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AND
PAEDIATRIC COMMITTEE (PDCO)

GUIDELINE ON THE INVESTIGATION OF MEDICINAL PRODUCTS IN THE TERM AND PRETERM NEONATE

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EXECUTIVE SUMMARY

This guideline addresses the considerations and requirements for the design and conduct of clinical trials in premature and term neonates using medicinal products of relevance for the use by this population. It includes background information on the maturation of organs and of body functions.

1 INTRODUCTION

Neonates are the group of children from birth up to and including the age of 27 days, including term and preterm neonates. They represent a particularly vulnerable subgroup of the paediatric population. Whilst they account for a low percentage of the total use of medicines in childhood, up to 90 % of medicinal products are used unauthorised or off-label in this population, especially if treated on Neonatal Intensive Care Units (NICUs).

There are several reasons as to why few clinical trials of medicinal products have been performed in neonates (e.g. feasibility difficulties linked to: age, small patient group and uniqueness of their diseases.) The Regulation on Medicinal Products for Paediatric Use (Regulation (EC) 1901/2006) creates obligations with regards to conducting clinical trials in paediatric patients including neonates in order to meet the recognised need for authorised medicinal products and the information on the use of medicinal products in children. Therefore clinical trials to investigate medicinal products in the neonatal population have to address the needs of this population (section 9.1).

Neonatal studies encompass multiple difficulties, such as ethical (high vulnerability) and technical issues (immaturity, prematurity, lack of self assessment, need for specific formulations, high variability, etc). Notwithstanding the difficulties, the standards of the trials should remain the same.

2 SCOPE

The guideline aims to provide guidance for the development of medicinal products for use in the neonatal period, defined as from birth up to 27 days post-natal age in term neonates and from birth up to a post-menstrual age of 40 weeks and 27 days in preterm neonates.

However, it cannot encompass all potential aspects applying to all medicinal products in the various conditions affecting the neonate. In addition, the scientific development, rapid changes and the emergence of medical innovations especially in this therapeutic area will require revisions of the guideline and, on behalf of the sponsor or applicant, consideration of current scientific knowledge.

Due to the complexity of investigating medicinal products in the neonatal population and the high vulnerability of the neonatal population, applicants are therefore strongly advised to seek further expert opinion and European regulatory scientific advice in this regard.

This guideline shall be relevant to all investigations of medicinal products that include participation of the neonatal population.

The guideline is based on several concept papers released by the Paediatric Working Party (PEG) addressing the impact of immaturity of different organ systems when investigating medicinal products in the neonate. It therefore contains specific aspects related to organ development that should be considered during the development of medicinal products in the neonate.

3 LEGAL BASIS

This guideline should be read in conjunction with:

- Regulation on Medicinal Products for Paediatric Use (EC) 1901/2006 as amended by Regulation (EC) 1902/2006
- Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population CPMP/ICH/2711/99

- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/04
- Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population EMEA/CHMP/PhVWP/235910/2005- rev.1
- Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (2008, EudraLex Vol. 10 Chapter V)
- Reflection Paper on Formulations of Choice in Paediatric Population EMEA/196218/05
- Discussion Paper on the Impact of Renal Immaturity CHMP/PEG/35132/03
- Concept Paper on the Impact of Liver Immaturity CHMP/PEG/194605/05
- Concept Paper on the Impact of Lung and Heart Immaturity CHMP/PEG/114218/06
- Concept Paper on the Impact of Brain Immaturity CHMP/PEG/181377/06
- Guideline on Clinical Trials in small populations CHMP/EWP/83561/05
- Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications CHMP/SWP/169215/05 (draft)
- Regulation No (EC) 141/2000 on orphan medicinal products
- Annex I to Directive 2001/83/EC, as amended
- Other relevant Agency (including ICH) Guidelines

GUIDELINE TEXT

1 DEFINITIONS

For the purpose of this guideline, the following definitions are used.

