IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 12/821,020	Examiner	: Ernst V. Arnold
Filed	: June 22, 2010	Conf. No.	: 3179
Title	: Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Children in Need of Treatment with Inhaled Nitric Oxide		

SUPPLEMENTAL REMARKS

This application has been granted special status under the prioritized examination (Track 1) program. An Office action was mailed January 31, 2012, setting a three-month deadline for response of April 30, 2012. As indicated in the Interview Summary mailed by the Office on April 24, 2012, the Examiner spoke by telephone with an assistant of the undersigned on April 20, 2012, stating that the Office action would be replaced with a new Office action. This message was confirmed by the Examiner in a telephone conference with the undersigned on April 23, 2012. In addition, the transaction history for this application on PAIR has two entries dated April 24, 2012: "Mail Notice of Withdrawn Action" and "Withdrawing/Vacating Office Action Letter." Applicants thus assume that there is no longer a pending deadline for response, and there will be no deadline for response until the new Office action is mailed and thereby resets a new deadline.

Applicants filed a Supplemental Amendment on April 30, 2012, with amendments intended to address potential issues under 35 U.S.C.§ 101 described by SPE Marjorie Moran in a telephone conference with the undersigned on April 30, 2012. The amendments are based on SPE Moran's helpful suggestions, so presumably fully address the potential issues described by her as arising under § 101. Applicants ask that the Supplemental Amendment be entered and considered prior to preparation of a new Office action.

As noted on page 10 of the Supplemental Amendment, applicants request that SPE Brian Kwon and QAS Julie Burke continue to participate actively in the prosecution of this application as a panel with Examiner Arnold. Applicants gratefully note that their perspective on the case has been very helpful to date in moving the case forward.

The remarks below are intended to assist the Examiner in understanding some technical points that appear to applicants to be a source of confusion in this case. The technical points are:

(1) the significance of the claim language "wherein the child is not dependent on right-to-left shunting of blood";

(2) the description of the child who is the subject of the claimed method; and

(3) the disclosures of the various references cited in the obviousness rejection set forth in the prior Office action dated January 31, 2012.

By resolving the apparent confusion regarding those three topics, applicants believe that these remarks should be very useful in moving the case forward efficiently.

(1) The significance of the claim language "*wherein the child is not dependent on right-to-left shunting of blood.*"

This language (or its equivalent "wherein the children are not dependent on right-to-left shunting of blood") appears in step (a) of each of the pending independent claims, as amended in the Supplemental Amendment filed April 30, 2012. It effectively narrows the scope of the claimed method by excluding outright some children from the set of children who are the subject of the method.

The term "dependent on right-to-left shunting of blood" is well understood in the medical art. See, for example, the use of this term in the 2007 INOmax prescribing information[1] cited in the January 31, 2012 Office action as the "INOmax insert" (page 2, left column, under "Contraindications"). The INOmax insert refers to a condition occasionally seen in neonates born with an absent or nonfunctional left ventricle -- the ventricle that normally pumps blood into the systemic circulation. Ordinarily, such a neonate will die immediately from a lack of systemic circulation. Under certain circumstances, however, these neonates may survive: i.e., when two other independent conditions both exist concurrently with the nonfunctional left ventricle: (i) an open (patent) ductus arteriosus, and (ii) an abnormally high level of pulmonary vascular resistance (routinely arising from pulmonary hypertension). When both of these

[1] Also commonly referred to as the "package insert" or "PI".

conditions exist concurrently in a neonate who lacks a functional left ventricle, the neonate's right ventricle (which normally pumps blood only into the lungs) can take over the left ventricle's normal function of supplying blood flow to the systemic circulation. The right ventricle would have no outlet into the systemic circulation unless the infant's ductus arteriosus, a vascular connection between the pulmonary artery (which exits the right ventricle) and the aorta (which feeds the systemic circulation), remains open after birth. The ductus arteriosus normally closes at birth. If instead it remains open in a neonate who has no functioning left ventricle, the ductus arteriosus will provide a conduit for some of the blood pumped by the right ventricle to shunt into the systemic circulation rather than taking its normal route into the lungs. This is termed a right-to-left shunt through a patent ductus arteriosus (PDA). If the neonate concurrently has pulmonary hypertension, this means relatively less blood goes from the right ventricle into the vasoconstricted lungs, thereby allowing more blood to shunt from the right ventricle through the PDA. In some cases, enough blood shunts through the PDA to sustain the systemic circulation. If the amount of blood flowing from the right ventricle through the PDA into the systemic circulation is sufficient to maintain life, and if the neonate's left ventricle is so severely dysfunctional that, absent this shunt through the PDA, the neonate would die from an inadequate systemic circulation, the neonate is said to be "***dependent*** on right-to-left shunting of blood." The reason this dependence on right-to-left shunting of blood has always been a contraindication on the INOmax® package insert since the product was first marketed is because it was known in the art that a patient who has pulmonary hypertension and is dependent on right-to-left shunting of blood, and who is treated with inhaled nitric oxide to open up the pulmonary blood vessels and thereby allow more blood to flow through the lungs, can suffer a catastrophic loss of the right-to-left blood flow through the PDA on which the patient depends for life.

