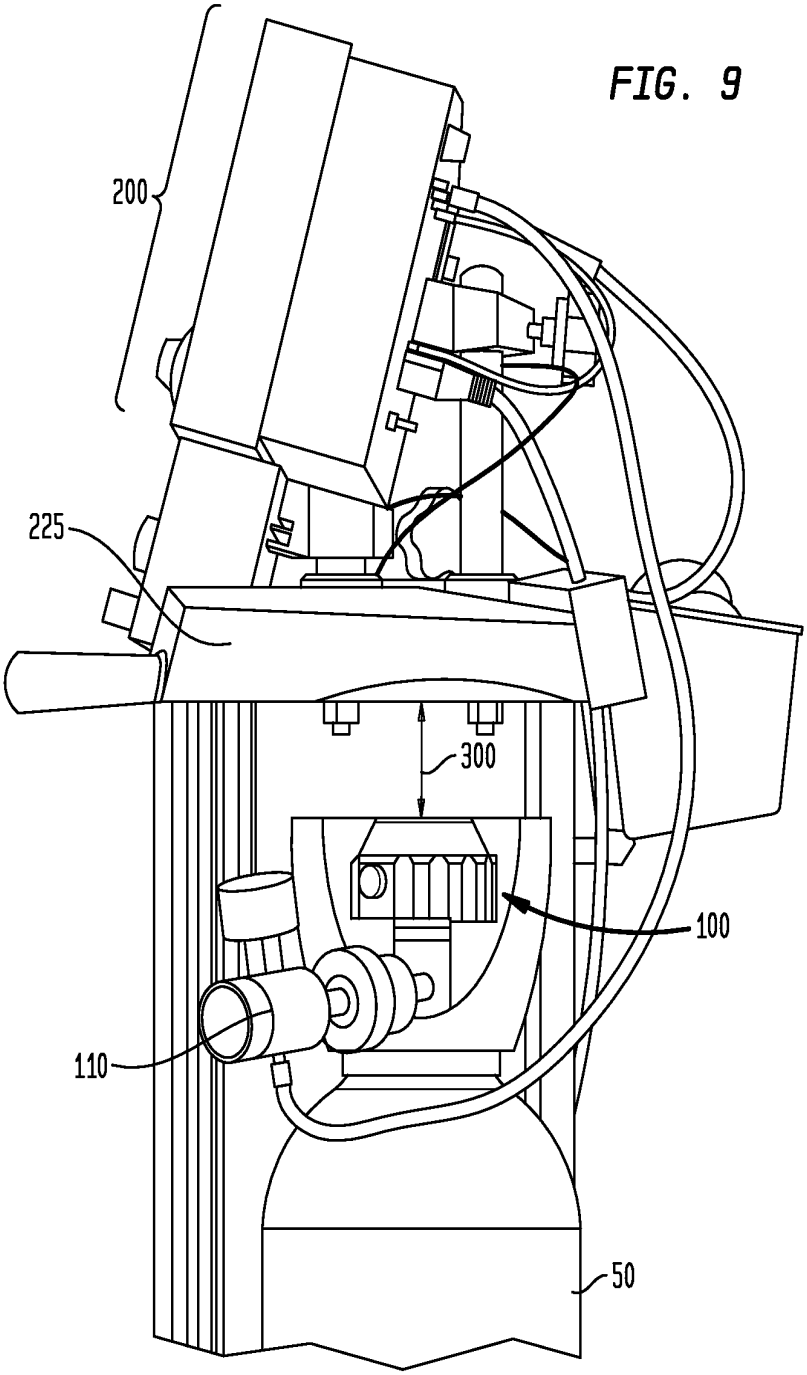


FIG. 10

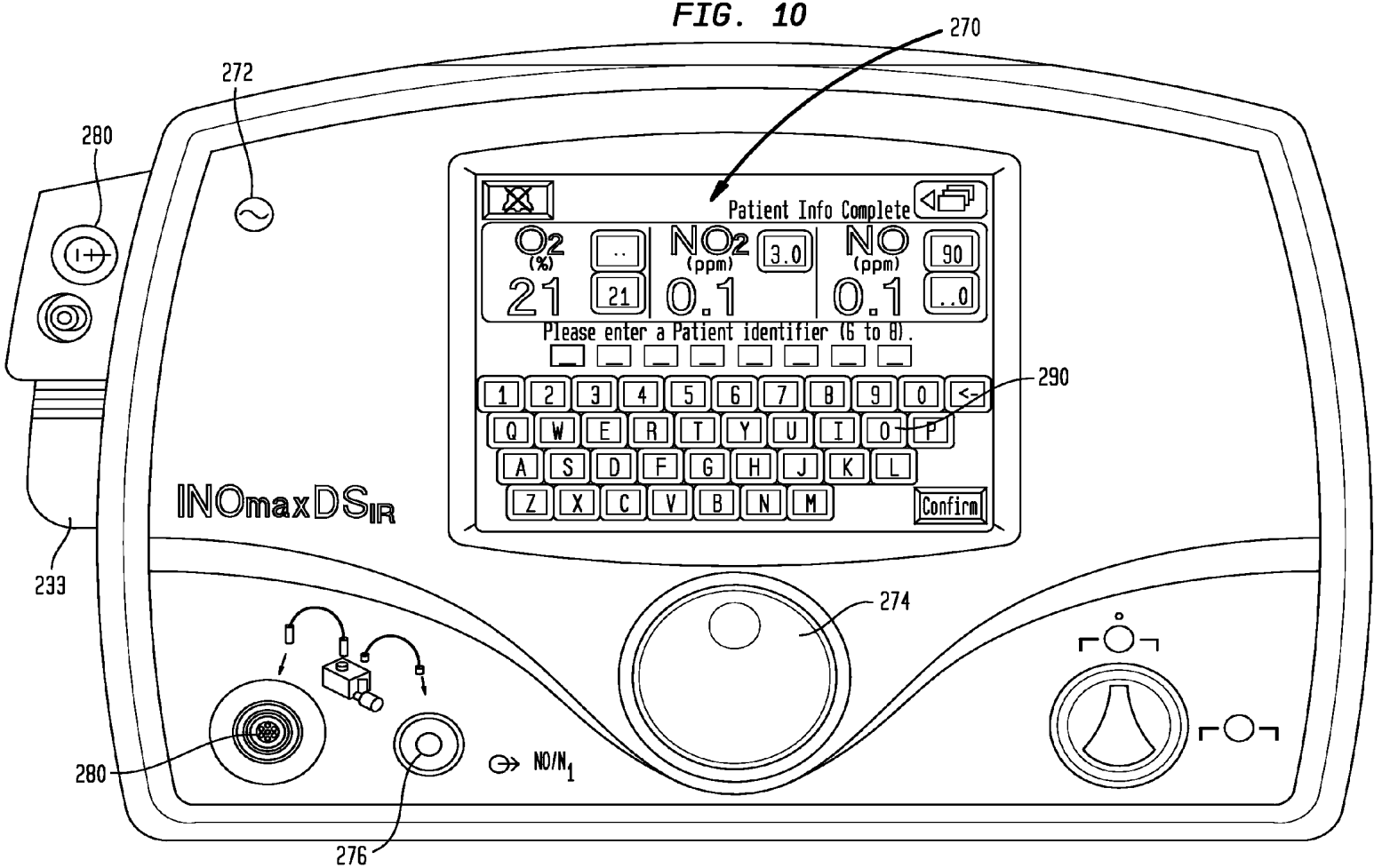

270
272
280
Patient Info Complete
O2 (%)
NO2 (ppm)
3.0
NO (ppm)
90
21
21
0.1
0.1
..0
Please enter a Patient identifier (6 to 8).
290
1 2 3 4 5 6 7 8 9 0 <-
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
Confirm
INOmaxDS IR
233
274
280
NO/N1
276

FIG. 11

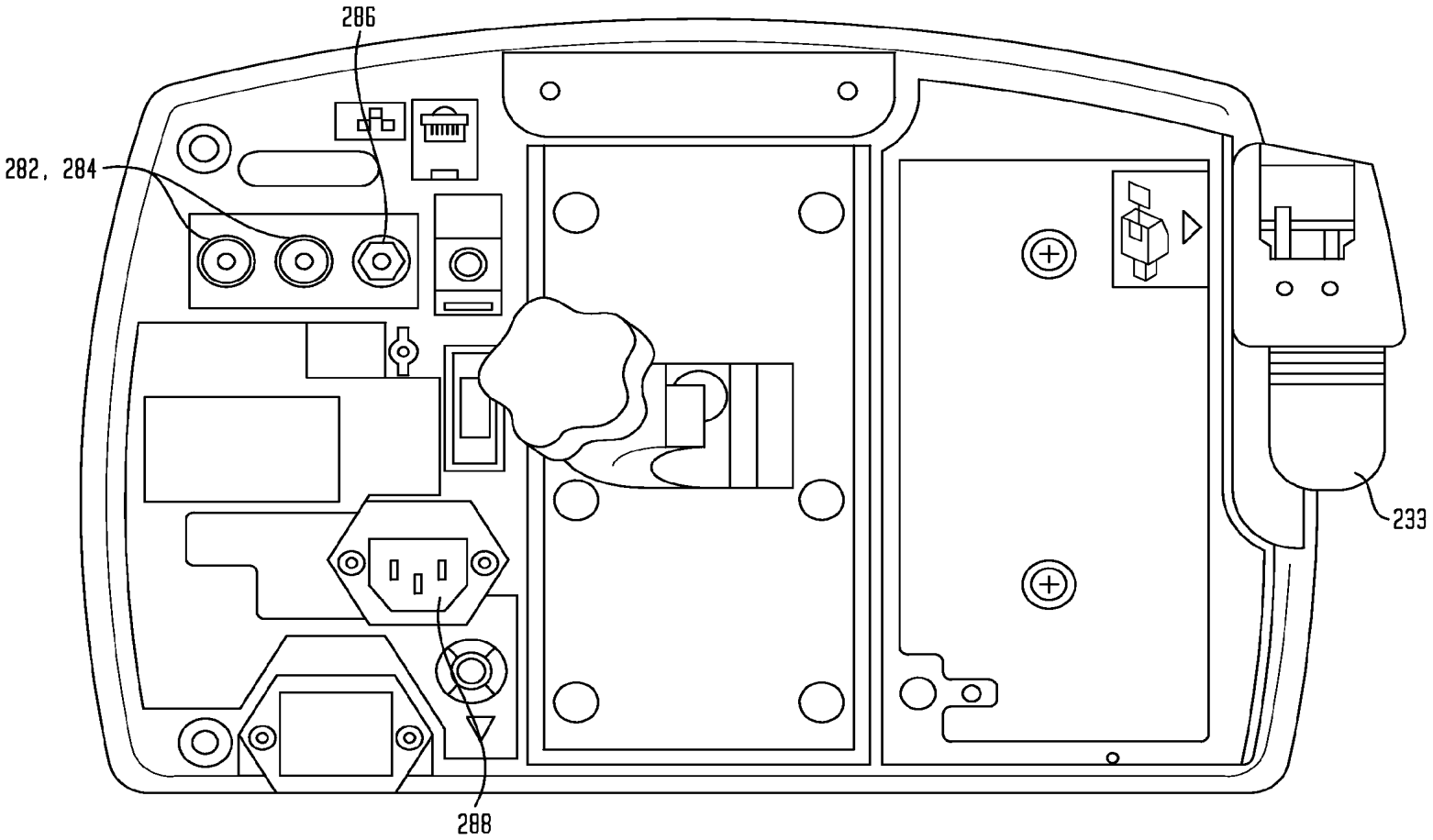


FIG. 12

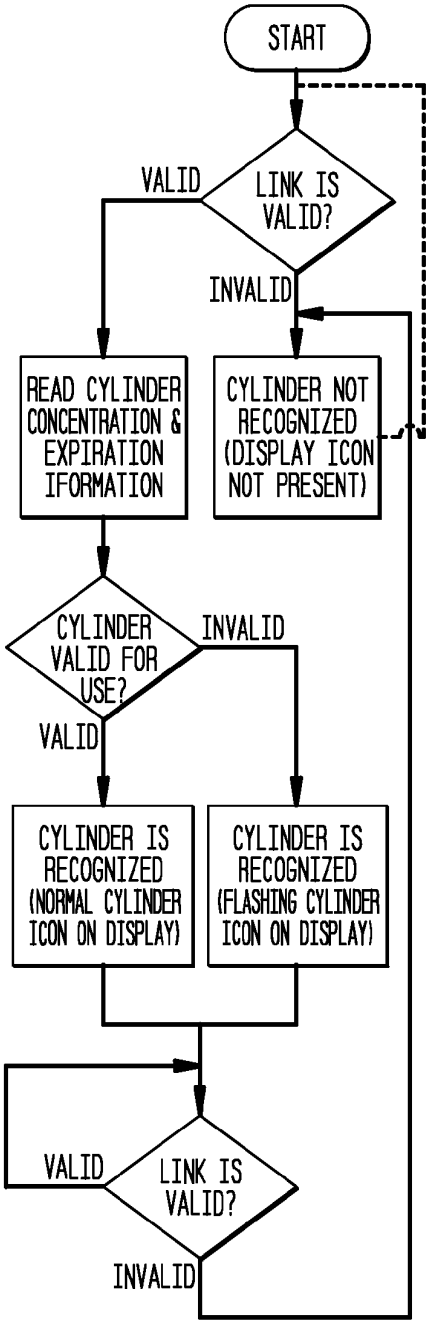
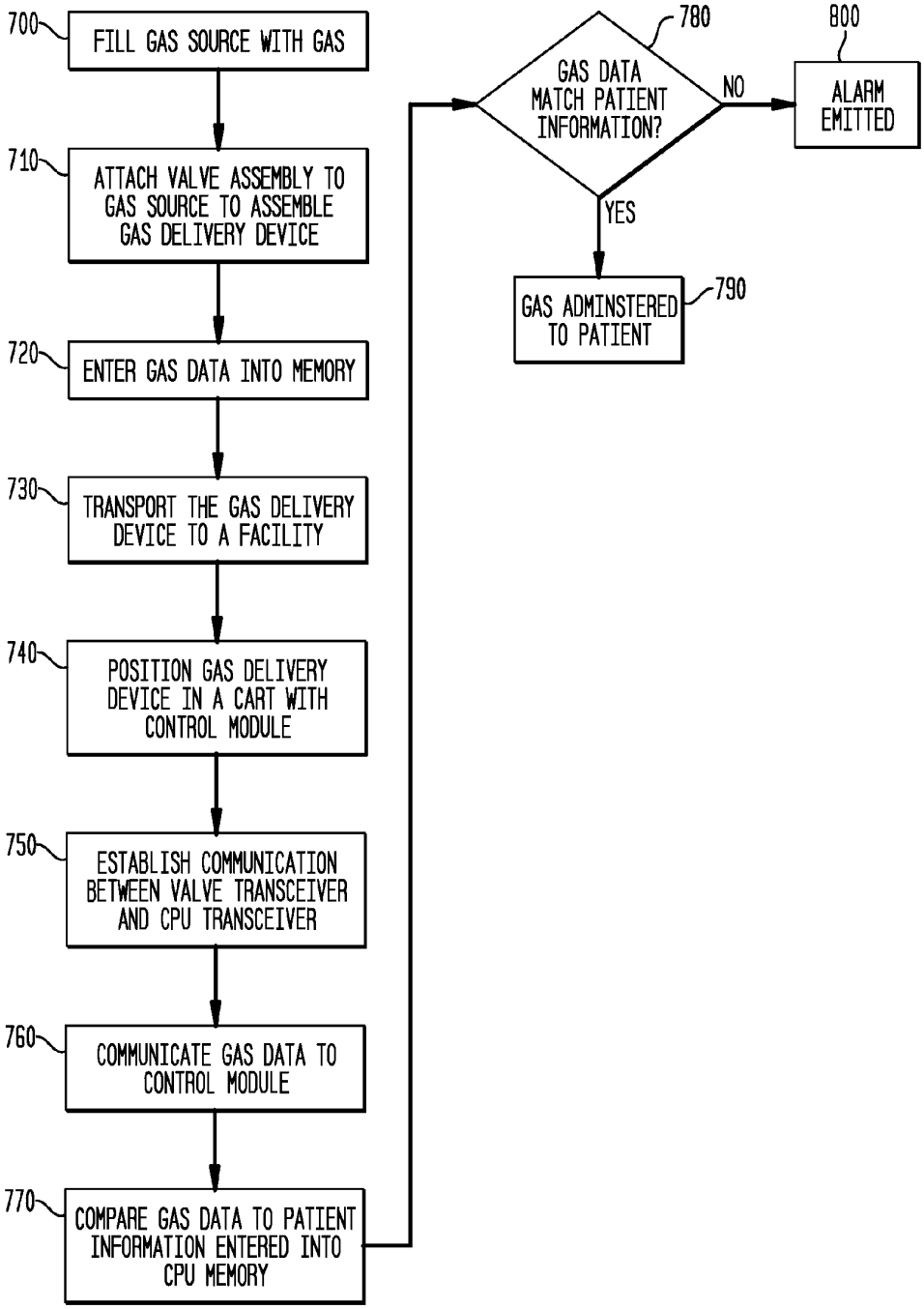

START
LINK IS VALID?
VALID
INVALID
READ CYLINDER CONCENTRATION & EXPIRATION IFORMATION
CYLINDER NOT RECOGNIZED (DISPLAY ICON NOT PRESENT)
CYLINDER VALID FOR USE?
INVALID
VALID
CYLINDER IS RECOGNIZED (NORMAL CYLINDER ICON ON DISPLAY)
CYLINDER IS RECOGNIZED (FLASHING CYLINDER ICON ON DISPLAY)
LINK IS VALID?
VALID
INVALID

FIG. 13


700
FILL GAS SOURCE WITH GAS
710
ATTACH VALVE ASSEMBLY TO GAS SOURCE TO ASSEMBLE GAS DELIVERY DEVICE
720
ENTER GAS DATA INTO MEMORY
730
TRANSPORT THE GAS DELIVERY DEVICE TO A FACILITY
740
POSITION GAS DELIVERY DEVICE IN A CART WITH CONTROL MODULE
750
ESTABLISH COMMUNICATION BETWEEN VALVE TRANSCEIVER AND CPU TRANSCEIVER
760
COMMUNICATE GAS DATA TO CONTROL MODULE
770
COMPARE GAS DATA TO PATIENT INFORMATION ENTERED INTO CPU MEMORY
780
GAS DATA MATCH PATIENT INFORMATION?
NO
800
ALARM EMITTED
YES
GAS ADMINSTERED TO PATIENT
790

NITRIC OXIDE DELIVERY DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/677,483 filed on Nov. 15, 2012, which is a continuation-in-part application of U.S. patent application Ser. No. 13/509,873 filed on May 15, 2012, which is the National Phase entry of PCT/US2011/020319, filed Jan. 6, 2011, the entire content of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

Embodiments of the present invention relate to gas delivery device for use in a gas delivery system for administering therapy gas and methods of administering therapy gas.