- Neonatal period: Period from birth up to and including 27 days in term neonates, or from birth up to a post-menstrual age of 40 weeks and 27 days in preterm neonates
- Gestational age (GA): Time from first day of last normal menstrual period to date of birth, usually expressed in completed weeks; GA is determined at birth using methods such as “best obstetrical estimate” (including first day of last menstrual period, physical examination of mother, prenatal ultrasound, history of assisted reproduction) and specific postnatal physical examinations. When a pregnancy has been achieved by assisted reproductive technology, GA is calculated from two weeks before the date of conception.
- Post-natal age (PNA) or chronological age: Age calculated from date of birth (days, weeks, months or years)
- Post-menstrual age (PMA): Time from first day of last normal menstrual period to day of assessment, that is, gestational age plus post-natal age, usually expressed in weeks
- Corrected age (of preterm neonates): Age calculated from expected date of delivery; usually used for children up to about 3 years, expressed in weeks or months
- Preterm neonate: < 37 weeks of GA (equal or less than 36 weeks and 6 days of gestation)
- Extremely preterm neonate: < 28 weeks of GA
- Very preterm neonate: 28-32 weeks of GA
- Term neonate: 37-42 weeks of GA
- Post-term neonate: > 42 weeks of GA

- Low birth weight (LBW): Birth weight < 2500 g
- Very low birth weight (VLBW): Birth weight < 1500 g
- Extremely low birth weight (ELBW): Birth weight < 1000 g
- Small for gestational age (SGA): Birth weight below 10th percentile for gestational age
- Large for gestational age (LGA): Birth weight above 90th percentile for gestational age

It might be appropriate to use different definitions or classifications depending on the context of use. For example, developmental issues of the neonate are often related to gestational age whereas birth weight based classification is often used in relation to dosing in the neonate. Post-conceptional age reflecting the time since conception should not be used because the day of conception is most often unknown.

2 ORGAN MATURATION IN THE NEONATE

Most organ functions are physiologically immature in the neonatal period. The degree of immaturity may be aggravated due to prematurity, intrauterine growth retardation or any potential pathologic condition affecting the neonate. Functional immaturity of physiological processes and organ function predispose neonates to altered pharmacokinetics and pharmacodynamics, leading to potential inefficacy or reduced safety of a medicinal product in the neonate.

Maturational changes are rapid in the post-natal period, and the resulting high variability of the neonates (both inter-individually and intra-individually) has to be considered when investigating medicinal products for use in the neonatal population. Additionally, any medicinal product administered to the neonate may affect the ongoing maturation processes. Major developmental changes should be identified that could significantly influence exposure, safety and efficacy for a given medicinal product. If adequate and possible, not only pharmacokinetic changes due to ongoing maturation but also pharmacodynamic changes as a function of maturation itself should be investigated.

The following sections address specific issues of immaturity of different organ systems. It has to be emphasised that in addition to the organs outlined below, several other organ systems (e.g. eye, ear; immune, haematopoietic or coagulation system) may show significant maturation during the neonatal period, and this has to be taken into consideration as well. The sections should be viewed as a reminder of the specific considerations in the neonates related to immaturity. The considerations and investigations needed depend on the pharmacokinetic and pharmacodynamic characteristics of the medicinal product investigated. However, an isolated view of single organs should be avoided since organ systems and functions are closely interrelated.

2.1 Heart and lung

The post-natal cardiopulmonary system adaptation marks the most prominent changes during and after birth. Some of these changes occur instantaneous with the first breath, whereas others occur within hours or days after birth. In general, the impact of lung and heart maturation on PK/PD relationship (e.g., closure of the ductus arteriosus) has to be considered.

Due to the complexity of anatomic and functional adaptation processes even subtle variations (e.g., through administration of drugs) can impede the smooth transition to extrauterine life. This may be aggravated through congenital structural cardiac defects or any other condition affecting physiological maturation.