There are many other situations in which a patient who is a candidate for treatment with inhaled nitric oxide (e.g., because the patient has pulmonary hypertension) exhibits a right-to-left shunt, a left-to-right shunt, or even a bi-directional shunt. Such a shunt can be through a PDA; through a hole between the right and left atria, termed the foramen ovale; or through a hole in the septum (wall) between the left and right ventricles, termed a ventricular-septal defect. Except for the situation described above with the particular combination of conditions specified above (i.e., nonfunctional left ventricle, pulmonary hypertension, and a PDA through which blood shunts

right-to-left in a volume that is sufficient to maintain the systemic circulation despite the nonfunctional left ventricle), the patient is not "dependent" on any of these shunts—i.e., his/her life does not depend on maintaining the shunt. In fact, it is more common that a shunt is harmful rather than helpful to the patient, because it diverts blood away from its normal path through the right side of the heart to the lungs (where it is oxygenated), then into the left side of the heart, and from there into the systemic circulation for delivery to all parts of the body. For example, a right-to-left shunt at the atrial level, i.e., through the foramen ovale, means some of the deoxygenated blood entering the right atrium is shunted into the left atrium instead of taking its normal path into the right ventricle and then into the lungs. In such a patient, the "shunted" deoxygenated blood then passes from the left atrium into the left ventricle and is pumped by the left ventricle into the systemic circulation, still in its deoxygenated state, leaving the infant chronically poorly oxygenated. Far from being "dependent" on this right-to-left-shunt through the foramen ovale, the patient would be much better off without it.

The articles cited by the Examiner in the obviousness rejection described in the January 31, 2012 Office action discuss in various contexts right-to-left shunts and left-to-right shunts (sometimes referring to the shunt as "exclusively" right-to-left or "exclusively" left-to-right). These shunts may occur at an open foramen ovale, at a PDA, or at a ventricular-septal defect. The sole situation in which the patient is "dependent" on a shunt is the one described above, where the patient has a combination of pulmonary hypertension, a severely dysfunctional or absent left ventricle, and a right-to-left shunt through a PDA. (As described on page 452, left column, of Atz & Wessel, Seminars in Perinatology 1997, 21(5): 441-455 (one of the references cited in the January 31, 2012 Office action), such a patient may also have, in addition to that combination of conditions, a left-to-right shunt through an open foramen ovale; such a patient is still characterized as "dependent on a right-to-left shunt" because of the critical role played by the right-to-left shunt through the PDA.) Characterizing a shunt as "exclusively" right-to-left or "exclusively" left-to-right means that the blood flows only in the indicated direction through that shunt. It does not mean, and does not even imply, that the patient is "dependent" on the shunt. In fact, most patients who have a shunt that is exclusively in one direction are harmed by the shunt, far from being "dependent" on it.

Applicants hope that the above discussion helps to clarify the significance of the word "dependent" in the claim language "dependent on right-to-left shunting of blood."

(2) The description of the child who is the subject of the claimed method.

During the April 13, 2012 Interview, QAS Burke mentioned that the negative limitations of claim 31 made the claim somewhat difficult to parse. Applicants have attempted to simplify the claims by omitting the words "known to be" in step (a) of each independent claim. (See the Supplemental Amendment filed April 30, 2012.) Claim 31 is a drawn to a method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, where the method includes identifying a narrowly defined category of children who are in need of nitric oxide treatment but who are at particular risk of pulmonary edema from that treatment, and excluding from the treatment any child who falls into that defined category of at-risk patients. It is important to note that the prior art was unaware that any children were at particular risk of pulmonary edema when treated with inhaled nitric oxide. The prior art did know that some children (i.e., neonates who are dependent on right-to-left shunting of blood) were at risk of systemic hypotension when treated with inhaled nitric oxide, but this risk has nothing to do with a risk of pulmonary edema and does not predict a risk of pulmonary edema. *Thus, the claim would be novel and nonobvious regardless of how the category of children to be excluded from the treatment is defined in the claim.* Since the basis for the invention was the discovery that children who have left ventricular dysfunction are surprisingly at risk for pulmonary edema when they are treated with inhaled nitric oxide, the claims include a limitation that the child to be excluded from treatment due to this risk is determined to have left ventricular dysfunction. In addition to this limitation on the scope of the claim, applicants have chosen to narrow the scope even further by explicitly requiring that the category of children covered by the claim not include those who are dependent on right to left shunting of blood.

Applicants hope that this discussion of the claims will help the Examiner understand the nature of the claims and the effect of the various limitations on claim scope.

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