BACKGROUND

Certain medical treatments include the use of gases that are inhaled by the patient. Gas delivery devices are often utilized by hospitals to deliver the necessary gas to patients in need. It is important when administering gas therapy to these patients to verify the correct type of gas and the correct concentration are being used. It is also important to verify dosage information and administration.

Known gas delivery devices may include a computerized system for tracking patient information, including information regarding the type of gas therapy, concentration of gas to be administered and dosage information for a particular patient. However, these computerized systems often do not communicate with other components of gas delivery devices, for example, the valve that controls the flow of the gas to the computerized system and/or ventilator for administration to the patient. In addition, in known systems, the amount of gas utilized by a single patient is often difficult or impossible to discern, leading to possible overbilling for usage.

There is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is to be delivered by the gas delivery device. There is also a need for such an integrated device that does not rely on repeated manual set-ups or connections and which can also track individual patient usage accurately and simply.

SUMMARY

Aspects of the present invention pertain to a gas delivery device that may be utilized with a gas delivery system and methods for administering therapy gas to a patient. The therapy gas may comprise nitric oxide (NO). One or more embodiments of the gas delivery devices described herein may include a valve and a circuit with a valve memory in communication with a valve processor and a valve transceiver. One or more embodiments of the gas delivery systems described herein incorporate the gas delivery devices described herein with a control module including a central processing unit (CPU) in communication with a CPU memory and CPU transceiver. As will be described herein, the valve transceiver and the CPU transceiver may be in communication such that information or data from the valve memory and the CPU memory may be communicated to one another. The information communicated between the valve memory and the CPU memory may be utilized for selecting a therapy for delivery to a patient and controlling delivery of the selected therapy to the patient. The gas delivery devices and systems described herein may be utilized with medical devices such as ventilators and the like to delivery gas to a patient.

A first aspect of the present invention pertains to a gas delivery device. In one or more embodiments, the gas delivery device administers therapy gas from a gas source containing NO under the control of a control module. The control module may deliver the gas comprising NO to a patient in an amount effective to treat and/or prevent hypoxic respiratory failure and/or pulmonary hypertension. In one variant, the gas delivery device may include a valve attachable to the gas source and a circuit. The valve may include an inlet and an outlet in fluid communication and a valve actuator to open and close the valve to allow the gas to flow through the valve to a control module. The circuit of one or more embodiments includes a memory, a processor and a transceiver in communication with the memory to send wireless optical line-of-sight signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject. In one or more alternative embodiments, the signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject may be communicated via a wire. Examples of such wired signals may incorporate or utilize an optical cable, wired pair and/or coaxial cable. The circuit may include a memory to store gas data, which may include one or more of gas identification, gas expiration date and gas concentration. The transceiver may communicate to send the gas data to the control module via wireless optical line-of-sight signals.

In one or more embodiments, the valve may include a data input in communication with said memory, to permit a user to enter the gas data into the memory. The gas data may be provided in a bar code that may be disposed on the gas source. In such embodiments, the gas data may be entered into the data input of the valve for storage in the memory by a user-operated scanning device in communication with the data input. Specifically, the user may scan the bar code to communicate the gas data stored therein to the valve memory via the data input.

In one or more embodiments, the valve may include a power source. In such embodiments, the power source may include a battery or other portable power source. In one or more embodiments, the valve transceiver may periodically send the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent. In one or more specific embodiments, the duration of time at which no signal is sent comprises about 10 seconds.

A second aspect of the present invention pertains to a gas delivery device, as described herein, and a control module in fluid communication with the outlet of the valve of the gas delivery device and with a gas delivery mechanism, such as a ventilator. In one or more embodiments, the control module may include a CPU transceiver to receive line-of-sight signals from the transceiver and a CPU in communication with the CPU transceiver. The CPU carries out the instructions of a computer program or algorithm. As used herein the phrase "wireless optical line-of-sight signal" includes infrared signal and other signals that require a transmitter and receiver or two transceivers to be in aligned such that the signal may be transmitted in a straight line. The CPU may include a CPU memory that stores the gas data that is communicated by the valve transceiver of the gas delivery device to the CPU transceiver.

In one or more embodiments, the gas delivery system may incorporate a valve with a timer including a calendar timer and an event timer for determining or marking the date and time that the valve is opened and closed and the duration of time the valve is opened. In such embodiments, the valve memory stores the date and time of opening and closing of the valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

In one or more variants, the gas delivery system may incorporate a control module that further includes an input means to enter patient information into the CPU memory. The control module may also have a real time clock built into the CPU module such that the control module knows what the current time and date is and can compare that to the expiration date stored in the gas delivery device. If the expiration date is passed the current date then the control module can cause an alarm and not deliver drug to the patient. When the term "patient information" is used, it is meant to include both patient information entered by the user and information that is set during manufacturing, such as the gas identification and the gas concentration that the control module is setup to deliver. The control module may also include a display. In one or more embodiments, the display incorporates an input means for entering patient information into the CPU memory. In one or more embodiments, the CPU of the control module compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver. The CPU or control module may include comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match or conflict. As used herein the phrase "do not match," includes the phrase "are not identical," "are not substantially identical," "do conflict" and/or "do substantially conflict." The CPU determines whether the patient information and additional data, or other data set matches by performing a matching algorithm which includes criteria for establishing whether one set of data (i.e. patient information) and another set of data match. The algorithm may be configured to determine a match where every parameter of the data sets match or selected parameters of the data sets match. The algorithm may be configured to include a margin of error. For example, where the patient information require a gas concentration of 800 ppm, and the additional data includes a gas concentration of 805 ppm, the algorithm may be configured to include a margin of error of ±5 ppm such it determines that the patient information and the additional data match. It will be understood that determining whether the patient information and additional data match will vary depending on the circumstances, such as variables in measuring gas concentration due to temperature and pressure considerations.

A third aspect of the present invention pertains to a control module memory comprising instructions that cause a control module processor to receive gas data from a valve via a wireless optical line-of-sight signal. The valve may be connected to a gas source containing NO and may include a memory for storing the gas data. The control module memory may include instructions that cause the control module processor to compare the gas data with user-inputted patient information. The user-inputted patient information may be stored within the control module memory. Gas data may be selected from one or more of gas identification, gas expiration date and gas concentration. In one or more embodiments, the control module memory may include instructions to cause the control module processor to coordinate delivery of therapy to the patient with a medical device, such as a ventilator and the like for delivering gas to a patient, via the wireless optical line-of-sight signal. The control module memory may also include instructions to cause the control module processor to select a therapy for delivery to a patient based on the received patient information and control delivery of the selected therapy to the patient.

In one or more embodiments, the memory may include instructions to cause the processor to detect the presence of more than one valve and whether more than one valve is open at the same time. In accordance with one or more specific embodiments, the memory includes instructions to cause the processor to receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas source, receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas source, compare the first valve status and the second valve status, and emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position. In one or more alternative embodiments, the first valve status and the second valve status may be communicated to the processor via a single wireless optical line-of-sight signal, instead of separate wireless optical line-of-sight signals. In a more specific embodiment, the memory of one or more embodiments may include instructions to cause the processor to terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

In one or more embodiments, the memory may include instructions to cause the processor to emit an alarm when a desired dose has been delivered through a valve. In such embodiments, the processor may include a memory to store the desired dose or dosage information. In such embodiments, the memory may include instructions to cause the processor to receive gas delivery information or information regarding the amount of gas delivered and compare the gas delivery information to the dosage information and emit an alarm when the gas delivery information and the dosage information match. As used herein, the term "dosage information" may be expressed in units of parts per million (ppm), milligrams of the drug per kilograms of the patient (mg/kg), millimeters per breath, and other units known for measuring and administering a dose. In one or more embodiments, the dosage information may include various dosage regimes which may include administering a standard or constant concentration of gas to the patient, administering a gas using a pulsed method. Such pulsing methods includes a method of administering a therapy gas to a patient during an inspiratory cycle of the patient, where the gas is administered over a single breath or over a plurality of breaths and is delivery independent of the respiratory pattern of the patient.

A fourth aspect of the present invention pertains to a method for administering a therapy gas to a patient. The therapy gas may comprise NO. In one or more embodiments, the method includes establishing communication between the patient and a gas delivery device via a transceiver, wherein the gas delivery device comprises a first memory including gas data, comparing the gas data with patient information stored within a second memory. The second memory may be included within a control module in communication with the gas delivery device. After comparing the gas data and the patient information, the method may further include coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal, selecting a

therapy for delivery to the patient based on the comparison of the gas data and the patient information and controlling delivery of the selected therapy to the patient. In one or more specific embodiments, the method may include entering the gas data into the first memory of the gas delivery device and/or entering the patient information into the second memory. In embodiments in which the method includes entering the patient information into the second memory, the control module may include input means by which patient information may be entered into the second memory. In one or more variants, the method includes ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information. The method may include emitting an alert based on the comparison of the gas data and the patient information.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of a gas delivery system including a gas delivery device, a gas source, a control module and a gas delivery mechanism, according to one or more embodiments;

FIG. **2** illustrates a valve assembly of the gas delivery device according to one or more embodiments attached to a gas source;

FIG. **3** illustrates a disassembled view of the valve assembly shown in FIG. **2**;

FIG. **4** is a diagram showing a circuit supported in the valve assembly shown in FIG. **2**, according to one or more embodiments;

FIG. **5** illustrates an exemplary gas source for use with the valve assembly shown in FIG. **2**;

FIG. **6** is an operational flow diagram of the communication between the circuit of the gas delivery device shown in FIG. **1** with a control module regarding the establishment of communication between the circuit and the control module

FIG. **7** illustrates a front view of an exemplary gas delivery system;

FIG. **8** illustrates a back view of the gas delivery system shown in FIG. **7**;

FIG. **9** illustrates a partial side view of the gas delivery system shown in FIG. **7**;

FIG. **10** illustrates a front view of a control module according to one or more embodiments;

FIG. **11** illustrates a back view of the control module shown in FIG. **10**;

FIG. **12** is an operational flow diagram of the communication between the circuit of the gas delivery device and the control module shown in FIG. **1** regarding the gas contained within a gas source; and

FIG. **13** is an operational flow diagram of the preparation of a gas delivery device and use within the gas delivery system according to one or more embodiments.

DETAILED DESCRIPTION

Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

A system for the administration of therapy gas is described. A first aspect of the present invention pertains to a gas delivery device. The gas delivery device may include a valve assembly including at least one valve with a circuit. The gas delivery system may include the gas delivery device (e.g. valve assembly, including a valve and a circuit) in communication with a control module to control the delivery of gas from a gas source to a ventilator or other device used to introduce the gas into the patient, for example, a nasal cannula, endotracheal tube, face mask or the like. Gas source, as used herein, may include a gas source, gas tank or other pressured vessel used to store gases at above atmospheric pressure. The gas delivery system **10** is shown in FIG. **1**. In FIG. **1**, the valve assembly **100**, including a valve **107** or valve actuator and a circuit **150**, is in communication with a control module **200** via a wireless line-of-sight connection **300**. In one or more alternative embodiments, communication between the valve assembly **100** and the control module **200** may be established via a wired signal. The gas delivery system **10** also includes a gas source **50** including a gas attached to the valve assembly **100** and a gas delivery mechanism, which includes a ventilator **400** and a breathing circuit **410**, in communication with the control module **200**.

FIGS. **2-4** illustrate the components of the valve assembly **100**. The valve assembly **100** includes a valve **107** and a circuit **150** supported in the valve assembly. FIG. **3** illustrates a disassembled view of the valve assembly **100**, showing components of the physical circuit **150** and the valve **107**. As shown in FIG. **4**, which will be described in more detail below, the circuit **150** of the gas delivery device includes a valve transceiver **120** for establishing communication with the control module **200**, which will also be discussed in greater detail below.

Referring to FIG. **2**, the valve **107** includes an attachment portion **102** for attaching the valve assembly **100** to the gas source **50**, an inlet **104** and an outlet **106** in fluid communication with the inlet **104**, as more clearly shown in FIG. **2**.

FIG. **3** illustrates a disassembled view of the valve assembly **100** and illustrates an actuator **114** is disposed on the valve **107** and is rotatable around the valve **107** for opening and closing the valve **107**. The actuator **114** includes a cap **112** mounted thereto. As shown in FIG. **3**, the circuit **150** may include a data input **108** disposed on the actuator **114**. The data input **108** may be disposed at other locations on the valve **107**. In one or more variants, the data input may include a port such as a USB port, a receiver for receiving electronic signals from a transmitted or other known input means known in the art for entering information or data into a memory.

FIG. **4** illustrates a block diagram of the circuit **150**. The circuit **150** shown in FIG. **4** includes a valve processor **122**, a valve memory **134**, a reset **128**, a valve transceiver **120** and a power source **130**. The circuit **150** may also include support circuits a timer **124**, a sensor **126** and/or other sensors. Referring to FIG. **3**, the circuit **150** is supported within the valve assembly **100**, with the physical components of the circuit **150** specifically disposed between actuator **114** and the cap **112**. As shown in FIG. **3**, the valve display **132** and the valve transceiver **120** are disposed adjacent to the cap **112**, such that the valve display **132** is visible through a window **113**. The sensor **126** and the valve processor **122** are disposed beneath the valve display **132** and the valve transceiver **120**, within the actuator **114**.

The valve processor **122** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The valve memory **134**, or computer-readable medium, may be one or more of readily available memory such as electrically erasable programmable read only memory (EEPROM), random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the valve processor **122**. The support circuits may be coupled to the valve processor **122** for supporting the circuit **150** in a conventional manner.

These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like.

In the embodiment shown, the valve memory **134** communicates with a data input **108** disposed on the side of the actuator **114**. The data input **108** shown in FIGS. **3-4** is used to transfer data from the valve memory **134** to other devices or to input data into the valve memory **134**. For example, gas data, which includes information regarding the gas contained within the gas source, may be entered into the valve memory **134** via the data input **108**. In one or more alternative embodiments, the gas data may be programmed or directly entered into the valve memory **134** by the gas supplier. In one or more embodiments, the gas data may be provided in the form of a bar code **610** that is disposed on a label **600** that is affixed on a to the side of the gas source, as shown in FIG. **5**. The bar code **610** may be disposed directly on the gas source. An external scanning device in communication with the electronic data input **108** may be provided and may be used to scan the bar code **610** and convey the information from the bar code **610** to the valve memory **134**. Gas data may include information regarding the gas composition (e.g., NO, O_2, NO_2, CO, etc.), concentration, expiration date, batch and lot number, date of manufacturing and other information. Gas data may be configured to include one or more types of information. The valve processor **122** may include instructions to convey all or a pre-determined portion of the gas data via the valve transceiver **120** to another transceiver.

In embodiments that utilize a timer **124**, the timer **124** may include two sub-timers, one of which is a calendar timer and the other of which is an event timer. The reset **128** may be located inside the actuator **114** and may be depressed to reset the event timer. The cap **112** also includes a window **113** that allows the user to see the valve display **132** disposed within the cap **112** that displays information regarding whether the actuator **114** is opened or closed and the duration the valve **107** was opened or closed. In one or more embodiments, the valve display **132** may alternate flashing of two different numbers, a first number may be accumulated open time, and the second number may be the time at which the valve **107** was opened for the current event. The time at which the valve **107** was opened for a current event may be preceded by other indicators.

The sensor **126** disposed within the actuator **114** may include a proximity switch model MK20-B-100-W manufactured by Meder Inc. The sensor **126** utilized in one or more embodiments may cooperate with a magnet (not shown) to sense whether the actuator **114** is turned on or turned off. Such sensors are described in U.S. Pat. No. 7,114,510, which is incorporated by reference in its entirety.

For example, the sensor **126** and a corresponding magnet (not shown) may be disposed on a stationary portion of the valve **107**. When the actuator **114** is rotated to the closed position, the sensor **126** is adjacent to the magnet that is in a fixed position on the valve **107**. When the sensor **126** is adjacent to the magnet, it sends no signal to the valve processor **122**, thereby indicating that the actuator **114** is in the "closed" position or has a valve status that includes an open position or a closed position. When the actuator **114** is rotated to open the valve **107**, the sensor **126** senses that it has been moved away from the magnet and sends a signal to the valve processor **122**, indicating an "open" position. The valve processor **122** instructs the valve memory **134** to record the event of opening the valve **107** and to record the time and date of the event as indicated by the calendar timer. The valve processor **122** instructs the valve memory **134** to continue checking the position of the valve **107** as long as the valve **107** is open. When the valve **107** is closed, the valve processor **122** uses the logged open and close times to calculate the amount of time the valve **107** was open and instructs the valve memory **134** to record that duration and the accumulated open time duration. Thus, every time the valve **107** is opened, the time and date of the event is recorded, the closing time and date is recorded, the duration of time during which the valve **107** is open is calculated and recorded, and the accumulated open time is calculated and recorded.

In one or more embodiments in which the power source **130** includes a battery, the valve transceiver **120** may be configured to communicate with the CPU transceiver **220** to preserve the life of the battery. In this embodiment the valve transceiver **120** is only turned on to receive a signal from the Control Module CPU transceiver **220** for 20 msec every second. The control module CPU transceiver **220** sends out a short transmit signal continuously and if the valve transceiver **120** is present it responds in the 20 msec interval. This conserves battery power as the valve transceiver **120** is only powered on for 20 msec every second. When the valve transceiver **120** responds it includes in its signal information regarding whether the communication from the control module CPU transceiver **220** was early or late within this 20 msec window. This ensures that once communications has been established it is synchronized with the 20 msec window that the valve transceiver **120** is powered on and able to receive communications. For example, as shown in FIG. **6**, the valve transceiver **120** sends a wireless optical line-of-sight signal during a pre-determined interval in response to a signal from the control module CPU transceiver **220**. The wireless optical line-of-sight signals sent by the valve transceiver **120** are a series of on off cycles where the transmitter is either transmitting light or is not and these correspond to digital binary signals. The mechanism by which the valve transceiver sends a wireless optical line-of-sight signal may be construed as a series of digital on off signals that correspond to data being transmitted. Once communications has been established between the control module CPU transceiver **220** and the valve transceiver **120**, the interval between communication signals may be in the range from about 20 seconds to about 5 seconds. In one or more specific embodiments, the interval or duration between transceiver signals may be about 10 seconds.

As will be described in more detail below, the control module **200** includes a CPU **210** which is connected to a CPU transceiver **220** which can send and receive wireless optical line-of-sight signals. The CPU transceiver **220** sends out a signal and waits for a response from the valve transceiver **120** when communication or more specifically, line-of-sight communication is established between the CPU transceiver **220** and the valve transceiver **120**. If no response is sent by the valve transceiver **120**, the CPU transceiver **220** sends another signal after a period of time. This configuration preserves battery life because the valve transceiver **120** does not continuously send a signal unless requested to by the CPU **210**. This is important as the gas delivery device and gas source spends most of its time in shipping and storage prior to being placed on the gas delivery system, if it was transmitting all this time trying to establish communications with the control module it would be consuming the battery life significantly.

The valve processor **122** may include link maintenance instructions to determine whether the interval should be increased or decreased. As shown in FIG. **6**, when a valid link is established between the valve transceiver **120** and CPU transceiver **121**, the valve processor **122** executes the link maintenance instructions to increase the interval or decrease the interval.