As adequate cardiopulmonary function is paramount to maintain organ function in general (e.g., renal blood flow, brain perfusion, liver function), any potential impact on either cardiac or pulmonary function needs to be carefully monitored in neonatal clinical trials. The influence of cardiopulmonary function as the basis to maintain hepatic drug metabolism and excretion as well as renal excretion has to be considered. For the purpose of clinical trial protocols, it has to be considered that clinical symptoms and signs of cardiopulmonary dysfunction in the neonate differ compared to older children and adults. Distinct cardiac (e.g., patent ductus arteriosus) and pulmonary (e.g., respiratory distress syndrome) conditions specific for the neonatal population may need to be taken into consideration

when planning a trial protocol. Stratification according to the clinical state or condition may be appropriate in some cases.

As cardiovascular receptors (e.g., adrenergic) are often immature in the neonate, ongoing receptor maturation has to be taken into account including potential desensitisation of receptors with ongoing treatment. Dose adjustment, especially in maintenance therapy may need to be considered. Both receptors in the heart as well as in other parts of the vascular system can differ in expression, which may cause unexpected alterations and reactions involving the whole cardiovascular system.

Specific adverse reactions may be seen due to the immaturity of the cardiopulmonary system of the neonate, especially if congenital or concomitant diseases are superimposed. For instance, cardiac malformations affecting the neonatal myocardium may increase the susceptibility to QT prolongation and Torsade-de-Points.

Monitoring of cardiopulmonary function

Cardiopulmonary monitoring of hospitalised neonates is carried out on a routine basis and these findings should be used and documented for the purpose of a clinical trial as appropriate. Less or non-invasive measures should be used whenever possible (e.g., measurement of blood pressure, heart rate, respiratory excursions and rate; pulse oximetry in at least one site, transcutaneous pO_2 and / or pCO_2 measuring, electrocardiogram [ECG], echocardiography, and Doppler sonography). Radiologic (e.g. X-ray, MRI) and laboratory (e.g., blood gases, haematocrit) assessments may additionally be required and would need to be synchronised with routine assessments and limited as much as possible.

2.2 Central nervous system (CNS)

Critical processes of brain development consist of neuronal proliferation, migration, organisation and myelination. Two main phases can be distinguished with the first occurring between the 8th and 16^{th} week of gestation, consisting of neuronal proliferation and generation of radial glia, and the second phase between 5 months and 1 year of life, consisting of glial multiplication (with neurogenesis and neuroproliferation continuing).

Transport across the blood brain barrier by both passive diffusion and by active transporters is age-related and undergoes constant maturational changes in the neonate. This may contribute to a significantly altered distribution of active substances or metabolites into the CNS with a potential impact on both clinical efficacy and adverse effects. Medicinal products known or expected to be substrate for specific transporters (e.g., P glycoprotein [Pgp]) require specific consideration. Any medicinal product interacting with glutamic acid and other neurotransmitters is expected to have an effect on brain development in the neonate. This should be carefully considered and monitored where possible. Presence and distribution of drug receptors in the brain undergoes major changes. Insensitiveness or increased sensitivity may lead to unexpected effects.

Even if a medicinal product is not primarily developed for an indication related to the CNS, the distribution and penetration into the CNS and the potential effects and neuro-developmental sequelae should be addressed.

Hypoglycemia is an important risk factor for perinatal brain injury. Due to the high metabolic rate and the dependence on glucose as unique source of energy of the brain, any medicinal product affecting glucose metabolism in the neonate may have an effect on the developing brain. This should be carefully taken into consideration when planning a neonatal study.

Increased intracerebral bilirubin concentrations may lead to bilirubin encephalopathy and severe brain damage (kernicterus). The pathogenesis of bilirubin encephalopathy is multifactorial and involves an interaction between unconjugated and free bilirubin levels, albumin binding capacity, blood brain barrier development, acid-base status and neuronal susceptibility to injury. Compounds with a presumed effect on any of these factors and particularly compounds interacting with the UGT1A1 enzyme, the hepatic uptake transporter OATP2, the efflux transporter MRP2 or compounds with a competitive binding to albumin may increase the risk of developing bilirubin encephalopathy. This should be carefully taken into consideration when planning a neonatal study.

