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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

**DRAFT 1**

# CONCEPT PAPER ON THE IMPACT OF LUNG AND HEART IMMATURITY WHEN INVESTIGATING MEDICINAL PRODUCTS INTENDED FOR NEONATAL USE

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## 1. INTRODUCTION

This paper is third in a series of documents aiming at recognising the uniqueness of neonates if exposed to medicines. The document specifically discusses the impact of lung and heart immaturity when investigating medicinal products in term and preterm newborns and infants. Besides the dramatic physiological changes during the transition from fetal to neonatal circulation, potential diseases affecting the cardiopulmonary system may have additional major impact and should therefore be considered when investigating medicinal products. It is also obvious that any medicinal product given to a term and preterm newborn or infant during or shortly after birth might have an potential effect on the physiological changes of the heart and lung. In return, any effect intended by a medicinal product will be likewise affected by the immaturity of the heart and lung. This applies even more when products are given which are specifically intended to treat conditions relating to immaturity and therefore directly affect the cardiopulmonary system of the newborn. This concept paper aims to approach these various issues and their complex interactions when investigating medicinal products in the neonate.

## 2. BACKGROUND

Birth is accompanied by unique and major physiological changes. Lung ventilation and changes in cardiopulmonary circulation render the fetus able to adapt to extra-uterine life. Inflation of the lungs with air is accompanied by a rapid removal of lung liquid from the alveoli into the lymphatic vessels. This creation of alveolar air volume and increased pulmonary blood volume results in decreased pulmonary vascular resistance and improved blood oxygenation. The increase in cardiac output, which encompasses these adjustments to extra-uterine life can be attributed to closing of the placental shunt, contributing to an increased heart rate and ameliorated function of the cardiac ventricles. It will optimise perfusion of every organ in the body and consequently increase the drug metabolising capacity of the liver and the drug clearing capacity of the kidney.

## 3. PROBLEM STATEMENT

Basic reasons and consequences of immature or impaired cardiopulmonary function in the neonate must be considered in order to ensure adequate investigation of medicinal products in very young children and neonates. Gestational age at birth and the type of delivery (vaginal vs. caesarean section) have an impact on the postnatal capability of removing liquid from the lungs, and aeration of the lungs. Referring solely to lung immaturity, the synthesis as well as the secretion of surfactant are decreased in prematurely born babies. It leads to the classical respiratory insufficiency of preterm newborns, namely the respiratory distress syndrome (RDS). In pathological circumstances, severe meconium aspiration syndrome and lung infection may induce various degrees of pulmonary oedema and hypoxaemia. It may also affect liquid resorption and worse lung gas exchanges. Whatever the cause, insufficient lung inflation at birth associated with decreased lung compliance can rapidly result in increased pulmonary vascular resistance returning to the antenatal condition (Persistent Pulmonary Hypertension of the Newborn (PPHN)). This will result in decreased cardiac output and eventually cardiac failure due to right and left ventricular dysfunction. The patency of the ductus arteriosus (PDA) which is most often seen in premature newborns and various congenital cardiac malformations may further worsen the cardiac failure and the perfusion of the body organs. The signs and symptoms of cardiopulmonary dysfunction in the neonate are not similar to that of the older child. Therefore, any pharmacological approach aiming at supporting the cardiopulmonary function of these patients will have to take into account the gestational or post conceptional age of the patient.

In the field of neonatal pulmonary disease several randomised studies have investigated the benefits of accelerating fetal lung maturation by giving corticosteroids to pregnant women. In addition, exogenous surfactants have also been studied in premature newborns suffering from pulmonary disease due to surfactant deficiency. These investigations have resulted in the labelling of these products for neonates. Yet, many pharmacological interventions have already been used in the treatment of cardiopulmonary insufficiency and immaturity of the neonate, but the majority are still used unauthorised and/or off-label as no adequate studies were performed in this population. Most dosage recommendations are based on data derived from adults. As there is an obvious need for

further development, future investigations should carefully consider potential particularities deriving from immaturity of the cardiopulmonary system. This applies to any medicinal product studied for neonatal use.