As shown more clearly in FIG. **1**, valve assembly **100** and gas source **50** is in communication with a control module **200**, which is in communication with a gas delivery mechanism. The gas delivery mechanism shown in FIG. **1** includes a ventilator **400** with associated breathing circuit **410**. The control module **200** may include a CPU **210** and a CPU transceiver **220** in communication with the circuit **150** via the valve transceiver **120**. The control module **200** also includes a CPU memory **212** in communication with the CPU transceiver **220** to store patient information, information or data received from the valve transceiver **120** and other information. The control module **200** may also include support circuits. The CPU **210** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The CPU memory **212**, or computer-readable medium, may be one or more of readily available memory such as random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the CPU **210**. The support circuits may be coupled to the CPU **210** for supporting the control module **200** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like. The CPU **210** may also include a speaker **214** for emitting alarms. Alternatively, alarms may also be displayed visually on a display. As shown in FIG. **1**, the control module **200** may also include a regulator **110** and, optionally, pressure gauges and flow meters for determining and/or controlling the gas flow from the gas source **50**.

In one or more embodiments, the CPU transceiver **220** is disposed on a cover portion **225** (shown more clearly in FIG. **7**), that is part of a cart **500** (show more clearly in FIG. **7**) onto which the control module **200** is disposed. The cover portion **225** in one or more embodiments is in communication with the control module **200**. Communication between the cover portion **225** and the control module **200** may be established wirelessly or via a cable. As will be discussed in greater detail below, the valve assembly **100**, including the valve **107**, the circuit **150** and a gas source **50** attached to the valve **107**, are placed on the cart **500** in proximity and in a light-of-sight path with the CPU transceiver **220**. When properly configured such that communication is established between the valve transceiver **120** and the CPU transceiver **220**, the CPU transceiver **220** is positioned directly above the valve transceiver **120**, as shown more clearly in FIG. **9**. In one or more alternative embodiments, the CPU transceiver **220** may be disposed on the CPU **210**.

The CPU **210** may be in communication with a plurality of gas sensors **230** for determining the concentration of a sample of gas drawn via a sample line **232** and a sample line inlet **280** (shown more clearly in FIG. **1**) disposed on the control module **200**. As will be discussed in greater detail, the sample line **232** draws a sample of gas from a breathing circuit **410** of a ventilator **400** when the ventilator is in fluid communication with the control module **200** and gas is being delivered to the ventilator. The CPU **210** may also be in communication with a sample flow sensor **234** for sensing the flow of the sample drawn via sample line **232**, a pump **236** for drawing the sample via the sample line **232** to the flow sensor **234** and zero valve **238** controlling the flow of the sample via the sample line **232** to the sample pump **236**, sample flow sensor **234** and the plurality of CPU sensors. The sample line **232** may include a water trap **233** for collecting any water or liquid from the sample.

The control module **200** may also include a delivery module **260** for regulating the flow of gas from the gas source **50** to the ventilator **400**. The delivery module **260** may include a pressure switch **262** for determining a gas supply pressure is present, a pressure shut-off valve **264**, a proportional valve **266** and a delivery flow sensor **268**. The delivery module **260** may also include a backup on/off switch **269**. The detailed method of how the delivery module delivers the gas to the ventilator circuit is described in U.S. Pat. No. 5,558,083 which is incorporated here by reference in its entirety.

The ventilator **400** shown in FIG. **1** is in fluid communication with the control module **200** via an injector tubing **440** and in electrical communication via an injector module cable **450**. The control module **200** and more specifically, the CPU **210**, is in fluid communication with the ventilator **400** via the sample line **232**. The ventilator **400** may include a breathing circuit **410** with an inspiratory limb **412** and an expiratory limb **414** in fluid communication with the ventilator **400**. The inspiratory limb **412** may be in fluid communication with a humidifier **420**, which is in fluid communication with the ventilator **400** via an injector module **430**. The inspiratory limb **412** carries gas to the patient and the expiratory limb **414** carries gas exhaled by the patient to the ventilator **400**. The injector module **430** shown in FIG. **1** is in fluid communication with the gas source **50** via the injector tubing **440** and in electronic communication with the delivery module **260** via the injector module cable **450** such that the delivery module **260** can detect and regulate the flow of gas from the gas source **50** to the ventilator **400**. Specifically, the injector module **430** is in fluid communication with the gas source **50** via an injector tubing **440**, which is in fluid communication with one or more of the pressure switch **262**, pressure shut-off valve **246**, proportional valve **266**, flow sensor **268** and the backup switch **269** of the delivery module **260**. The injector module **430** may also be in electronic communication with the delivery module **260** via the injector module cable **450**. The inspiratory limb **412** of the ventilator **400** may include a sample tee **416** for facilitating fluid communication between the inspiratory limb **412** of the breathing circuit and the sample line **232**.

As discussed above, the control module **200** may be disposed or attached on a cart **500**, as shown in FIGS. **7-9** to facilitate movement of the gas source **50** and the gas delivery device to a patient in need of gas therapy. The gas source **50** and the valve assembly **100** attached thereto may be placed on the cart **500** in proximity to the control module **200**. More specifically, as shown in FIG. **7**, the gas source **50** is placed on the cart **500** such that the valve transceiver **120** is in proximity of the CPU transceiver **220** and a line-of-sight path is established between the valve transceiver **120** and the CPU transceiver **220**. In this configuration, the CPU **210** detects the presence of the circuit **150** and thus the gas source **50** via the CPU transceiver **220**.

As shown in FIGS. **7-9**, the gas delivery device may include more than one valve, with each valve being attached to a single gas source. In such embodiments which utilize a second gas source **60** with a second valve assembly **101**, the second valve assembly **101** is positioned in proximity and in a light-of-sight path with a second CPU transceiver as the gas source **60** is loaded onto the cart. The second CPU transceiver **222** establishes communication with the second valve assembly **101** and thus detects the presence of a second gas source **60**. In the embodiment shown in FIGS. **7-9**, the second CPU transceiver **222** may also be disposed on the cover portion **225** of a cart. In one or more alternative embodiments, the second CPU transceiver **222** may be disposed on the CPU **210**.

As shown in FIG. **8**, the cart **500** may include an optional small bin **510**, a mount **512** for supporting the control module **200** on the cart **500**, at least one a holding bracket **520**, at least one mounting strap **530**, an auxiliary bracket **540**, for holding

an auxiliary gas source, a plurality of casters **550** and a caster lock lever **560** disposed on each of the plurality of casters **550**. The cart **500** may include a mount **570** for mounting the control module **200** on to the cart.

An exemplary control module **200** is shown in FIGS. **10-12** includes a display **270** for providing visual indication to the user the components of the gas being delivered from the gas source **50** to the ventilator **400** (e.g., NO, O_2, NO_2), the concentration of each component and whether communication has been established with one or more gas sources. Other information may also be displayed to the user. In addition, visual alarms may also be displayed on the display **270**. The control module **200** may also include a main power indicator **272** indicating whether the control module is connected to a power source, such as an AC/DC power source and/or a battery. The control module **200** may also include a control wheel **274** allowing the user to navigate through various displays or information displayed on the display. An injection module tubing outlet **276** may be disposed on the control module for providing fluid communication between the delivery module **260** and the injector module **430**. An injection module cable port **278** may also be provided on the control module to provide electronic communication between the delivery module **260** and the injector module **430**. The control module **200** shown in FIGS. **10-12** also includes the sample line inlet **280** in fluid communication with the sample line **232** and the inspiratory limb **412** of the ventilator **400**. In the embodiment shown in FIGS. **10-12**, the water trap **233** is disposed on the control module, adjacent to the sample line inlet **280**.

FIG. **11** illustrates a back view of the control module **200** and shows a plurality of inlets. In the embodiment shown, two gas inlets **282**, **284** for connecting the control module **200** to the gas source **50** are provided and one auxiliary inlet **286** for connecting the control module **200** to an auxiliary gas source, which may include oxygen or other gas. A power port **288** is also provided on the back of the control module to connect the control module to an AC/DC power source.

The control module **200** may also include an input means **290** for allowing the user to enter patient information, for example the identity of the patient, the type and concentration of the gas and dose of the gas to be administered to the patient, the patient's disease or condition to be treated by the gas or reason for treatment, gestational age of the patient and patient weight. The input means **290** shown in FIG. **12** includes a keyboard integrated with the display. In one or more alternative embodiments, the input means may include a USB port or other port for the connection of an external keyboard or other input mechanism known in the art. The information entered via the input means **290** is stored within the CPU memory **212**.

The control module **200** and the valve assembly **100** may be utilized in the gas delivery system **10** to improve patient safety. Specifically, the safety benefits of the gas delivery system described herein include detecting a non-confirming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like. In addition, embodiments of the gas delivery system described herein also improve efficiency of gas therapy.

FIG. **13** is a block diagram showing the sequence of how gas delivery device, including the valve assembly **100**, may be provided and its use within the gas delivery system **10**, according to one or more embodiments. As shown in FIG. **13**, the gas delivery device **10** is prepared for use by providing a gas source **50** in the form of a gas cylinder or other container for holding a gas and filling the gas source **50** with a gas (**700**) and attaching a valve assembly **100** as described herein, to assemble the gas delivery device **10** (**710**). These steps may be performed by a gas supplier or manufacturer. The gas data regarding the gas filled within the gas source **50** is entered into the valve memory **134** as described herein (**720**). The gas data may be entered into the valve memory **134** by the gas supplier or manufacturer that provides the gas source **50** and assembles the gas delivery device **10**. Alternatively, the hospital or other medical facility may enter the gas data into the valve memory **134** after the gas delivery device has been transported to the hospital or medical facility (**730**). The gas delivery device **10** is positioned on a cart **500** (**740**) and communication between the CPU transceiver **220** and the valve transceiver **120** is established (**750**). The gas data stored within the valve memory **134** is conveyed to the control module **200** (**760**) via the wireless optical line-of-sight communication between valve transceiver **120** and the CPU transceiver **220**. The CPU **210** compares the gas data to patient information entered into the CPU memory **212** (**770**). The patient information may be entered into the CPU memory after the gas data is entered into the CPU memory **212**. The patient information may be entered into the CPU memory before the gas delivery device **10** is positioned in the cart or before communication between the CPU transceiver **220** and the valve transceiver is established. In one or more alternative embodiments, the patient information may be entered into the CPU memory **212** before the gas delivery device **10** is prepared or transported to the hospital or facility. The CPU **210** then compares whether the gas data and the patient information match (**780**). If the gas data and the patient information match, then gas is administered to the patient (**790**), for example through a ventilator or other gas delivery mechanism. If the gas data and the patient information do not match, then an alarm is emitted (**800**). As described otherwise herein, the alarm may be audible and emitted through the speaker **214** and/or may be visual and displayed on the display **270**.

The gas delivery system described herein simplifies set-up procedures by utilizing wireless line-of-sight signals to establish communication. The user does not need to ensure all the cables are correct connected and can freely load new gas sources onto a cart without disconnecting cables linking the control module **200** and the valve assembly **100** or circuit **150**. This reduces set-up time and any time spent correcting errors that may have occurred during the set-up process. The control module **200** and the circuit **150** are further designed to automatically send and detect information to establish delivery of a correct gas having the correct concentration and that is not expired. In one or more specific embodiments, such automated actions prevent the use of the gas delivery system by preventing gas flow to a patient, without user intervention.

In one or more embodiments, after communication between the valve transceiver **120** and the CPU transceiver **220** is established, the valve processor **122** includes instructions to convey the gas data stored in the valve memory **134** via the valve transceiver **120** to the CPU transceiver **220**. The CPU **210** includes instructions to store the gas data received from the CPU transceiver **220** in the CPU memory. The CPU **210** also includes an algorithm that compares the gas data with patient information that is entered into the CPU memory **212**. If the gas data and the patient information do not match, the CPU **210** includes instructions to emit an alarm, which may be audible, visual or both, alerting the user that the gas contained within the gas source is different from the gas to be administered to the patient. For example, as illustrated in FIG. **12**, if the gas data includes gas expiration date, the CPU memory **212** includes information regarding the current date and the CPU **210** compares the gas expiration date with the current date. If the gas expiration date is earlier than the

current date, the CPU **210** emits an alarm. The alarm may be emitted through one or both the speaker **214** and display **270**. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of an expired gas by the CPU **210** may be stored within the CPU memory **212**.

If the gas data includes gas concentration information or data, the CPU memory **212** includes information regarding the desired concentration of gas to be administered to the patient. The control module **200** may be configured to alert the user that the gas contained within a gas source has incorrect concentration or a concentration that does not match the desired gas concentration. For example, a user may enter a concentration of 800 ppm into the CPU memory **212** and this concentration is compared to the gas concentration conveyed from the valve memory **134** to the CPU memory **212**. As illustrated in FIG. **12**, the CPU **210** includes instructions to compare the gas concentration of the gas with the concentration entered by the user. If the gas concentration does not match the concentration entered by the user, the CPU **210** emits an alarm, which may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of a gas with incorrect concentration may be stored within the CPU memory **212**.

In one or more embodiments, the control module **200** may be configured to detect more than one valve and to detect whether more than one valve is turned on. This configuration eliminates waste because it alerts a user that both valves are turned on and thus unnecessary gas is being delivered to via the delivery module **260**. In addition, such a configuration improves safety because it avoids the issues related to having two regulators pressurized at the same time and connected to the delivery module **260**. In one or more embodiments, the cover portion **225** of the control module **200** may include a second CPU transceiver **222** and the CPU **210** may include instructions for the second CPU transceiver **222** to detect wireless optical line-of-sight signals from a second valve assembly **101**, and more specifically, a second valve transceiver **121**. The CPU **210** may also include instructions that once a second valve assembly **101** is detected by the CPU transceiver **222**, whether both valve assemblies **100**, **101** are opened or have a valve status that includes an open position. In operation, a first valve assembly **100** includes a circuit with a valve processor with instructions to covey an open or closed position via the first valve transceiver **120**. The circuit of the second valve assembly similarly includes a valve processor with instructions to convey an open or closed position via a second valve transceiver **121**. The first CPU transceiver **220** and the second CPU transceiver **222** detect the valve statuses for each respective valve assembly from the first valve transceiver **120** and the second valve transceiver **121** via the wireless optical line-of-sight signals sent by both transceivers. The CPU **210** instructs the CPU transceivers **220**, **222** to collect the valve statuses for both valve assemblies **100**, **101** and the memory to store the valve statuses. The CPU **210** then compares the valve status information from the first valve assembly **100** and the second valve assembly **101** and, if the valve statuses both comprise an open position, the CPU **210** emits an alarm. The alarm may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas through either the first valve assembly or the second valve assembly. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas. The detection that more than one valve assembly had a valve that was turned on or had a valve status including an open position may be stored within the CPU memory.

In one or more embodiments, the control module **200** may be configured to alert a user when the desired dose has been delivered. In such embodiments, the patient information entered into the CPU memory **212** may include dosage information or the dose to be delivered to a patient. The valve processor **122** may include instructions to convey gas usage information from the valve memory **134**, including the amount of gas delivered, to the CPU memory **212** via the valve transceiver **120**. Alternatively, the valve processor **122** may include instructions to covey the duration of time the valve **170** has been turned on or has a valve status including an open position to the CPU memory **212** via the valve transceiver **120**. The CPU **210** may include instructions to compare the dosage information entered by the user and stored within the CPU memory **212** with the gas usage information. The CPU **210** may include instructions to emit an alarm when the dosage information and the gas usage information match. The CPU **210** may include instructions to emit the same or different alarm to alert the user to turn off the valve or, more specifically, the actuator **114** when the dose has been delivered. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas.

In addition, the control module **200** may be configured to alert the user that a detected valve is and remains closed and no gas is being delivered to the patient. This configuration expedites treatment time and increases efficiency for the hospital. In such embodiments, the valve processor **122** may include instructions for the valve transceiver **120** to convey the valve status to the CPU **210** via a wireless optical line-of-sight signal. The CPU **210** includes instructions to collect the valve status information and emit an alert if the dosage information is set or other input has been entered into the CPU memory **212** to commence treatment and the valve status includes a closed position.

The control module **200** may be configured to alert the user that no valve assembly or gas source has been detected. In such embodiments, the CPU **210** includes instructions to detect the presence of a wireless optical line-of-sight signal from another transceiver, for example, the valve transceiver **120**. The CPU **210** may include instructions to emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected. Similarly, the control module **200** may be configured to emit an alarm if communication between one or both of the CPU transceiver(s) **220**, **222** and one or both of the valve transceivers **120**, **121** has been lost during gas delivery. In such embodiments, the CPU **210** may include instructions to continuously detect the presence of a signal from another transceiver and emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected.

The CPU **210** may include instructions to alert a user when sensors in the control module **200** must be calibrated to ensure accurate delivery of gas to a patient. In addition, the CPU **210** may include instructions to correlate gas usage information from the circuit **150** of the valve assembly **100** to the patient information entered into the CPU memory **212**. The CPU **210** may also have instructions to store the correlated gas usage information and the patient information in the CPU memory **212**. The valve processor **122** may also include instructions detect patient information from the CPU memory **212**. Specifically, the valve processor **122** may include instructions to collect patient information via the valve transceiver **120** from the CPU transceiver **220** and store the collected patient information in the valve memory **134**. In such embodiments in which information from the CPU **210** is collected and stored in the valve memory **134**, the CPU **210** may include instructions that the patient information and/or correlated patient information and gas usage information be conveyed from the CPU memory **212** via the CPU transceiver **220** to the valve transceiver **120**. The valve processor **122** may also include instructions to correlate gas usage information with the collected patient information and store the correlated gas usage information and collected patient information in the valve memory **134**. Alternatively, the valve processor **122** may include instructions to collect the correlated patient information and gas usage information from the CPU **210**. The correlated information may be utilized to bill the user according to patient. In addition, the correlated information may be utilized as patient demographic data, which can assist hospitals or other facilities to generate budget reports, determine usage per department, determine usage per patient diagnosis and link usage of multiple gas sources to individual patients.

In one or more embodiments, the gas used for treatment comprises nitric oxide. Nitric oxide relaxes vascular smooth muscle and when inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature. Accordingly, nitric oxide may be used to treat or prevent pulmonary hypertension and/or hypoxic respiratory failure in a patient by administering an effective amount of a gas comprising nitric oxide. As used herein, a patient refers to a mammal at risk for developing or diagnosed with the referenced disorder. According to one or more embodiments, the patient is a human. In some embodiments, the patient may be term or near-term neonate (i.e. >34 weeks).

Nitric oxide is commercially available as INOmax® from Ikaria, Inc. INOmax® is currently indicated for the treatment of term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiological evidence of pulmonary hypertension.

The gas source may comprise a container having a gas comprising nitric oxide. The nitric oxide may be stored in a carrier gas, such as nitrogen, with a known concentration of nitric oxide. In some embodiments, the nitric concentration in the container may be in the range from 20 ppm to 10,000 ppm or from 100 ppm to 5000 ppm. Exemplary nitric oxide storage concentrations include 100 ppm, 800 pm, 2440 ppm and 4880 ppm. The concentration of nitric oxide delivered to the patient's lungs may vary depending on the patient or the condition treated, but generally may be in the range from 5 ppm to 100 ppm for preventing or treating various forms of pulmonary hypertension and/or hypoxic respiratory failure. In one or more embodiments, the nitric oxide is delivered at a concentration of about 20 ppm. In some embodiments where the condition being treated or prevented is hypoxic respiratory failure, the nitric oxide concentration may be delivered at a dose of about 20 ppm.