Autoregulation of cerebral blood flow is limited in the immature brain. Hyperoxaemia and hypocapnia (especially when associated), hypoxia as well as vasoactive substances may have a marked impact on cerebral blood flow in the neonate during the first days of life. The neonate, in particular the premature neonate, subsequently is at high risk of cerebral bleeding (subependymal and intraventricular haemorrhage) due to changes in blood pressure, pCO_2 and stress even with routine care procedures. Therefore optimal handling should always be ensured especially in premature neonates.

Monitoring of brain function

Measures to monitor brain function include EEG (electroencephalography), amplitude-integrated EEG (aEEG), ultrasonography, Doppler sonography, auditory and visual evoked potential measurements (AEP, VEP), cerebrospinal fluid (CSF) sampling, near-infrared spectroscopy (NIRS), (functional) magnetic resonance imaging (MRI) and positron emission tomography (PET). These measures have different utility, e.g. NIRS allows to continuously assess brain perfusion and oxygen consumption in neonates. The choice of a measure(s) for a trial in neonates should be specific, and in relation to the expected medicinal product's effect. Use of invasive and risk-associated measures (CSF sampling, PET) as well as sedation or anaesthesia of the neonate required for measures needs to be fully justified. Any use of general anaesthesia for trial purposes should occur in exceptional circumstances only, but should not prohibit the development of medicinal products for anaesthesia.

Clinical monitoring of CNS function and side effects is difficult in the neonate population due to CNS immaturity (e.g., seizures may show only very subtle motor signs), to severe disease state and potentially due to iatrogenic sedation, anaesthesia or paralysis (cf. 9). Measurement of head circumference remains one of the most readily available and useful means for evaluating the status of the CNS in newborns, and longitudinal measurements provide valuable information and should be obtained regularly to detect abnormal growth, e.g., due to hydrocephalus.

2.3 Kidney and renal function

Renal clearance mechanisms include glomerular filtration (GFR), tubular secretion and reabsorption. Glomerular filtration matures faster than the tubular function, and both depend not only on age and maturational status but also on adverse factors occurring in the pre- and post-natal period, including for example intrauterine growth retardation or administration of nephrotoxic drugs to the mother and the neonate.

Due to the high renal vascular resistance and low blood pressure in utero, GFR is significantly reduced during foetal development. In addition, foetal tubular function is programmed for producing hypotonic urine contributing to amniotic fluid formation. Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area (BSA) increases more slowly to reach adult levels between 1 to 2 years of age.

Extremely and very preterm neonates exhibit lower GFR values at birth and a slower pattern of GFR development because the complete nephrogenesis is not achieved before 34 weeks of post-menstrual age (PMA). This functional delay in getting sufficient GFR in the very preterm neonate has to be considered when estimating infant renal elimination capacity in such a group of neonates and stratification is necessary. Two subsets of preterm neonates should therefore be distinguished in neonatal clinical trials: before and after 34 weeks of PMA. Before 34 weeks of PMA, only a small increase in GFR is observed until the nephrogenesis is fully achieved. As a consequence, it should be noted that post-natal improvements in GFR correlate with PMA rather than PNA alone.

Renal tubules are significantly immature in the neonatal period. This is based on both anatomic and functional immaturity, poor peritubular blood flow, reduced urine concentrating ability and lower urinary pH values. Maturation of tubular function generally takes longer than GFR maturation. The resulting functional glomerulotubular imbalance has to be considered when investigating drugs in neonates and persists until tubular maturation is completed between one and two years of age. Function of protein carrier systems at the renal tubular epithelium and their impact on renal elimination in neonates is still largely unknown. Therefore medicinal products known to be excreted via active tubular secretion require special attention when studied in neonates. As pointed out in different studies, the pathway undergoes more rapid maturation for organic anions than that for organic cations.

Additionally, certain adverse drug reactions affecting the renal system may only be seen in preterm neonates (e.g. nephrocalcinosis in loop diuretics).