## 4. DISCUSSION

Before conducting studies in neonates, the needs and the methods of assessment have to be defined for each medicinal product intended to be investigated. In order to prevent unnecessary studies in neonates, there should be thorough considerations of potential in-vitro or in-vivo models to study the effects of a medicinal product on the immature cardiopulmonary system. When investigating a medicinal product in the neonate, particular attention should always be paid to potential complex interactions between the product and the ongoing physiological maturation process of the cardiopulmonary system. In practice, the following specifics of heart and lung immaturity should be addressed when investigating medicinal products for neonatal use:

*Changes (physiological and iatrogenic) of the lung and heart after birth:*

- Any pharmacological study will have to take into account the gestational age and the maturation stage of the patient at birth. This includes the determination of the best plasma concentration leading to the desired receptor response with respect to the postnatal and postconceptional age.

- In general, the influence of ongoing changes during lung and heart maturation on PK/PD relationship, including e.g. closure of the ductus arteriosus (either physiological or iatrogenic) and fall in pulmonary vascular resistance has to be considered.

- As sympathic tone predominates over parasympathic tone in the newborn and the α-and β-adrenergic receptors may not be mature, the role of ongoing receptor maturation and potential desensitisation have to be considered when studying medicinal products in neonates. This applies in particular to cardiovascular medicinal products and long term pharmacological management. Potential changes in maintenance dose have to be borne in mind accordingly.

*The clinical condition of the neonate:*

- The clinical condition of the patient and the severity of additional diseases should be taken into account as a possible confounder when investigating medicinal products in neonates. Correspondingly, a stratification of the population according to the clinical status (e.g. acid base status) has to be considered.

- Pharmacodynamics of catecholamines given to the neonate could be modulated by local tissue hormones such as prostaglandins and neuropeptides. Especially in the asphyctic state, a frequent state in neonates, adenosine and endorphins may reduce the β-adrenergic effect on the target cell. This should also be addressed as a potential confounder where appropriate.

*Ante- and postnatal therapy:*

- Careful evaluation of the products to which the fetus has been exposed in utero is needed as any medicinal product given to the mother may influence the PK/PD relationship of the medicine administered postnatally to the neonate.

- The optimal route and postnatal timing of medicinal product administration in preterm and term newborns and infants, and its influence on safety and efficacy should be addressed.

- Neonates hospitalised in the neonatal intensive care units often need to be considered as multi-drug users. This complicates any evaluation of the outcome when a given product is assessed in the neonatal period. Other concomitantly administered medicinal products might adversely influence metabolism, PK/PD relationship and PK interactions and/or generate unexpected adverse reactions. Accordingly, possible interactions of medicinal products frequently

administered concomitantly should be investigated to provide reliable information in real clinical conditions.

- Specific adverse reactions or interactions of a medicinal product resulting from heart and lung immaturity have to be considered (e.g. Q-T prolongation in the immature heart).

- The influence of high-level oxygen administration, relating also to the techniques of administration (nasal canula, continous positive airway pressure, endotracheal tube) has to be taken into account when studying medicinal products in neonates.

*Long-term effects*

- Besides short-term and intermediate effects on lung and heart maturation, potential long-term effects of a medicinal product administered to the neonate should be followed-up carefully when investigating a medicinal product for neonatal use.

## 5. RECOMMENDATION

Since there is a lack of established guidelines while investigating a medicinal product in the neonate, a guideline is in preparation, which will summarise the challenges for studies of medicinal products for neonatal use.

## 6. PROPOSED TIMETABLE

It can be anticipated that the Guideline for the investigation of medicinal products for neonatal use will be available by the end of 2006.

## 7. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will involve the PEG and other relevant CHMP Working Parties.

## 8. IMPACT ASSESSMENT

The development of this Guideline will help industry and other parties to study medicinal products in the neonates in view of the upcoming Paediatric Regulation and this is likely to increase the interest for applying for MA in this neglected population.

## 9. INTERESTED PARTIES

Interested parties with specific interest in this topic will also be consulted during the preparation of this guideline.