A second aspect of the present invention pertains to a method for administering a therapy gas to a patient. The method includes providing a gas in a gas source. The gas source may be prepared by a supplier to contain a gas having a predetermined composition, concentration and expiration date. The method may include providing a valve assembly **100** attached to a gas source **50** to dispense the gas contained within the gas source **50** to a patient. The method may include entering gas data, which may include gas composition, gas concentration and gas expiration date, into the valve memory **134**. In one or more embodiments, the supplier may enter the gas data directly into the valve memory **134**. In another variant, the gas data is provided in the form of a bar code disposed on the gas source. In such embodiments, the method includes providing a scanner in communication with the data input **108**, scanning the bar code to collect the gas data information and conveying the gas data to the valve memory **134** via the data input **108**. These steps may be repeated for a second gas source. The gas source(s), with the valve assembly mounted thereon may be transported to a hospital or other facility for administration to a patient. The gas source(s) are then mounted onto the cart **500** and secured by the holding bracket **520** and mounting strap **530**. The method includes establishing communication between the valve transceivers disposed on each valve and the CPU transceivers **220**, **222**. Establishing communication may include positioning the valve assembly **100** in a line-of-sight path with at least one of the CPU transceivers **220**, **222**. As otherwise described herein, communication may be established by instructing the valve transceivers to send a wireless optical line-of-sight signal to the CPU transceivers **220**, **222**. The method may include instructing the valve transceiver **120** to send a wireless optical line-of-sight signal at pre-determined intervals, as otherwise described herein.

The method may include entering patient information into the CPU memory **212**. This step may be performed before or after the gas source(s) are mounted onto the cart. The method may specifically include entering patient information such as dosage information into the valve memory **134**. The method includes coordinating delivery of the gas to the patient by collecting gas data from the valve memory **134** and comparing the gas data with the patient information according to an algorithm and determining if the gas data and patient information match, according to the algorithm. Coordinating delivery of the gas may include turning on the actuator **114** of the valve **107** such that gas can flow from the inlet **104** to the outlet **106**. After the dose has been delivered, the method may include correlating the gas usage information and the patient information. The method may also include recording the patient information, gas usage information and/or the correlated patient information and gas usage information in the CPU memory **212** and/or the valve memory **134**. In one or more variants, the method may include utilizing the patient information, gas usage information and/or correlated patient information and gas usage information to generate invoices identifying the use of the gas by individual patients.

Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the par-

ticular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A gas delivery device comprising:

a gas source to provide therapy gas comprising nitric oxide;

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that delivers the therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure; and

a circuit including:

a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and

a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to the control module that controls gas delivery to a subject and to verify one or more of the gas identification, the gas concentration and that the gas is not expired.

2. The device of claim **1**, wherein the valve further comprises a data input in communication with said memory, to permit a user to enter the gas data into the memory.

3. The device of claim **1**, wherein the signals comprise wireless optical line-of-sight signals.

4. The device of claim **1**, further comprising a power source, wherein the transceiver periodically sends the signals to the control module and the signals are interrupted by a duration of time at which no signal is sent to conserve the power source.

5. The device of claim **4**, wherein the duration of time at which no signal is sent is in the range from about 5 seconds to about 20 seconds.

6. The device of claim **1**, wherein the memory is disposed between the actuator and a cap.

7. A therapy gas delivery system comprising:

a gas delivery device comprising:

a gas source to provide therapy gas comprising nitric oxide;

a valve attached to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve; and

a circuit comprising:

a first memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source; and

a first processor and a first transceiver in communication with the first memory; and

a control module that delivers the therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure, the control module comprising a second memory, a second transceiver and a second processor, wherein the second transceiver and the second processor are in communication with the second memory,

wherein the first transceiver and the second transceiver send and receive signals to communicate the gas data to the control module and to verify one or more of the gas identification, the gas concentration and that the gas is not expired.

8. The system of claim **7**, wherein the control module further comprises a display to enter patient information into the second memory.

9. The system of claim **8**, wherein the second processor compares the patient information entered into the second memory via the display and the gas data that the first transceiver communicated to the second transceiver.

10. The system of claim **9**, wherein the control module comprises an alarm that is triggered when the patient information entered into the second memory and the gas data from the valve transceiver do not match.

11. The system of claim **7**, wherein the second memory comprises instructions that cause the second processor to:

receive gas data from the gas delivery device;

compare the gas data with user-inputted patient information; and

control delivery of the therapy gas to the patient.

12. The system of claim **11**, wherein the second processor verifies one or more of the gas identification, the gas concentration and that the gas is not expired prior to delivery of the therapy gas to the patient.

13. The system of claim **7**, wherein the second memory comprises instructions that cause the second processor to:

receive a first valve status selected from a first open position and a first closed position from a first valve connected to a first gas source;

receive a second valve status selected from a second open position and a second closed position from a second valve connected to a second gas source;

compare the first valve status and the second valve status; and

emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position.

14. The system of claim **7**, wherein the signals comprise wireless optical line-of-sight signals.

15. A method for administering a therapy gas to a patient, comprising:

establishing communication between a gas delivery device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver, wherein the gas delivery device comprises a gas source and the first transceiver is in communication with a first memory that stores gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source, wherein the control module comprises the second transceiver and a second memory;

communicating the gas data from the first transceiver to the second transceiver via wired or wireless signals;

comparing the gas data with patient information stored in the second memory to verify the gas data; and

delivering therapy gas comprising nitric oxide to the patient in an amount effective to treat or prevent hypoxic respiratory failure.

16. The method of claim **15**, wherein the signals comprise wireless optical line-of-sight signals.

17. The method of claim **15**, further comprising preventing or ceasing delivery of the therapy gas to the patient based on the comparison of the gas data and the patient information.

18. The method of claim **15**, further comprising emitting an alert based on the comparison of the drug data and the patient information.

19. The method of claim **15**, further comprising entering the drug data into the first memory.

20. The method of claim **15**, further comprising entering the patient information into the second memory.

* * * * *

EXHIBIT J

US008776795B2

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Bathe et al.

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(45) **Date of Patent: *Jul. 15, 2014**

(54) **GAS DELIVERY DEVICE AND SYSTEM**

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(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Oct. 29, 2013**

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US 2014/0048064 A1 Feb. 20, 2014

Related U.S. Application Data

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A62B 9/02 (2006.01)
F16K 31/02 (2006.01)

(52) **U.S. Cl.**
USPC **128/205.24**; 128/203.14; 128/204.21

(58) **Field of Classification Search**
CPC . A61M 5/168; A61M 5/16831; A61M 5/172; A61M 16/10; A61M 16/20; A61M 16/00; A61M 2205/14; A61M 2205/276; A61M 2205/3546; A61M 2205/3553; A61M 2205/3561; A61M 2205/3569; A61M 2205/60; A61M 2205/0072; A61M 2205/6081; A61M 2016/122; A61M 2016/1005; A61M 2016/012; A61M 2016/1025; A61M 2016/103; A61M 2016/1035; A61M 2016/20; A61M 2016/201; A61M 2016/202; A61M 2016/203; A61M 2016/204; A61M 2016/205; A62B 9/00; A62B 18/00
USPC 128/203.12, 203.14, 204.18, 128/204.21–204.23, 205.24
See application file for complete search history.

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Primary Examiner — Justine Yu
Assistant Examiner — Michael Tsai
(74) *Attorney, Agent, or Firm* — Servilla Whitney LLC

(57) **ABSTRACT**

A gas delivery system including a gas delivery device, a control module and a gas delivery mechanism is described. An exemplary gas delivery device includes a valve assembly with a valve and circuit including a memory, a processor and a transceiver in communication with the memory. The memory may include gas data such as gas identification, gas expiration and gas concentration. The transceiver on the circuit of the valve assembly may send wireless optical line-of-sight signals to communicate the gas data to a control module. Exemplary gas delivery mechanisms include a ventilator and a breathing circuit. Methods of administering gas are also described.

20 Claims, 12 Drawing Sheets

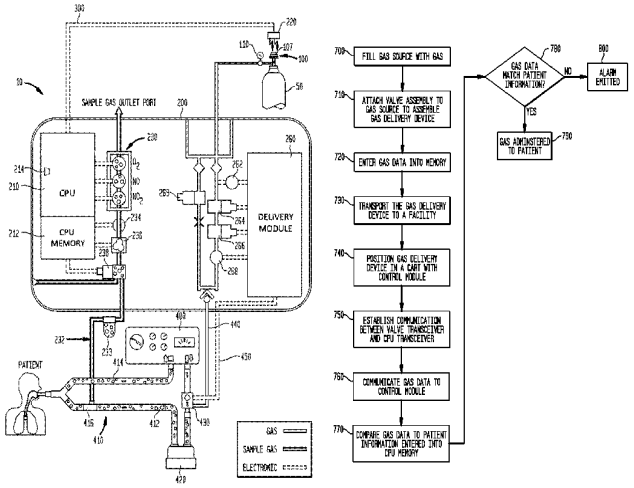

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FIG. 1

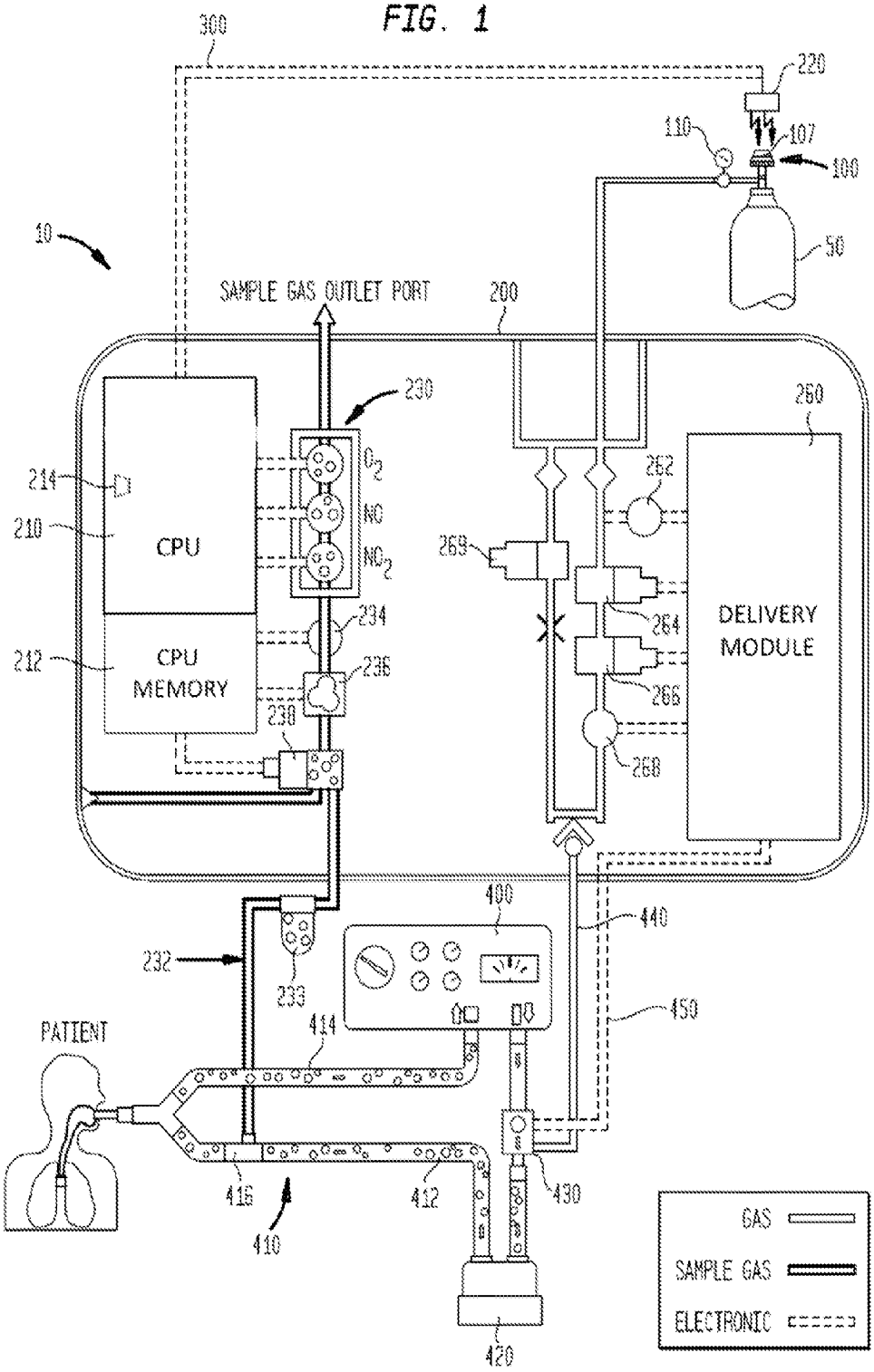

300
220
110
107
100
10
50
SAMPLE GAS OUTLET PORT
200
230
260
214
210
CPU
O_2
NO
NO_2
252
269
264
DELIVERY MODULE
212
CPU MEMORY
234
236
238
266
268
400
440
232
233
450
PATIENT
414
416
412
430
410
420
GAS
SAMPLE GAS
ELECTRONIC

FIG. 2

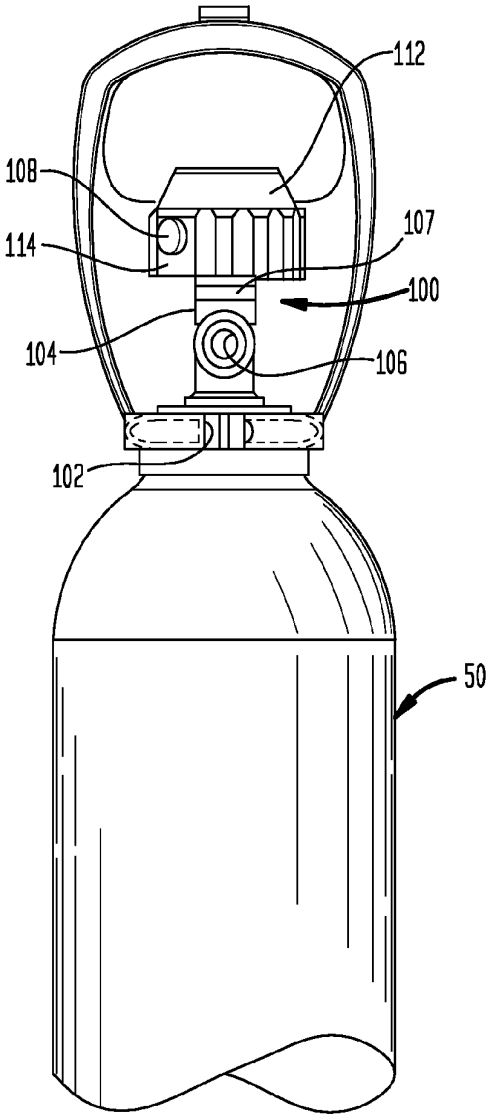


FIG. 3

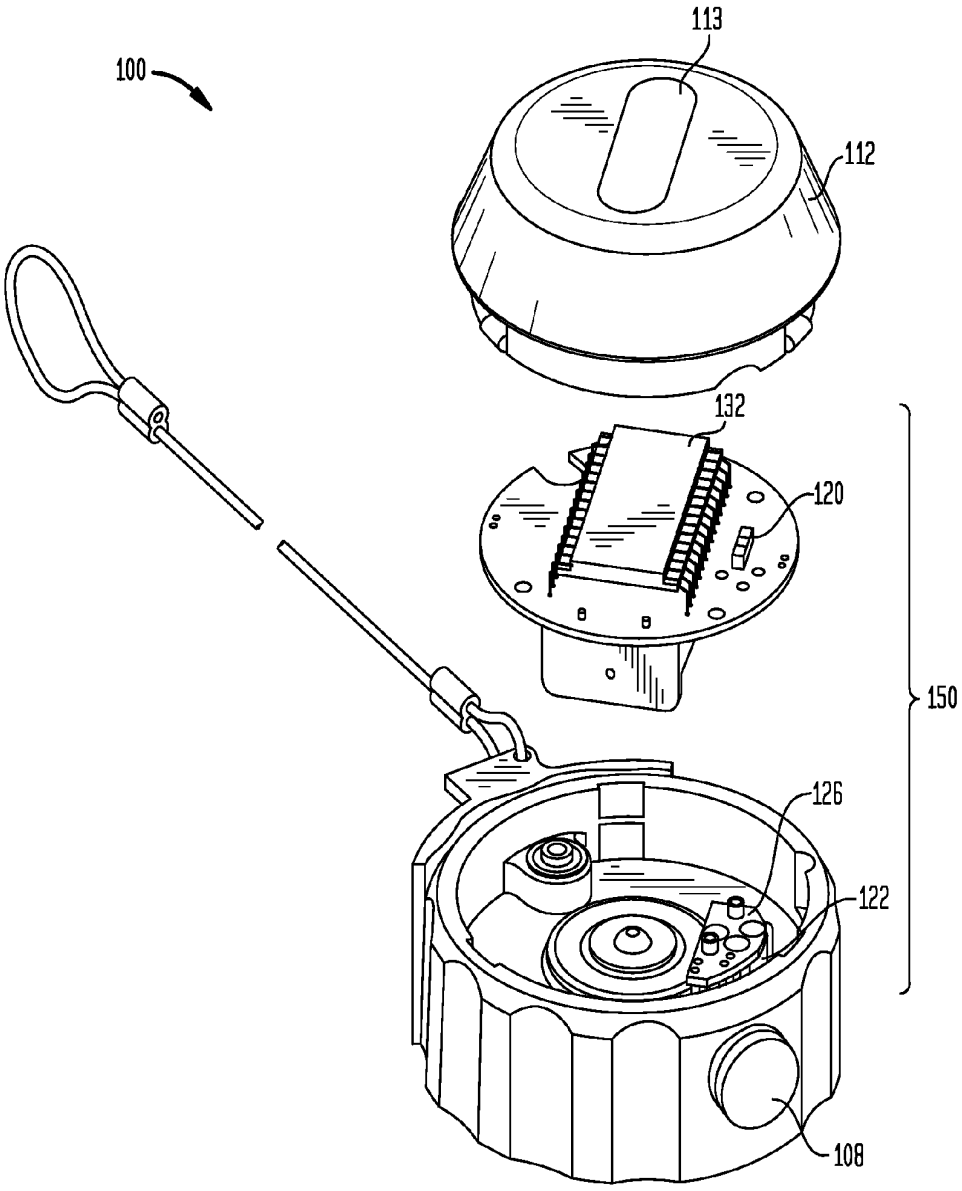


FIG. 4

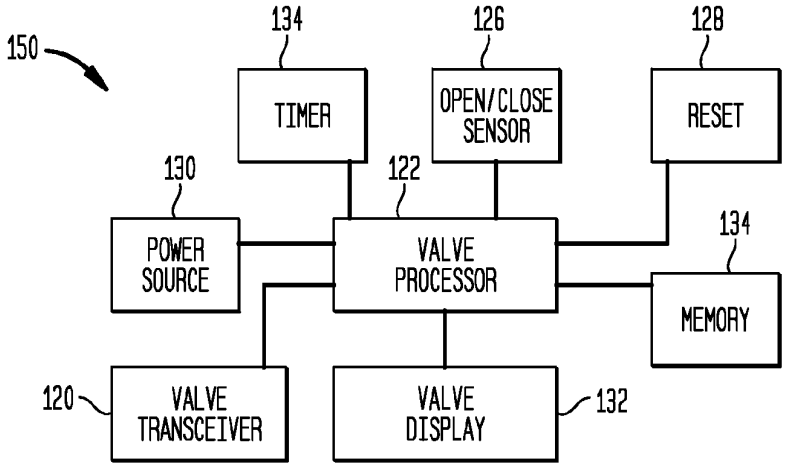

150
134
TIMER
126
OPEN/CLOSE SENSOR
128
RESET
130
POWER SOURCE
122
VALVE PROCESSOR
134
MEMORY
120
VALVE TRANSCEIVER
VALVE DISPLAY
132