Monitoring renal function

Serum creatinine is elevated in the first days of life and reflects maternal creatinine and low GFR in the neonate. In premature neonates, the persistence of an elevated serum creatinine during the first weeks of life is the result of a transitory process of tubular creatinine reabsorption.

Therefore, to monitor renal function serum creatinine is used after the first week of life in term neonates and after 4 weeks in premature neonates. Before these times, intra-individual changes (related to post-menstrual age) in serum creatinine are used as a guide to renal function.

The method of monitoring depends on the investigational drug, but should always be the least invasive. Each approach should be individualised and justified based on the condition to be treated, the clinical state of the neonatal population under investigation and the pharmacokinetic and pharmacodynamic properties of the product under investigation. There are additional methods to monitor renal function and toxicity, including diuresis (e.g., using an indwelling bladder catheter or measuring nappy/diaper weight); also refer to the Discussion Paper on the Impact of Renal Immaturity.

2.4 Liver and hepatic function

Hepatic blood flow, plasma protein binding and intrinsic clearance determining hepatic clearance undergo significant post-natal changes. Most enzymatic microsomal systems responsible for drug metabolism are present at birth and their activities increase with advancing post-natal and gestational age. Rapid maturational changes occur during the first weeks of life. Hepatic clearance may be influenced by premature birth, pathologic conditions of the neonate or administration of drugs to the mother or to the neonate.

To predict the exact nature of these consequences requires an understanding of post-natal maturation and main involved enzymes. The ontogeny of specific enzymes is partly described in the scientific literature and may allow estimations of drug metabolism in the neonate. These data should be considered when planning neonatal studies.

The main elimination pathway as well as pathway of metabolism may be different in neonates as compared to adults. The applicant should consider this when assessing exposure margins of metabolites to the animals used in preclinical studies and also when using human safety data obtained in adults and older children for safety predictions. The relevant hepatic phase I and II metabolic pathways should be identified.

If pharmacologically active metabolites are known to be formed, potential differences in exposure of such metabolites should be considered. If feasible, the applicant is encouraged to perform studies investigating drug metabolism *in vitro* in neonatal hepatic material (microsomes, hepatocytes etc.).

In utero exposure to enzyme inducing agents (e.g., antiepileptic drugs, glucocorticosteroids, anti-infective agents) and the potential to temporarily alter post-natal drug elimination need to be considered when planning a study in neonates and in the interpretation of data.

Monitoring of liver function

If the medicinal product investigated is likely to be eliminated mainly through hepatic metabolism, markers of reduced/normal hepatic function could be included as covariates in the pharmacokinetic data analysis (e.g., in population PK analysis) as well as included in the safety assessment. Monitoring could include standard laboratory and imaging procedures.

2.5 Gastrointestinal system

Data concerning maturational changes of the neonatal gastrointestinal tract that may influence bioavailability are still limited.

Gastrointestinal absorption is influenced by factors such as gastric and intestinal pH and motility, blood flow and tissue perfusion, surface area, pancreatic function, intestinal microbial flora, transit

time as well as maturation of transporters and receptors. In principle, all these factors are reduced or immature in the neonate. The post-natal developmental pattern of these factors may additionally be highly variable due to environmental factors (i.e., diet, drug administration), genetic factors and underlying pathophysiology. Changes in bioavailability during the early post-natal period have to be considered and need to be predicted as accurate as possible in clinical trials including drugs administered orally.

A delayed maturation of (mucosal) enzymes and transporters of the gastrointestinal system as well as reductions of microvillus height may follow from reduced blood flow as in sick neonates and when using only parenteral nutrition, and may at least partly be prevented by maintaining minimal enteral feeding. Gastrointestinal absorption may be influenced by the type and amount of nutrition, enteral vs. parenteral.

Gastric pH is neutral at birth with gastric acid secretory capacity appearing after the first 24 to 48 hours of life. Post-natal increases in gastric acid production generally correlate with post-natal age and adult pH levels are reached by approximately 2 years of age. Generation of titrable acid and pepsin may however be lower for a longer period.

High gastric pH in the neonate may lead to increased bioavailability of weak basic compounds and reduced bioavailability of weak acid compounds. Additionally, in premature neonates, gastric pH may remain elevated due to immature acid secretion. This may lead to higher serum concentrations of orally administered acid labile drugs in the premature neonate.

As pancreatic and biliary functions are immature at birth, drugs requiring exocrine pancreatic and biliary function may have reduced bioavailability. Both functions develop rapidly in the neonatal period, requiring careful consideration on formulation and increased bioavailability of orally administered drugs in neonatal clinical trials.

Reduced gastrointestinal motility may have unpredictable effects on bioavailability in neonates. It may reduce the rate of drug absorption or conversely improve drug bioavailability due to longer retention times in the small intestine. Additionally, maturation of intestinal metabolising enzymes and transport proteins remains largely unknown, further leading to the unpredictability of oral bioavailability and intestinal first-pass effect of orally administered drugs in the neonate. Drugs undergoing secondary metabolism and secretion into the gut, especially when glucuronidation with enterohepatic recirculation occurs in adults and older children, may have different bioavailability and exposure because of reduced glucuronidation and bacterial activity in the intestine of neonates. Reduced gastrointestinal motility, often present in sick neonates, is therefore particularly important to consider.

Additionally, the susceptibility of neonates to necrotising enterocolitis (NEC) should be taken into consideration when studying drugs administered orally, as any intestinal damage may increase the risk of NEC especially in premature neonates. Intestinal damage may also result from a high osmolality burden. The clinical assessments should include to carefully examine the neonate for enteral feeding tolerability, gastric residuals, regurgitation, reflux, distended abdomen, reduced alertness, signs of an infection, occult or macroscopic faecal blood.

2.6 Immune system

Lymphoid stem cells develop from precursors and differentiate into T, B or NK cells, as well as Antigen presenting cells (APCs) depending on the organs or tissues to which the stem cells traffic. Indeed, both the initial organogenesis and the continued immune system cell differentiation occur as a consequence of the interaction of a vast array of lymphocytic and microenviromental cell surface molecules and proteins secreted by the involved cells. De novo T-cell generation requires a functional thymus. The current paradigm is that the human T-cell repertoire is established during late foetal development and that, by the time of birth, thymectomy does not cause immediate immune deficiency. Thymic epithelial cells - the component of the thymus relevant for T-cell production and selection - involute rapidly after birth. Compared with adult T cells, neonatal T cells secrete increased levels of interleukin-10 (IL-10) following stimulation, but reduced levels of many other cytokines, including IL-2, IL-4, IL-8, interferon gamma (IFN-gamma), transforming growth factor beta (TGF-beta) and tumor-necrosis factor alfa (TNF-alfa).

Although the foetal immune system has the potential to respond to large numbers of foreign antigens, few foreign antigens are present in utero and cells of the immune system are therefore, primarily "naïve" at birth. The neonate is, in part, protected against disease by maternal immunoglobulins (Ig).

Maternal IgG, in particular IgG_1, is actively transported across the placenta before birth mainly during the last 4 weeks of term gestation, and maternal secretory IgA is present in breast milk and colostrum. These passively acquired antibodies provide protection against pathogens to which the mother was immune. However, the neonatal/infant period is marked by an increased susceptibility to infections: protection provided by passively transferred antibodies is short-lived since declines during the first few months of life. More importantly, maternal antibodies offer limited immunologic protection when compared with protection afforded by an infant's active immune response. Active adaptive immunity can be readily generated in the newborn and this includes the full range of B-cell responses with the production of IgM, IgG and IgA, as well as the development of helper T-cell (Th) and cytotoxic T-cell responses.

Indeed, neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-mediated immune responses and Th2 type cells that are primarily involved in promoting B-cell responses.