FIG. 5

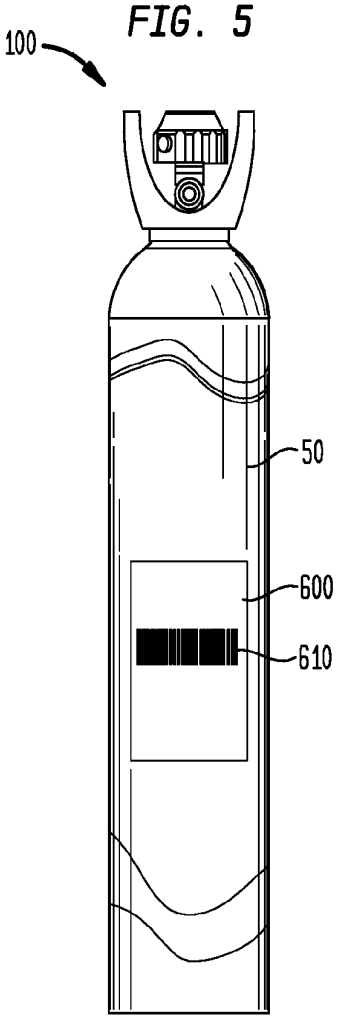

100
50
600
610

FIG. 6

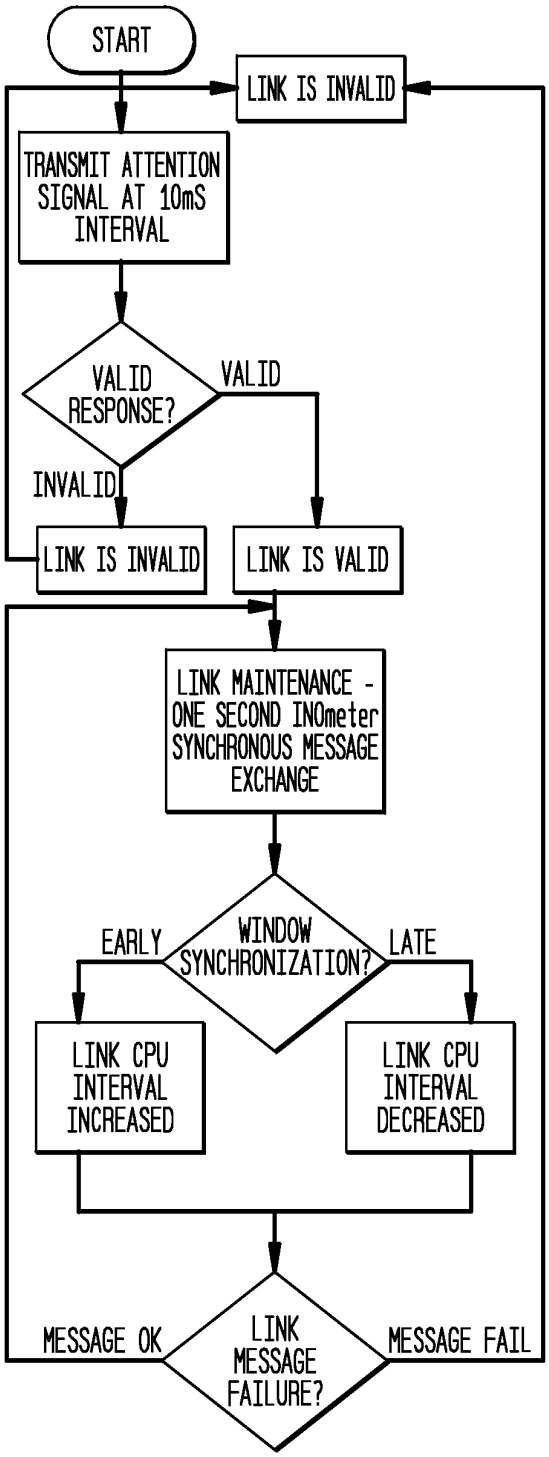

START
LINK IS INVALID
TRANSMIT ATTENTION SIGNAL AT 10mS INTERVAL
VALID RESPONSE?
VALID
INVALID
LINK IS INVALID
LINK IS VALID
LINK MAINTENANCE - ONE SECOND INOmeter SYNCHRONOUS MESSAGE EXCHANGE
WINDOW SYNCHRONIZATION?
EARLY
LATE
LINK CPU INTERVAL INCREASED
LINK CPU INTERVAL DECREASED
LINK MESSAGE FAILURE?
MESSAGE OK
MESSAGE FAIL

FIG. 7

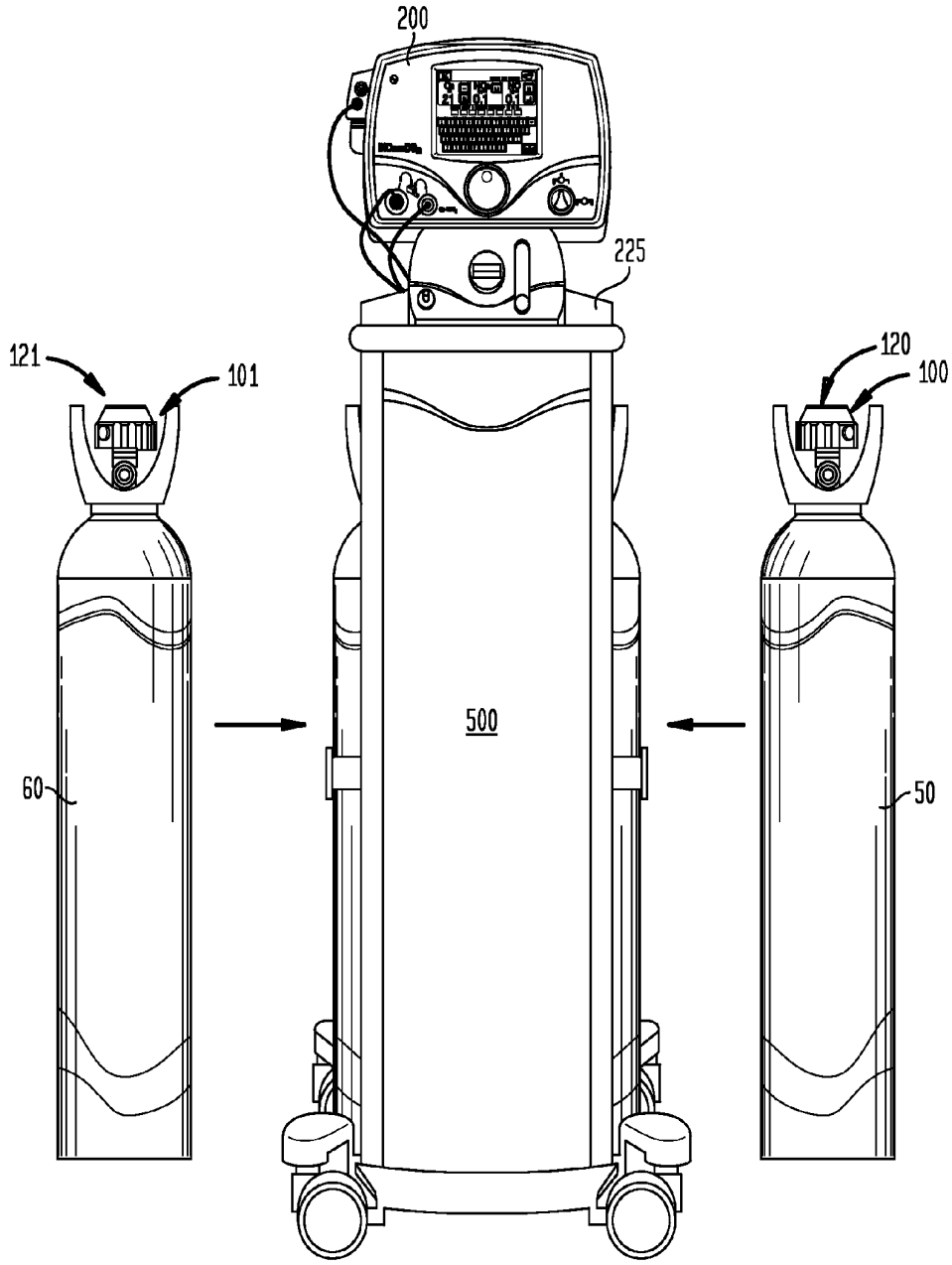


FIG. 8

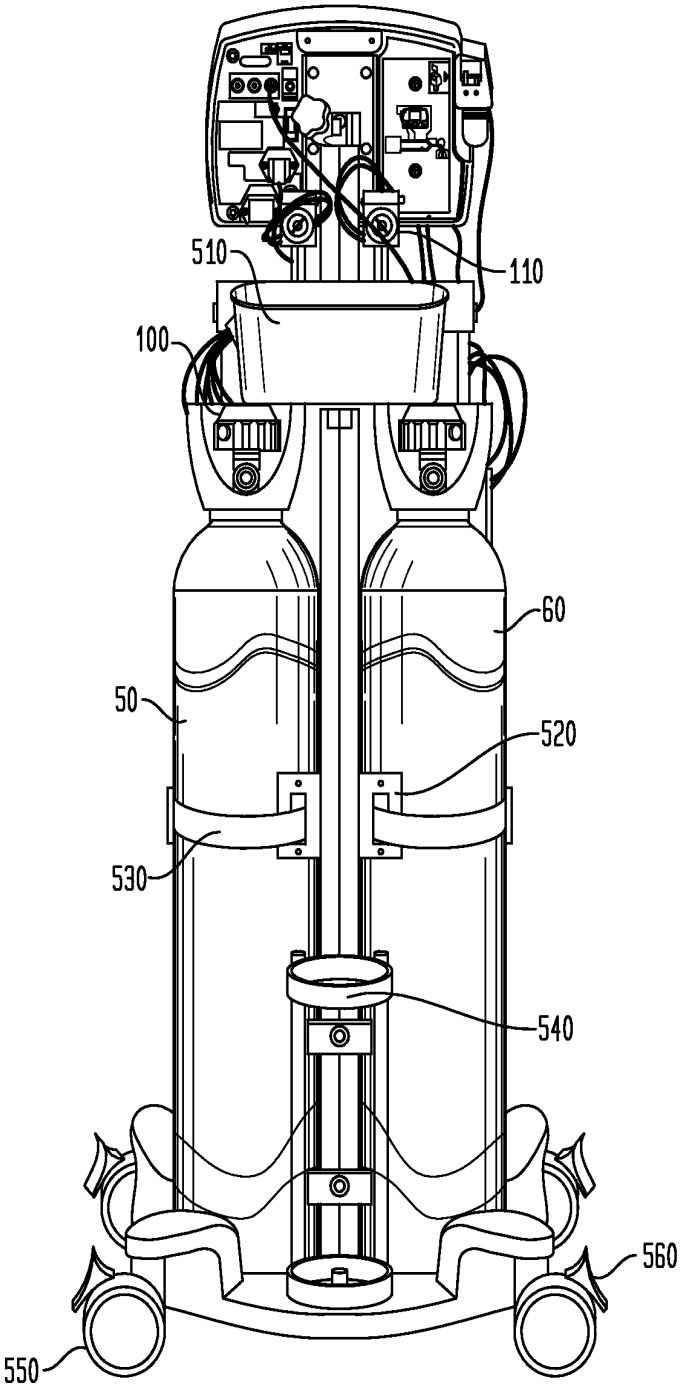


FIG. 9

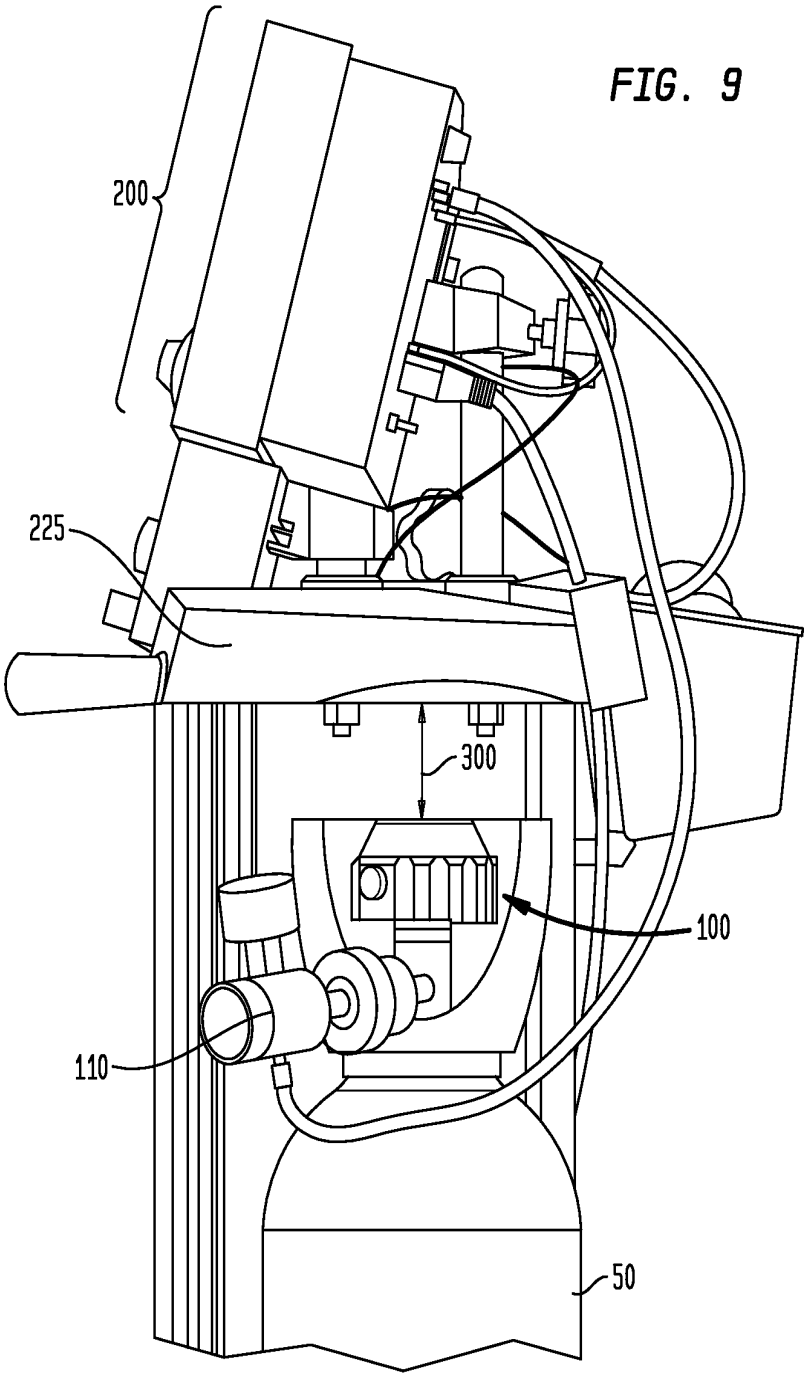


FIG. 10

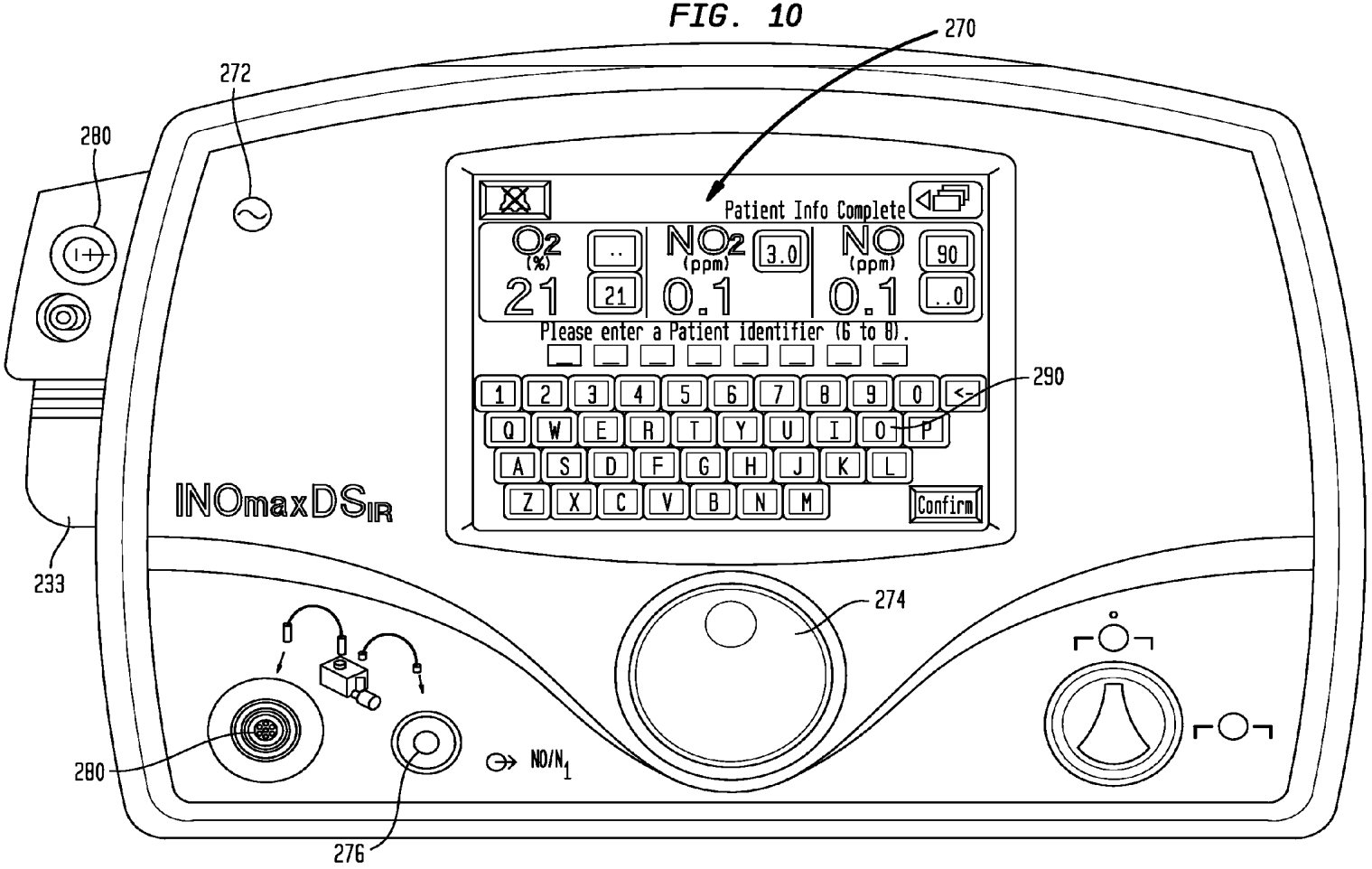

270
272
280
Patient Info Complete
O2 (%)
NO2 (ppm)
3.0
NO (ppm)
90
21
21
0.1
0.1
..0
Please enter a Patient identifier (6 to 8).
1 2 3 4 5 6 7 8 9 0 <-
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
Confirm
290
INOmaxDS IR
233
274
280
NO/N1
276