The innate immune mechanisms also mediate the protection against infections during the first months of life. Natural antibodies such as IgM, NK activity as well as toll-like receptors mediated cell activation has been shown to play a role in development of adaptive immunity and to serve as a bridge between antigen non-specific and antigen-specific immune responses.

In addition, bacterial colonisation from maternal and environmental microflora is an important determinant of the induction of innate immunity and of adaptive immunity later. This step is crucial to allow diet antigen tolerance induction. Inadequate interaction between bacteria and enterocytes may be responsible for misbalancing the homeostasis between tolerance and activation; in addition, antibiotic medicinal products may impact on bowel colonisation. Any such impact on gut colonisation should be divided according whether it is temporary or permanent.

These complex interactions and the interference of maternal antibodies have to be considered when evaluating the effect on immune response of immunomodulatory drugs both in terms of immunosuppression and immune activation.

Monitoring of immune functions

Antibody response can readily be detected upon challenge in neonates provided to take into account the presence of interfering maternal antibodies. Modern multiparameter cytofluorimetric technology can be employed to assess not only the number of immune cells but also some immune functions such as cytokine production or cytolytic activity. However an effort to develop microassays has to be done to truly assess the different pattern of immune responses in the neonate and in infants in the first years of life. Molecular techniques such as spectratyping for T and B cell repertoire assessment can also be of value.

2.7 Body composition

Changes in body composition during the neonatal period are important factors for altered pharmacodynamic and pharmacokinetic characteristics. Body composition correlates with both gestational and post-natal age, and it continues to change significantly during the first years of life. Age related changes in fat, muscle and total body water composition may produce significant quantitative changes in pharmacokinetic parameters such as volume of distribution. For instance, total body water is highest in the newborn and decreases substantially in the first 4 months of life therefore high water soluble drugs will present a larger Volume of Distribution in the neonatal period potentially requiring larger doses than older children in order to achieve the same desired therapeutic plasma concentrations. On the contrary, the amount of body fat is low at birth and increases progressively in the first months of life. Iatrogenic interventions in neonates could also significantly shift body composition characteristics.

Other components such as plasma proteins may also be different in the neonatal age with lower concentrations, reduced numbers of protein binding sites and even uncertain binding affinity, this may be even more aggravated if the baby is critically ill.

3 CONDITIONS AFFECTING SPECIFICALLY THE NEONATAL POPULATION

Neonates frequently suffer from conditions that are specific for this subset of the paediatric population, for example respiratory distress syndrome (RDS) or patent ductus arteriosus (PDA). In addition, neonates hospitalised on NICUs often suffer from multiple concomitant conditions, requiring administration of a combination of medicinal products resulting in a high risk of drug interactions. Additionally, adverse reactions in neonates, especially in preterms may trigger specific complications, as for example in relation to susceptibility to necrotising enterocolitis (NEC) or retinopathy of prematurity (ROP). As a further complicating factor, in utero growth retardation may affect pharmacokinetics and pharmacodynamics of drugs at birth and therefore may change the safety and efficacy profile of drugs used in the neonatal period.

With more experience, disease specific guidelines on how to investigate medicinal products in the neonatal population may become available.

4 TIMING OF DEVELOPMENT OF MEDICINAL PRODUCTS IN NEONATES

The timing of studying a medicinal product in the neonate will depend on the seriousness and uniqueness of the condition to be treated as well as on the availability of alternative treatment options, the potential benefit of a new product, and the target population. Sponsors should refer to ICH Guideline E11.

5 DATA REQUIRED BEFORE THE FIRST ADMINISTRATION TO A NEONATE IN A CLINICAL TRIAL

If possible, clinical data should always be obtained in the least vulnerable population. Depending on the condition, the new product, the target population and further factors according to section 2.1 of the ICH Guideline E11, initial tolerability, PK and safety data should be collected in adults before initiating studies in the neonatal population.

If older children are affected by the same disease or another disease for which the medicinal product may be of use, in general older (less vulnerable) paediatric age groups should be studied before studying the product in the neonatal population.