FIG. 11

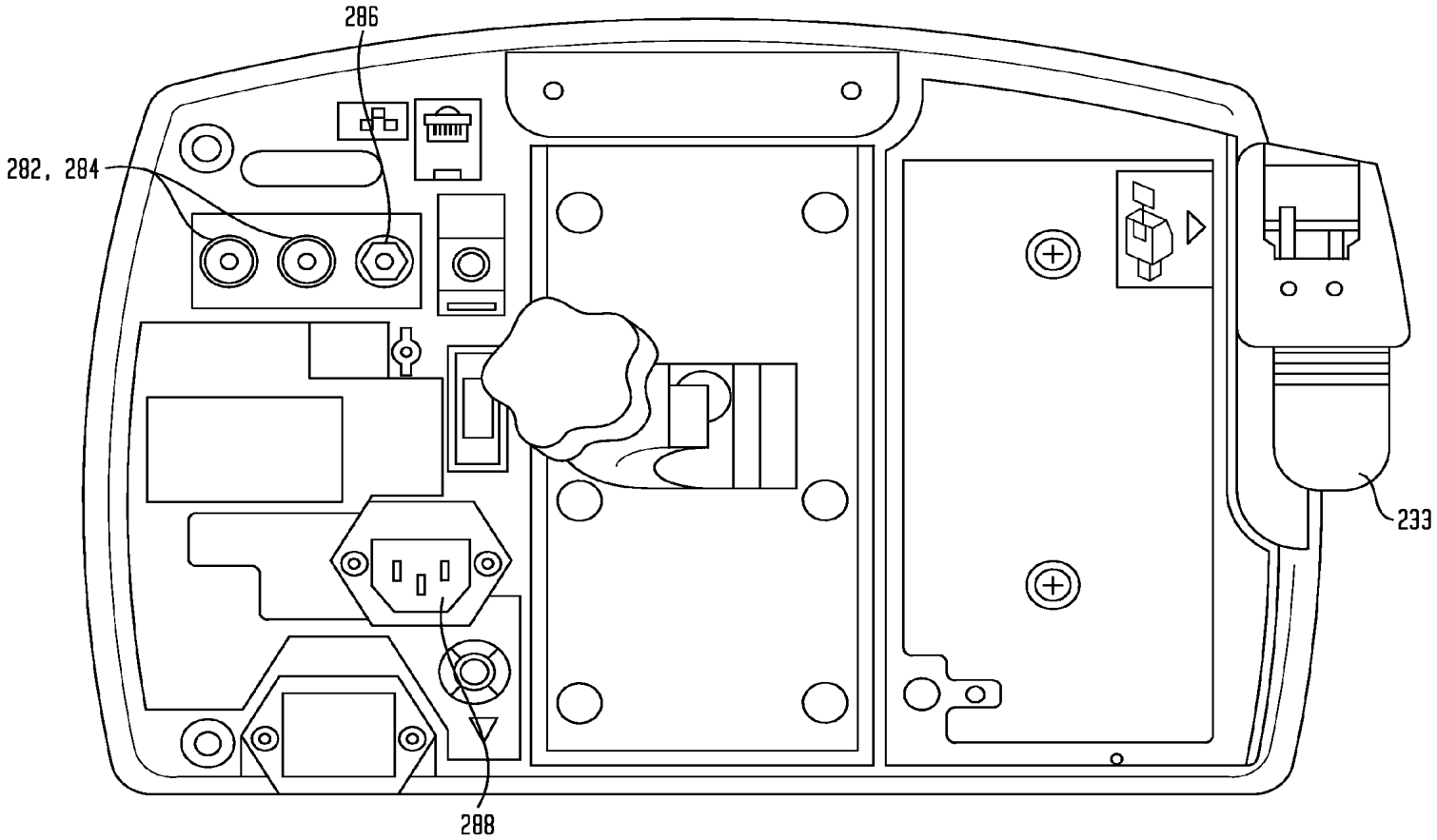


FIG. 12

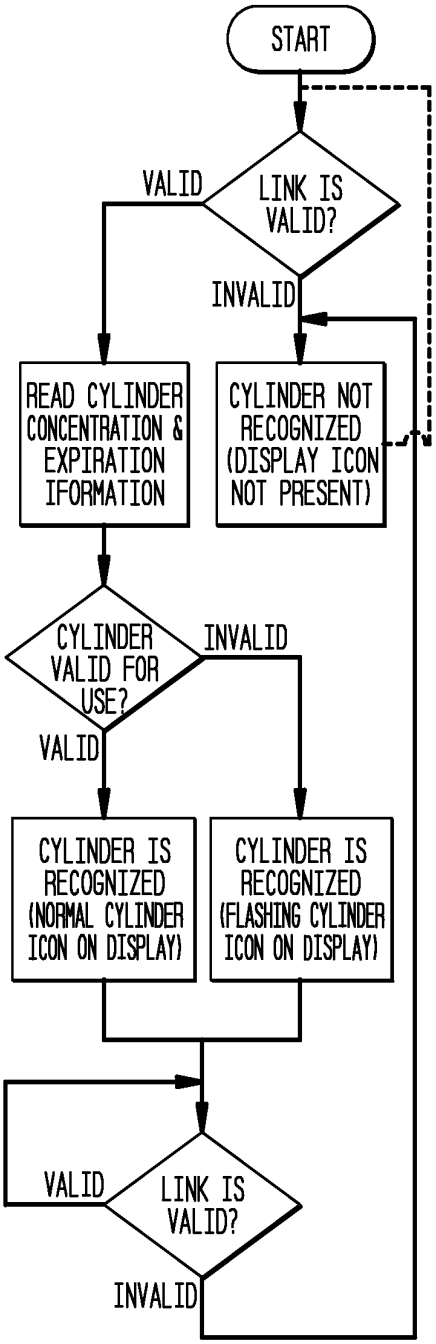
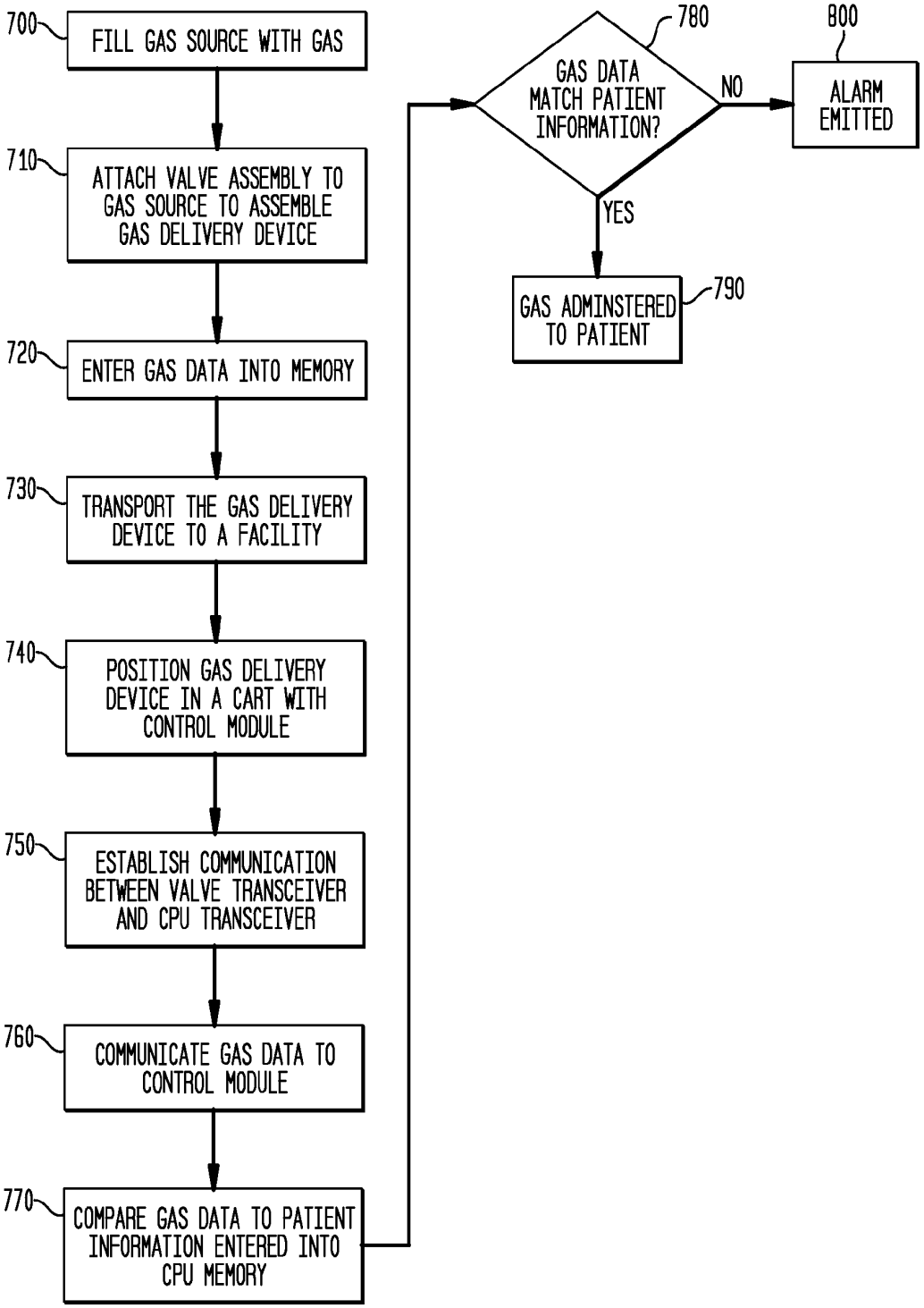

START
LINK IS VALID?
VALID
INVALID
READ CYLINDER CONCENTRATION & EXPIRATION IFORMATION
CYLINDER NOT RECOGNIZED (DISPLAY ICON NOT PRESENT)
CYLINDER VALID FOR USE?
INVALID
VALID
CYLINDER IS RECOGNIZED (NORMAL CYLINDER ICON ON DISPLAY)
CYLINDER IS RECOGNIZED (FLASHING CYLINDER ICON ON DISPLAY)
LINK IS VALID?
VALID
INVALID

FIG. 13


700
FILL GAS SOURCE WITH GAS
710
ATTACH VALVE ASSEMBLY TO GAS SOURCE TO ASSEMBLE GAS DELIVERY DEVICE
720
ENTER GAS DATA INTO MEMORY
730
TRANSPORT THE GAS DELIVERY DEVICE TO A FACILITY
740
POSITION GAS DELIVERY DEVICE IN A CART WITH CONTROL MODULE
750
ESTABLISH COMMUNICATION BETWEEN VALVE TRANSCEIVER AND CPU TRANSCEIVER
760
COMMUNICATE GAS DATA TO CONTROL MODULE
770
COMPARE GAS DATA TO PATIENT INFORMATION ENTERED INTO CPU MEMORY
780
GAS DATA MATCH PATIENT INFORMATION?
NO
800
ALARM EMITTED
YES
790
GAS ADMINSTERED TO PATIENT

GAS DELIVERY DEVICE AND SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/509,873 filed on May 15, 2012, which is the National Phase entry of PCT/US2011/020319, filed Jan. 6, 2011, the entire content of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

Embodiments of the present invention relate to gas delivery device for use in a gas delivery system for administering therapy gas and methods of administering therapy gas.

BACKGROUND

Certain medical treatments include the use of gases that are inhaled by the patient. Gas delivery devices are often utilized by hospitals to deliver the necessary gas to patients in need. It is important when administering gas therapy to these patients to verify the correct type of gas and the correct concentration are being used. It is also important to verify dosage information and administration.

Known gas delivery devices may include a computerized system for tracking patient information, including information regarding the type of gas therapy, concentration of gas to be administered and dosage information for a particular patient. However, these computerized systems often do not communicate with other components of gas delivery devices, for example, the valve that controls the flow of the gas to the computerized system and/or ventilator for administration to the patient. In addition, in known systems, the amount of gas utilized by a single patient is often difficult or impossible to discern, leading to possible overbilling for usage.

There is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is to be delivered by the gas delivery device. There is also a need for such an integrated device that does not rely on repeated manual set-ups or connections and which can also track individual patient usage accurately and simply.

SUMMARY

Aspects of the present invention pertain to a gas delivery device that may be utilized with a gas delivery system and methods for administering therapy gas to a patient. One or more embodiments of the gas delivery devices described herein may include a valve and a circuit with a valve memory in communication with a valve processor and a valve transceiver. One or more embodiments of the gas delivery systems described herein incorporate the gas delivery devices described herein with a control module including a central processing unit (CPU) in communication with a CPU memory and CPU transceiver. As will be described herein, the valve transceiver and the CPU transceiver may be in communication such that information or data from the valve memory and the CPU memory may be communicated to one another. The information communicated between the valve memory and the CPU memory may be utilized for selecting a therapy for delivery to a patient and controlling delivery of the selected therapy to the patient. The gas delivery devices and systems described herein may be utilized with medical devices such as ventilators and the like to delivery gas to a patient.

A first aspect of the present invention pertains to a gas delivery device. In one or more embodiments, the gas delivery device administers therapy gas from a gas source under the control of a control module. In one variant, the gas delivery device may include a valve attachable to the gas source and a circuit. The valve may include an inlet and an outlet in fluid communication and a valve actuator to open and close the valve to allow the gas to flow through the valve to a control module. The circuit of one or more embodiments includes a memory, a processor and a transceiver in communication with the memory to send wireless optical line-of-sight signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject. In one or more alternative embodiments, the signals to communicate information stored or retained within the memory to the control module that controls gas delivery to a subject may be communicated via a wire. Examples of such wired signals may incorporate or utilize an optical cable, wired pair and/or coaxial cable. The circuit may include a memory to store gas data, which may include one or more of gas identification, gas expiration date and gas concentration. The transceiver may communicate to send the gas data to the control module via wireless optical line-of-sight signals.

In one or more embodiments, the valve may include a data input in communication with said memory, to permit a user to enter the gas data into the memory. The gas data may be provided in a bar code that may be disposed on the gas source. In such embodiments, the gas data may be entered into the data input of the valve for storage in the memory by a user-operated scanning device in communication with the data input. Specifically, the user may scan the bar code to communicate the gas data stored therein to the valve memory via the data input.

In one or more embodiments, the valve may include a power source. In such embodiments, the power source may include a battery or other portable power source. In one or more embodiments, the valve transceiver may periodically send the wireless optical line-of-sight signals to the control module, wherein the signals are interrupted by a duration of time at which no signal is sent. In one or more specific embodiments, the duration of time at which no signal is sent comprises about 10 seconds.

A second aspect of the present invention pertains to a gas delivery device, as described herein, and a control module in fluid communication with the outlet of the valve of the gas delivery device and with a gas delivery mechanism, such as a ventilator. In one or more embodiments, the control module may include a CPU transceiver to receive line-of-sight signals from the transceiver and a CPU in communication with the CPU transceiver. The CPU carries out the instructions of a computer program or algorithm. As used herein the phrase "wireless optical line-of-sight signal" includes infrared signal and other signals that require a transmitter and receiver or two transceivers to be in aligned such that the signal may be transmitted in a straight line. The CPU may include a CPU memory that stores the gas data that is communicated by the valve transceiver of the gas delivery device to the CPU transceiver.

In one or more embodiments, the gas delivery system may incorporate a valve with a timer including a calendar timer and an event timer for determining or marking the date and time that the valve is opened and closed and the duration of time the valve is opened. In such embodiments, the valve memory stores the date and time of opening and closing of the

valve and the duration of time that the valve is open and the valve transceiver communicates the date and time of opening and closing of the valve to the CPU transceiver for storage in the CPU memory.

In one or more variants, the gas delivery system may incorporate a control module that further includes an input means to enter patient information into the CPU memory. The control module may also have a real time clock built into the CPU module such that the control module knows what the current time and date is and can compare that to the expiration date stored in the gas delivery device. If the expiration date is passed the current date then the control module can cause an alarm and not deliver drug to the patient. When the term "patient information" is used, it is meant to include both patient information entered by the user and information that is set during manufacturing, such as the gas identification and the gas concentration that the control module is setup to deliver. The control module may also include a display. In one or more embodiments, the display incorporates an input means for entering patient information into the CPU memory. In one or more embodiments, the CPU of the control module compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver. The CPU or control module may include comprises an alarm that is triggered when the patient information entered into the CPU memory and the gas data from the transceiver do not match or conflict. As used herein the phrase "do not match," includes the phrase "are not identical," "are not substantially identical," "do conflict" and/or "do substantially conflict." The CPU determines whether the patient information and additional data, or other data set matches by performing a matching algorithm which includes criteria for establishing whether one set of data (i.e. patient information) and another set of data match. The algorithm may be configured to determine a match where every parameter of the data sets match or selected parameters of the data sets match. The algorithm may be configured to include a margin of error. For example, where the patient information require a gas concentration of 800 ppm, and the additional data includes a gas concentration of 805 ppm, the algorithm may be configured to include a margin of error of ±5 ppm such it determines that the patient information and the additional data match. It will be understood that determining whether the patient information and additional data match will vary depending on the circumstances, such as variables in measuring gas concentration due to temperature and pressure considerations.

A third aspect of the present invention pertains to a control module memory comprising instructions that cause a control module processor to receive gas data from a valve via a wireless optical line-of-sight signal. The valve may be connected to a gas source and may include a memory for storing the gas data. The control module memory may include instructions that cause the control module processor to compare the gas data with user-inputted patient information. The user-inputted patient information may be stored within the control module memory. Gas data may be selected from one or more of gas identification, gas expiration date and gas concentration. In one or more embodiments, the control module memory may include instructions to cause the control module processor to coordinate delivery of therapy to the patient with a medical device, such as a ventilator and the like for delivering gas to a patient, via the wireless optical line-of-sight signal. The control module memory may also include instructions to cause the control module processor to select a therapy for delivery to a patient based on the received patient information and control delivery of the selected therapy to the patient.

In one or more embodiments, the memory may include instructions to cause the processor to detect the presence of more than one valve and whether more than one valve is open at the same time. In accordance with one or more specific embodiments, the memory includes instructions to cause the processor to receive a first valve status selected from a first open position and a first closed position from a first valve via a first wireless optical line-of-sight signal with the first valve connected to a first gas source, receive a second valve status selected from a second open position and a second closed position from a second valve via a second wireless optical line-of-sight signal with the second valve connected to a second gas source, compare the first valve status and the second valve status, and emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position. In one or more alternative embodiments, the first valve status and the second valve status may be communicated to the processor via a single wireless optical line-of-sight signal, instead of separate wireless optical line-of-sight signals. In a more specific embodiment, the memory of one or more embodiments may include instructions to cause the processor to terminate delivery of therapy if the first valve status comprises the first open position and the second valve status comprises the second open position.

In one or more embodiments, the memory may include instructions to cause the processor to emit an alarm when a desired dose has been delivered through a valve. In such embodiments, the processor may include a memory to store the desired dose or dosage information. In such embodiments, the memory may include instructions to cause the processor to receive gas delivery information or information regarding the amount of gas delivered and compare the gas delivery information to the dosage information and emit an alarm when the gas delivery information and the dosage information match. As used herein, the term "dosage information" may be expressed in units of parts per million (ppm), milligrams of the drug per kilograms of the patient (mg/kg), millimeters per breath, and other units known for measuring and administering a dose. In one or more embodiments, the dosage information may include various dosage regimes which may include administering a standard or constant concentration of gas to the patient, administering a gas using a pulsed method. Such pulsing methods includes a method of administering a therapy gas to a patient during an inspiratory cycle of the patient, where the gas is administered over a single breath or over a plurality of breaths and is delivery independent of the respiratory pattern of the patient.

A fourth aspect of the present invention pertains to a method for administering a therapy gas to a patient. In one or more embodiments, the method includes establishing communication between the patient and a gas delivery device via a transceiver, wherein the gas delivery device comprises a first memory including gas data, comparing the gas data with patient information stored within a second memory. The second memory may be included within a control module in communication with the gas delivery device. After comparing the gas data and the patient information, the method may further include coordinating delivery of therapy to a patient with the gas delivery device via a wireless optical line-of-sight signal, selecting a therapy for delivery to the patient based on the comparison of the gas data and the patient information and controlling delivery of the selected therapy to the patient. In one or more specific embodiments, the method may include entering the gas data into the first memory of the gas delivery device and/or entering the patient information into the second memory. In embodiments in

which the method includes entering the patient information into the second memory, the control module may include input means by which patient information may be entered into the second memory. In one or more variants, the method includes ceasing delivery of the selected therapy to the patient based on the comparison of the gas data and the patient information. The method may include emitting an alert based on the comparison of the gas data and the patient information.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram of a gas delivery system including a gas delivery device, a gas source, a control module and a gas delivery mechanism, according to one or more embodiments;

FIG. **2** illustrates a valve assembly of the gas delivery device according to one or more embodiments attached to a gas source;

FIG. **3** illustrates a disassembled view of the valve assembly shown in FIG. **2**;

FIG. **4** is a diagram showing a circuit supported in the valve assembly shown in FIG. **2**, according to one or more embodiments;

FIG. **5** illustrates an exemplary gas source for use with the valve assembly shown in FIG. **2**;

FIG. **6** is an operational flow diagram of the communication between the circuit of the gas delivery device shown in FIG. **1** with a control module regarding the establishment of communication between the circuit and the control module

FIG. **7** illustrates a front view of an exemplary gas delivery system;

FIG. **8** illustrates a back view of the gas delivery system shown in FIG. **7**;

FIG. **9** illustrates a partial side view of the gas delivery system shown in FIG. **7**;

FIG. **10** illustrates a front view of a control module according to one or more embodiments;

FIG. **11** illustrates a back view of the control module shown in FIG. **10**;

FIG. **12** is an operational flow diagram of the communication between the circuit of the gas delivery device and the control module shown in FIG. **1** regarding the gas contained within a gas source; and

FIG. **13** is an operational flow diagram of the preparation of a gas delivery device and use within the gas delivery system according to one or more embodiments.

DETAILED DESCRIPTION

Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

A system for the administration of therapy gas is described. A first aspect of the present invention pertains to a gas delivery device. The gas delivery device may include a valve assembly including at least one valve with a circuit. The gas delivery system may include the gas delivery device (e.g. valve assembly, including a valve and a circuit) in communication with a control module to control the delivery of gas from a gas source to a ventilator or other device used to introduce the gas into the patient, for example, a nasal cannula, endotracheal tube, face mask or the like. Gas source, as used herein, may include a gas source, gas tank or other pressured vessel used to store gases at above atmospheric pressure. The gas delivery system **10** is shown in FIG. **1**. In FIG. **1**, the valve assembly **100**, including a valve **107** or valve actuator and a circuit **150**, is in communication with a control module **200** via a wireless line-of-sight connection **300**. In one or more alternative embodiments, communication between the valve assembly **100** and the control module **200** may be established via a wired signal. The gas delivery system **10** also includes a gas source **50** including a gas attached to the valve assembly **100** and a gas delivery mechanism, which includes a ventilator **400** and a breathing circuit **410**, in communication with the control module **200**.

FIGS. **2-4** illustrate the components of the valve assembly **100**. The valve assembly **100** includes a valve **107** and a circuit **150** supported in the valve assembly. FIG. **3** illustrates a disassembled view of the valve assembly **100**, showing components of the physical circuit **150** and the valve **107**. As shown in FIG. **4**, which will be described in more detail below, the circuit **150** of the gas delivery device includes a valve transceiver **120** for establishing communication with the control module **200**, which will also be discussed in greater detail below.

Referring to FIG. **2**, the valve **107** includes an attachment portion **102** for attaching the valve assembly **100** to the gas source **50**, an inlet **104** and an outlet **106** in fluid communication with the inlet **104**, as more clearly shown in FIG. **2**.

FIG. **3** illustrates a disassembled view of the valve assembly **100** and illustrates an actuator **114** is disposed on the valve **107** and is rotatable around the valve **107** for opening and closing the valve **107**. The actuator **114** includes a cap **112** mounted thereto. As shown in FIG. **3**, the circuit **150** may include a data input **108** disposed on the actuator **114**. The data input **108** may be disposed at other locations on the valve **107**. In one or more variants, the data input may include a port such as a USB port, a receiver for receiving electronic signals from a transmitted or other known input means known in the art for entering information or data into a memory.

FIG. **4** illustrates a block diagram of the circuit **150**. The circuit **150** shown in FIG. **4** includes a valve processor **122**, a valve memory **134**, a reset **128**, a valve transceiver **120** and a power source **130**. The circuit **150** may also include support circuits a timer **124**, a sensor **126** and/or other sensors. Referring to FIG. **3**, the circuit **150** is supported within the valve assembly **100**, with the physical components of the circuit **150** specifically disposed between actuator **114** and the cap **112**. As shown in FIG. **3**, the valve display **132** and the valve transceiver **120** are disposed adjacent to the cap **112**, such that the valve display **132** is visible through a window **113**. The sensor **126** and the valve processor **122** are disposed beneath the valve display **132** and the valve transceiver **120**, within the actuator **114**.

The valve processor **122** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The valve memory **134**, or computer-readable medium, may be one or more of readily available memory such as electrically erasable programmable read only memory (EEPROM), random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the valve processor **122**. The support circuits may be coupled to the valve processor **122** for supporting the circuit **150** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like.

In the embodiment shown, the valve memory **134** communicates with a data input **108** disposed on the side of the actuator **114**. The data input **108** shown in FIGS. **3-4** is used to transfer data from the valve memory **134** to other devices or to input data into the valve memory **134**. For example, gas

data, which includes information regarding the gas contained within the gas source, may be entered into the valve memory **134** via the data input **108**. In one or more alternative embodiments, the gas data may be programmed or directly entered into the valve memory **134** by the gas supplier. In one or more embodiments, the gas data may be provided in the form of a bar code **610** that is disposed on a label **600** that is affixed on a to the side of the gas source, as shown in FIG. **5**. The bar code **610** may be disposed directly on the gas source. An external scanning device in communication with the electronic data input **108** may be provided and may be used to scan the bar code **610** and convey the information from the bar code **610** to the valve memory **134**. Gas data may include information regarding the gas composition (e.g., NO, O_2, NO_2, CO, etc.), concentration, expiration date, batch and lot number, date of manufacturing and other information. Gas data may be configured to include one or more types of information. The valve processor **122** may include instructions to convey all or a pre-determined portion of the gas data via the valve transceiver **120** to another transceiver.

In embodiments that utilize a timer **124**, the timer **124** may include two sub-timers, one of which is a calendar timer and the other of which is an event timer. The reset **128** may be located inside the actuator **114** and may be depressed to reset the event timer. The cap **112** also includes a window **113** that allows the user to see the valve display **132** disposed within the cap **112** that displays information regarding whether the actuator **114** is opened or closed and the duration the valve **107** was opened or closed. In one or more embodiments, the valve display **132** may alternate flashing of two different numbers, a first number may be accumulated open time, and the second number may be the time at which the valve **107** was opened for the current event. The time at which the valve **107** was opened for a current event may be preceded by other indicators.

The sensor **126** disposed within the actuator **114** may include a proximity switch model MK20-B-100-W manufactured by Meder Inc. The sensor **126** utilized in one or more embodiments may cooperate with a magnet (not shown) to sense whether the actuator **114** is turned on or turned off. Such sensors are described in U.S. Pat. No. 7,114,510, which is incorporated by reference in its entirety.

For example, the sensor **126** and a corresponding magnet (not shown) may be disposed on a stationary portion of the valve **107**. When the actuator **114** is rotated to the closed position, the sensor **126** is adjacent to the magnet that is in a fixed position on the valve **107**. When the sensor **126** is adjacent to the magnet, it sends no signal to the valve processor **122**, thereby indicating that the actuator **114** is in the "closed" position or has a valve status that includes an open position or a closed position. When the actuator **114** is rotated to open the valve **107**, the sensor **126** senses that it has been moved away from the magnet and sends a signal to the valve processor **122**, indicating an "open" position. The valve processor **122** instructs the valve memory **134** to record the event of opening the valve **107** and to record the time and date of the event as indicated by the calendar timer. The valve processor **122** instructs the valve memory **134** to continue checking the position of the valve **107** as long as the valve **107** is open. When the valve **107** is closed, the valve processor **122** uses the logged open and close times to calculate the amount of time the valve **107** was open and instructs the valve memory **134** to record that duration and the accumulated open time duration. Thus, every time the valve **107** is opened, the time and date of the event is recorded, the closing time and date is recorded, the duration of time during which the valve **107** is open is calculated and recorded, and the accumulated open time is calculated and recorded.

In one or more embodiments in which the power source **130** includes a battery, the valve transceiver **120** may be configured to communicate with the CPU transceiver **220** to preserve the life of the battery. In this embodiment the valve transceiver **120** is only turned on to receive a signal from the Control Module CPU transceiver **220** for 20 msec every second. The control module CPU transceiver **220** sends out a short transmit signal continuously and if the valve transceiver **120** is present it responds in the 20 msec interval. This conserves battery power as the valve transceiver **120** is only powered on for 20 msec every second. When the valve transceiver **120** responds it includes in its signal information regarding whether the communication from the control module CPU transceiver **220** was early or late within this 20 msec window. This ensures that once communications has been established it is synchronized with the 20 msec window that the valve transceiver **120** is powered on and able to receive communications. For example, as shown in FIG. **6**, the valve transceiver **120** sends a wireless optical line-of-sight signal during a pre-determined interval in response to a signal from the control module CPU transceiver **220**. The wireless optical line-of-sight signals sent by the valve transceiver **120** are a series of on off cycles where the transmitter is either transmitting light or is not and these correspond to digital binary signals. The mechanism by which the valve transceiver sends a wireless optical line-of-sight signal may be construed as a series of digital on off signals that correspond to data being transmitted. Once communications has been established between the control module CPU transceiver **220** and the valve transceiver **120**, the interval between communication signals may be in the range from about 20 seconds to about 5 seconds. In one or more specific embodiments, the interval or duration between transceiver signals may be about 10 seconds.

As will be described in more detail below, the control module **200** includes a CPU **210** which is connected to a CPU transceiver **220** which can send and receive wireless optical line-of-sight signals. The CPU transceiver **220** sends out a signal and waits for a response from the valve transceiver **120** when communication or more specifically, line-of-sight communication is established between the CPU transceiver **220** and the valve transceiver **120**. If no response is sent by the valve transceiver **120**, the CPU transceiver **220** sends another signal after a period of time. This configuration preserves battery life because the valve transceiver **120** does not continuously send a signal unless requested to by the CPU **210**. This is important as the gas delivery device and gas source spends most of its time in shipping and storage prior to being placed on the gas delivery system, if it was transmitting all this time trying to establish communications with the control module it would be consuming the battery life significantly.

The valve processor **122** may include link maintenance instructions to determine whether the interval should be increased or decreased. As shown in FIG. **6**, when a valid link is established between the valve transceiver **120** and CPU transceiver **121**, the valve processor **122** executes the link maintenance instructions to increase the interval or decrease the interval.

As shown more clearly in FIG. **1**, valve assembly **100** and gas source **50** is in communication with a control module **200**, which is in communication with a gas delivery mechanism. The gas delivery mechanism shown in FIG. **1** includes a ventilator **400** with associated breathing circuit **410**. The control module **200** may include a CPU **210** and a CPU trans-

ceiver **220** in communication with the circuit **150** via the valve transceiver **120**. The control module **200** also includes a CPU memory **212** in communication with the CPU transceiver **220** to store patient information, information or data received from the valve transceiver **120** and other information. The control module **200** may also include support circuits. The CPU **210** may be one of any form of computer processor that can be used in an industrial setting for controlling various actions and sub-processors. The CPU memory **212**, or computer-readable medium, may be one or more of readily available memory such as random access memory (RAM), read only memory (ROM), floppy disk, hard disk, or any other form of digital storage, local or remote, and is typically coupled to the CPU **210**. The support circuits may be coupled to the CPU **210** for supporting the control module **200** in a conventional manner. These circuits include cache, power supplies, clock circuits, input/output circuitry, subsystems, and the like. The CPU **210** may also include a speaker **214** for emitting alarms. Alternatively, alarms may also be displayed visually on a display. As shown in FIG. **1**, the control module **200** may also include a regulator **110** and, optionally, pressure gauges and flow meters for determining and/or controlling the gas flow from the gas source **50**.

In one or more embodiments, the CPU transceiver **220** is disposed on a cover portion **225** (shown more clearly in FIG. **7**), that is part of a cart **500** (show more clearly in FIG. **7**) onto which the control module **200** is disposed. The cover portion **225** in one or more embodiments is in communication with the control module **200**. Communication between the cover portion **225** and the control module **200** may be established wirelessly or via a cable. As will be discussed in greater detail below, the valve assembly **100**, including the valve **107**, the circuit **150** and a gas source **50** attached to the valve **107**, are placed on the cart **500** in proximity and in a light-of-sight path with the CPU transceiver **220**. When properly configured such that communication is established between the valve transceiver **120** and the CPU transceiver **220**, the CPU transceiver **220** is positioned directly above the valve transceiver **120**, as shown more clearly in FIG. **9**. In one or more alternative embodiments, the CPU transceiver **220** may be disposed on the CPU **210**.

The CPU **210** may be in communication with a plurality of gas sensors **230** for determining the concentration of a sample of gas drawn via a sample line **232** and a sample line inlet **280** (shown more clearly in FIG. **1**) disposed on the control module **200**. As will be discussed in greater detail, the sample line **232** draws a sample of gas from a breathing circuit **410** of a ventilator **400** when the ventilator is in fluid communication with the control module **200** and gas is being delivered to the ventilator. The CPU **210** may also be in communication with a sample flow sensor **234** for sensing the flow of the sample drawn via sample line **232**, a pump **236** for drawing the sample via the sample line **232** to the flow sensor **234** and zero valve **238** controlling the flow of the sample via the sample line **232** to the sample pump **236**, sample flow sensor **234** and the plurality of CPU sensors. The sample line **232** may include a water trap **233** for collecting any water or liquid from the sample.

The control module **200** may also include a delivery module **260** for regulating the flow of gas from the gas source **50** to the ventilator **400**. The delivery module **260** may include a pressure switch **262** for determining a gas supply pressure is present, a pressure shut-off valve **264**, a proportional valve **266** and a delivery flow sensor **268**. The delivery module **260** may also include a backup on/off switch **269**. The detailed method of how the delivery module delivers the gas to the ventilator circuit is described in U.S. Pat. No. 5,558,083 which is incorporated here by reference in its entirety.

The ventilator **400** shown in FIG. **1** is in fluid communication with the control module **200** via an injector tubing **440** and in electrical communication via an injector module cable **450**. The control module **200** and more specifically, the CPU **210**, is in fluid communication with the ventilator **400** via the sample line **232**. The ventilator **400** may include a breathing circuit **410** with an inspiratory limb **412** and an expiratory limb **414** in fluid communication with the ventilator **400**. The inspiratory limb **412** may be in fluid communication with a humidifier **420**, which is in fluid communication with the ventilator **400** via an injector module **430**. The inspiratory limb **412** carries gas to the patient and the expiratory limb **414** carries gas exhaled by the patient to the ventilator **400**. The injector module **430** shown in FIG. **1** is in fluid communication with the gas source **50** via the injector tubing **440** and in electronic communication with the delivery module **260** via the injector module cable **450** such that the delivery module **260** can detect and regulate the flow of gas from the gas source **50** to the ventilator **400**. Specifically, the injector module **430** is in fluid communication with the gas source **50** via an injector tubing **440**, which is in fluid communication with one or more of the pressure switch **262**, pressure shut-off valve **246**, proportional valve **266**, flow sensor **268** and the backup switch **269** of the delivery module **260**. The injector module **430** may also be in electronic communication with the delivery module **260** via the injector module cable **450**. The inspiratory limb **412** of the ventilator **400** may include a sample tee **416** for facilitating fluid communication between the inspiratory limb **412** of the breathing circuit and the sample line **232**.

As discussed above, the control module **200** may be disposed or attached on a cart **500**, as shown in FIGS. **7-9** to facilitate movement of the gas source **50** and the gas delivery device to a patient in need of gas therapy. The gas source **50** and the valve assembly **100** attached thereto may be placed on the cart **500** in proximity to the control module **200**. More specifically, as shown in FIG. **7**, the gas source **50** is placed on the cart **500** such that the valve transceiver **120** is in proximity of the CPU transceiver **220** and a line-of-sight path is established between the valve transceiver **120** and the CPU transceiver **220**. In this configuration, the CPU **210** detects the presence of the circuit **150** and thus the gas source **50** via the CPU transceiver **220**.

As shown in FIGS. **7-9**, the gas delivery device may include more than one valve, with each valve being attached to a single gas source. In such embodiments which utilize a second gas source **60** with a second valve assembly **101**, the second valve assembly **101** is positioned in proximity and in a light-of-sight path with a second CPU transceiver as the gas source **60** is loaded onto the cart. The second CPU transceiver **222** establishes communication with the second valve assembly **101** and thus detects the presence of a second gas source **60**. In the embodiment shown in FIGS. **7-9**, the second CPU transceiver **222** may also be disposed on the cover portion **225** of a cart. In one or more alternative embodiments, the second CPU transceiver **222** may be disposed on the CPU **210**.

As shown in FIG. **8**, the cart **500** may include an optional small bin **510**, a mount **512** for supporting the control module **200** on the cart **500**, at least one a holding bracket **520**, at least one mounting strap **530**, an auxiliary bracket **540**, for holding an auxiliary gas source, a plurality of casters **550** and a caster lock lever **560** disposed on each of the plurality of casters **550**. The cart **500** may include a mount **570** for mounting the control module **200** on to the cart.

An exemplary control module **200** is shown in FIGS. **10-12** includes a display **270** for providing visual indication to the user the components of the gas being delivered from the gas source **50** to the ventilator **400** (e.g., NO, O_2, NO_2), the concentration of each component and whether communication has been established with one or more gas sources. Other information may also be displayed to the user. In addition, visual alarms may also be displayed on the display **270**. The control module **200** may also include a main power indicator **272** indicating whether the control module is connected to a power source, such as an AC/DC power source and/or a battery. The control module **200** may also include a control wheel **274** allowing the user to navigate through various displays or information displayed on the display. An injection module tubing outlet **276** may be disposed on the control module for providing fluid communication between the delivery module **260** and the injector module **430**. An injection module cable port **278** may also be provided on the control module to provide electronic communication between the delivery module **260** and the injector module **430**. The control module **200** shown in FIGS. **10-12** also includes the sample line inlet **280** in fluid communication with the sample line **232** and the inspiratory limb **412** of the ventilator **400**. In the embodiment shown in FIGS. **10-12**, the water trap **233** is disposed on the control module, adjacent to the sample line inlet **280**.

FIG. **11** illustrates a back view of the control module **200** and shows a plurality of inlets. In the embodiment shown, two gas inlets **282**, **284** for connecting the control module **200** to the gas source **50** are provided and one auxiliary inlet **286** for connecting the control module **200** to an auxiliary gas source, which may include oxygen or other gas. A power port **288** is also provided on the back of the control module to connect the control module to an AC/DC power source.

The control module **200** may also include an input means **290** for allowing the user to enter patient information, for example the identity of the patient, the type and concentration of the gas and dose of the gas to be administered to the patient, the patient's disease or condition to be treated by the gas or reason for treatment, gestational age of the patient and patient weight. The input means **290** shown in FIG. **12** includes a keyboard integrated with the display. In one or more alternative embodiments, the input means may include a USB port or other port for the connection of an external keyboard or other input mechanism known in the art. The information entered via the input means **290** is stored within the CPU memory **212**.

The control module **200** and the valve assembly **100** may be utilized in the gas delivery system **10** to improve patient safety. Specifically, the safety benefits of the gas delivery system described herein include detecting a non-confirming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like. In addition, embodiments of the gas delivery system described herein also improve efficiency of gas therapy.

FIG. **13** is a block diagram showing the sequence of how gas delivery device, including the valve assembly **100**, may be provided and its use within the gas delivery system **10**, according to one or more embodiments. As shown in FIG. **13**, the gas delivery device **10** is prepared for use by providing a gas source **50** in the form of a gas cylinder or other container for holding a gas and filling the gas source **50** with a gas (**700**) and attaching a valve assembly **100** as described herein, to assemble the gas delivery device **10** (**710**). These steps may be performed by a gas supplier or manufacturer. The gas data regarding the gas filled within the gas source **50** is entered into the valve memory **134** as described herein (**720**). The gas data may be entered into the valve memory **134** by the gas supplier or manufacturer that provides the gas source **50** and assembles the gas delivery device **10**. Alternatively, the hospital or other medical facility may enter the gas data into the valve memory **134** after the gas delivery device has been transported to the hospital or medical facility (**730**). The gas delivery device **10** is positioned on a cart **500** (**740**) and communication between the CPU transceiver **220** and the valve transceiver **120** is established (**750**). The gas data stored within the valve memory **134** is conveyed to the control module **200** (**760**) via the wireless optical line-of-sight communication between valve transceiver **120** and the CPU transceiver **220**. The CPU **210** compares the gas data to patient information entered into the CPU memory **212** (**770**). The patient information may be entered into the CPU memory after the gas data is entered into the CPU memory **212**. The patient information may be entered into the CPU memory before the gas delivery device **10** is positioned in the cart or before communication between the CPU transceiver **220** and the valve transceiver is established. In one or more alternative embodiments, the patient information may be entered into the CPU memory **212** before the gas delivery device **10** is prepared or transported to the hospital or facility. The CPU **210** then compares whether the gas data and the patient information match (**780**). If the gas data and the patient information match, then gas is administered to the patient (**790**), for example through a ventilator or other gas delivery mechanism. If the gas data and the patient information do not match, then an alarm is emitted (**800**). As described otherwise herein, the alarm may be audible and emitted through the speaker **214** and/or may be visual and displayed on the display **270**.

The gas delivery system described herein simplifies set-up procedures by utilizing wireless line-of-sight signals to establish communication. The user does not need to ensure all the cables are correct connected and can freely load new gas sources onto a cart without disconnecting cables linking the control module **200** and the valve assembly **100** or circuit **150**. This reduces set-up time and any time spent correcting errors that may have occurred during the set-up process. The control module **200** and the circuit **150** are further designed to automatically send and detect information to establish delivery of a correct gas having the correct concentration and that is not expired. In one or more specific embodiments, such automated actions prevent the use of the gas delivery system by preventing gas flow to a patient, without user intervention.

In one or more embodiments, after communication between the valve transceiver **120** and the CPU transceiver **220** is established, the valve processor **122** includes instructions to convey the gas data stored in the valve memory **134** via the valve transceiver **120** to the CPU transceiver **220**. The CPU **210** includes instructions to store the gas data received from the CPU transceiver **220** in the CPU memory. The CPU **210** also includes an algorithm that compares the gas data with patient information that is entered into the CPU memory **212**. If the gas data and the patient information do not match, the CPU **210** includes instructions to emit an alarm, which may be audible, visual or both, alerting the user that the gas contained within the gas source is different from the gas to be administered to the patient. For example, as illustrated in FIG. **12**, if the gas data includes gas expiration date, the CPU memory **212** includes information regarding the current date and the CPU **210** compares the gas expiration date with the current date. If the gas expiration date is earlier than the current date, the CPU **210** emits an alarm. The alarm may be emitted through one or both the speaker **214** and display **270**. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent

delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of an expired gas by the CPU **210** may be stored within the CPU memory **212**.

If the gas data includes gas concentration information or data, the CPU memory **212** includes information regarding the desired concentration of gas to be administered to the patient. The control module **200** may be configured to alert the user that the gas contained within a gas source has incorrect concentration or a concentration that does not match the desired gas concentration. For example, a user may enter a concentration of 800 ppm into the CPU memory **212** and this concentration is compared to the gas concentration conveyed from the valve memory **134** to the CPU memory **212**. As illustrated in FIG. **12**, the CPU **210** includes instructions to compare the gas concentration of the gas with the concentration entered by the user. If the gas concentration does not match the concentration entered by the user, the CPU **210** emits an alarm, which may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent delivery of the gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of the gas. The detection of a gas with incorrect concentration may be stored within the CPU memory **212**.

In one or more embodiments, the control module **200** may be configured to detect more than one valve and to detect whether more than one valve is turned on. This configuration eliminates waste because it alerts a user that both valves are turned on and thus unnecessary gas is being delivered to via the delivery module **260**. In addition, such a configuration improves safety because it avoids the issues related to having two regulators pressurized at the same time and connected to the delivery module **260**. In one or more embodiments, the cover portion **225** of the control module **200** may include a second CPU transceiver **222** and the CPU **210** may include instructions for the second CPU transceiver **222** to detect wireless optical line-of-sight signals from a second valve assembly **101**, and more specifically, a second valve transceiver **121**. The CPU **210** may also include instructions that once a second valve assembly **101** is detected by the CPU transceiver **222**, whether both valve assemblies **100**, **101** are opened or have a valve status that includes an open position. In operation, a first valve assembly **100** includes a circuit with a valve processor with instructions to covey an open or closed position via the first valve transceiver **120**. The circuit of the second valve assembly similarly includes a valve processor with instructions to convey an open or closed position via a second valve transceiver **121**. The first CPU transceiver **220** and the second CPU transceiver **222** detect the valve statuses for each respective valve assembly from the first valve transceiver **120** and the second valve transceiver **121** via the wireless optical line-of-sight signals sent by both transceivers. The CPU **210** instructs the CPU transceivers **220**, **222** to collect the valve statuses for both valve assemblies **100**, **101** and the memory to store the valve statuses. The CPU **210** then compares the valve status information from the first valve assembly **100** and the second valve assembly **101** and, if the valve statuses both comprise an open position, the CPU **210** emits an alarm. The alarm may be audible and/or visual. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas through either the first valve assembly or the second valve assembly. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas. The detection that more than one valve assembly had a valve that was turned on or had a valve status including an open position may be stored within the CPU memory.

In one or more embodiments, the control module **200** may be configured to alert a user when the desired dose has been delivered. In such embodiments, the patient information entered into the CPU memory **212** may include dosage information or the dose to be delivered to a patient. The valve processor **122** may include instructions to convey gas usage information from the valve memory **134**, including the amount of gas delivered, to the CPU memory **212** via the valve transceiver **120**. Alternatively, the valve processor **122** may include instructions to covey the duration of time the valve **170** has been turned on or has a valve status including an open position to the CPU memory **212** via the valve transceiver **120**. The CPU **210** may include instructions to compare the dosage information entered by the user and stored within the CPU memory **212** with the gas usage information. The CPU **210** may include instructions to emit an alarm when the dosage information and the gas usage information match. The CPU **210** may include instructions to emit the same or different alarm to alert the user to turn off the valve or, more specifically, the actuator **114** when the dose has been delivered. In one or more embodiments, the CPU **210** may include instructions that the delivery module **260** cease or prevent further delivery of gas. In one or more embodiments, the CPU **210** includes instructions to turn the backup on/off switch **269** off if the delivery module **260** commences or continues delivery of gas.

In addition, the control module **200** may be configured to alert the user that a detected valve is and remains closed and no gas is being delivered to the patient. This configuration expedites treatment time and increases efficiency for the hospital. In such embodiments, the valve processor **122** may include instructions for the valve transceiver **120** to convey the valve status to the CPU **210** via a wireless optical line-of-sight signal. The CPU **210** includes instructions to collect the valve status information and emit an alert if the dosage information is set or other input has been entered into the CPU memory **212** to commence treatment and the valve status includes a closed position.

The control module **200** may be configured to alert the user that no valve assembly or gas source has been detected. In such embodiments, the CPU **210** includes instructions to detect the presence of a wireless optical line-of-sight signal from another transceiver, for example, the valve transceiver **120**. The CPU **210** may include instructions to emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected. Similarly, the control module **200** may be configured to emit an alarm if communication between one or both of the CPU transceiver(s) **220**, **222** and one or both of the valve transceivers **120**, **121** has been lost during gas delivery. In such embodiments, the CPU **210** may include instructions to continuously detect the presence of a signal from another transceiver and emit an alarm if the dosage information or other input to commence delivery of the gas has been entered into the CPU memory **212** and no signal from another transceiver has been detected.

The CPU **210** may include instructions to alert a user when sensors in the control module **200** must be calibrated to ensure accurate delivery of gas to a patient. In addition, the CPU **210** may include instructions to correlate gas usage information from the circuit **150** of the valve assembly **100** to the patient

information entered into the CPU memory **212**. The CPU **210** may also have instructions to store the correlated gas usage information and the patient information in the CPU memory **212**. The valve processor **122** may also include instructions detect patient information from the CPU memory **212**. Specifically, the valve processor **122** may include instructions to collect patient information via the valve transceiver **120** from the CPU transceiver **220** and store the collected patient information in the valve memory **134**. In such embodiments in which information from the CPU **210** is collected and stored in the valve memory **134**, the CPU **210** may include instructions that the patient information and/or correlated patient information and gas usage information be conveyed from the CPU memory **212** via the CPU transceiver **220** to the valve transceiver **120**. The valve processor **122** may also include instructions to correlate gas usage information with the collected patient information and store the correlated gas usage information and collected patient information in the valve memory **134**. Alternatively, the valve processor **122** may include instructions to collect the correlated patient information and gas usage information from the CPU **210**. The correlated information may be utilized to bill the user according to patient. In addition, the correlated information may be utilized as patient demographic data, which can assist hospitals or other facilities to generate budget reports, determine usage per department, determine usage per patient diagnosis and link usage of multiple gas sources to individual patients.

A second aspect of the present invention pertains to a method for administering a therapy gas to a patient. The method includes providing a gas in a gas source. The gas source may be prepared by a supplier to contain a gas having a predetermined composition, concentration and expiration date. The method may include providing a valve assembly **100** attached to a gas source **50** to dispense the gas contained within the gas source **50** to a patient. The method may include entering gas data, which may include gas composition, gas concentration and gas expiration date, into the valve memory **134**. In one or more embodiments, the supplier may enter the gas data directly into the valve memory **134**. In another variant, the gas data is provided in the form of a bar code disposed on the gas source. In such embodiments, the method includes providing a scanner in communication with the data input **108**, scanning the bar code to collect the gas data information and conveying the gas data to the valve memory **134** via the data input **108**. These steps may be repeated for a second gas source. The gas source(s), with the valve assembly mounted thereon may be transported to a hospital or other facility for administration to a patient. The gas source(s) are then mounted onto the cart **500** and secured by the holding bracket **520** and mounting strap **530**. The method includes establishing communication between the valve transceivers disposed on each valve and the CPU transceivers **220**, **222**. Establishing communication may include positioning the valve assembly **100** in a line-of-sight path with at least one of the CPU transceivers **220**, **222**. As otherwise described herein, communication may be established by instructing the valve transceivers to send a wireless optical line-of-sight signal to the CPU transceivers **220**, **222**. The method may include instructing the valve transceiver **120** to send a wireless optical line-of-sight signal at pre-determined intervals, as otherwise described herein.

The method may include entering patient information into the CPU memory **212**. This step may be performed before or after the gas source(s) are mounted onto the cart. The method may specifically include entering patient information such as dosage information into the valve memory **134**. The method includes coordinating delivery of the gas to the patient by collecting gas data from the valve memory **134** and comparing the gas data with the patient information according to an algorithm and determining if the gas data and patient information match, according to the algorithm. Coordinating delivery of the gas may include turning on the actuator **114** of the valve **107** such that gas can flow from the inlet **104** to the outlet **106**. After the dose has been delivered, the method may include correlating the gas usage information and the patient information. The method may also include recording the patient information, gas usage information and/or the correlated patient information and gas usage information in the CPU memory **212** and/or the valve memory **134**. In one or more variants, the method may include utilizing the patient information, gas usage information and/or correlated patient information and gas usage information to generate invoices identifying the use of the gas by individual patients.

Reference throughout this specification to "one embodiment," "certain embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

What is claimed is:

1. A gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising:

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve; and

a circuit including:

a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and

a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to a control module that controls gas delivery to a subject and to verify one or more of the gas identification, the gas concentration and that the gas is not expired.

2. The device of claim **1**, wherein the valve further comprises a data input in communication with said memory, to permit a user to enter the gas data into the memory.

3. The device of claim **1**, wherein the signals comprise wireless optical line-of-sight signals.

4. The device of claim **1**, further comprising a power source, wherein the transceiver periodically sends the signals to the control module and the signals are interrupted by a duration of time at which no signal is sent to conserve the power source.

5. The device of claim 4, wherein the duration of time at which no signal is sent is in the range from about 5 seconds to about 20 seconds.

6. The device of claim 1, wherein the memory is disposed between the actuator and a cap.

7. A therapy gas delivery system comprising:

a gas delivery device comprising:

a gas source;

a valve attached to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve; and

a circuit comprising:

a first memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source; and

a first processor and a first transceiver in communication with the first memory; and

a control module that controls delivery of therapy gas to a subject, the control module comprising a second memory, a second transceiver and a second processor, wherein the second transceiver and the second processor are in communication with the second memory,

wherein the first transceiver and the second transceiver send and receive signals to communicate the gas data to the control module and to verify one or more of the gas identification, the gas concentration and that the gas is not expired.

8. The system of claim 7, wherein the control module further comprises a display to enter patient information into the second memory.

9. The system of claim 8, wherein the second processor compares the patient information entered into the second memory via the display and the gas data that the first transceiver communicated to the second transceiver.

10. The system of claim 9, wherein the control module comprises an alarm that is triggered when the patient information entered into the second memory and the gas data from the valve transceiver do not match.

11. The system of claim 7, wherein the second memory comprises instructions that cause the second processor to:

receive gas data from the gas delivery device;

compare the gas data with patient information; and

control delivery of the therapy gas to the patient.

12. The system of claim 11, wherein the second processor verifies one or more of the gas identification, the gas concentration and that the gas is not expired prior to delivery of the therapy gas to the patient.

13. The system of claim 7, wherein the second memory comprises instructions that cause the second processor to:

receive a first valve status selected from a first open position and a first closed position from a first valve connected to a first gas source;

receive a second valve status selected from a second open position and a second closed position from a second valve connected to a second gas source;

compare the first valve status and the second valve status; and

emit an alarm if the first valve status comprises the first open position and the second valve status comprises the second open position.

14. The system of claim 7, wherein the signals comprise wireless optical line-of-sight signals.

15. A method for administering a therapy gas to a patient, comprising:

establishing communication between a gas delivery device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver, wherein the gas delivery device comprises a gas source and the first transceiver is in communication with a first memory that stores gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source, wherein the control module comprises the second transceiver and a second memory;

communicating the gas data from the first transceiver to the second transceiver via wired or wireless signals;

comparing the gas data with patient information stored in the second memory to verify the gas data; and

controlling delivery of the therapy gas to the patient.

16. The method of claim 15, wherein the signals comprise wireless optical line-of-sight signals.

17. The method of claim 15, further comprising preventing or ceasing delivery of the therapy gas to the patient based on the comparison of the gas data and the patient information.

18. The method of claim 15, further comprising emitting an alert based on the comparison of the drug data and the patient information.

19. The method of claim 15, further comprising entering the drug data into the first memory.

20. The method of claim 15, further comprising entering the patient information into the second memory.

* * * * *

JS 44 (Rev. 12/12)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
INO THERAPEUTICS LLC and IKARIA, INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Jack B. Blumenfeld 302-658-9200
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street; P.O. Box 1347; Wilmington, DE 19899

DEFENDANTS
PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing *(Do not cite jurisdictional statutes unless diversity)*:
35 U.S.C. § 271
Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER RULE 23, F.R.Cv.P. DEMAND $ CHECK YES only if demanded in complaint: JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY *(See instructions)*: JUDGE _____ DOCKET NUMBER _____

DATE February 19, 2015 SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

JS 44 Reverse (Rev. 12/12)

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) **Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) **County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) **Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; **NOTE: federal question actions take precedence over diversity cases.**)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerk(s) in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. **Origin.** Place an "X" in one of the six boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.