For conditions exclusively found in neonates, the development should primarily be made in neonates. However, also in such condition, the first studies in man should, if possible, be done in healthy adult volunteers. Sponsors should refer to the ICH Guideline E11.

5.1 In vitro data

In order to predict the *in vivo* situation as much as possible (i.e., as regards efficacy, pharmacokinetics, safety), *in vitro* studies on human biomaterial, (e.g., on human non-terminally differentiated cells or, if relevant, foetal or neonatal cell cultures) may provide relevant additional information. Examples include enzyme activity, receptor expression and mediator modulation.

5.2 Animal data

The conventional nonclinical studies should be performed including pharmacokinetic, primary pharmacodynamic, safety pharmacology, single- and repeated dose toxicity, genotoxicity, reproductive and developmental toxicity, including peri-/post-natal toxicity testing (e.g., transplacental exposure) and local tolerance studies.

In addition to these conventional non-clinical studies, juvenile animal data should be provided if needed. Juvenile toxicity studies will be necessary if available human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group. If such studies are considered to be not relevant or not feasible, a scientifically data based justification should be provided. The limitations of species specificity should be taken into account. Finding adequate animal juvenile animal models with similar organ maturation may be challenging. Relevance of the animal model should be based on demonstrating physiologic comparability with human. Available options should be investigated in depth including the use of in vitro assay based upon paediatric cell lines/tissues, and modified conventional study protocols. Relevant data may be obtained from repeat-dose studies starting with juvenile animals, or from modified peri-/post-natal studies.

This is addressed in the Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications.

6 FORMULATIONS AND ROUTE OF ADMINISTRATION

The choice of formulation and route of administration depend on the condition to be treated and the clinical state of the neonate. Age-appropriate formulations and strengths using appropriate excipients must be developed to avoid extemporaneous preparations, even more so for neonates. Novel formulations should be evaluated through preclinical studies and in adults or older children as appropriate before consideration for administration to neonates.

Medication errors in neonatal practice are commonly due to use of inappropriate formulations or strengths requiring complex calculations and measurement of very small volumes or multiple dilutions. Electronic prescribing systems may not be appropriate for neonatal use. Excipients used for adults and older children may be toxic in neonates because of immature metabolism and elimination. The salt of the active ingredient and the chemical nature of the preparation must be carefully considered to avoid administration of excessive amounts of electrolytes.

6.1 Routes of Administration

Intravenous (IV) use

The intravenous route will normally be used in clinically unstable term and preterm neonates. Neonates have a fragile vasculature system, and it may be very difficult to obtain appropriate peripheral or central access. Most common IV routes are peripheral veins (limbs, feet, hands or scalp), umbilical vein, or “long” peripheral lines that can be considered central, whereas internal jugular vein or femoral vein access is uncommon. Neonates may only have a small number of IV lines to administer all medicines as well as blood products, total parenteral nutrition (TPN) and fluid maintenance.

If the investigational medicinal product is likely to be administered in this setting using the same route, compatibility issues with concurrent medication should be studied. Concomitant administration with TPN using the same IV access is discouraged, as TPN formulations are highly variable and may induce oxidation.

When developing protocols for neonatal trials, devices designed for IV administration to neonates must be selected and specified. Adsorption to administration sets may result in significant underdosing in neonates even if a clinical difference may not be obvious in older patients (e.g., insulin). Account must be taken of the potential lag time between injection and delivery of the medicinal product to the blood circulation. Administration of the complete dose must be ensured.

Medicinal product preparations must allow accurate measurement and administration. The need for additional dilution and/or flushing may be important for effective administration and to avoid local (e.g., thrombophlebitis) and/or acute systemic adverse events (e.g., acute hypotension or hypertension). Fluid and electrolyte balance must be carefully taken into consideration (e.g., hypernatraemia may be caused by “flushing” with physiological sodium chloride solution).

Local tolerance and toxicity of the preparation must be investigated (see also section 5.2; inadvertent extravasation is frequent) and every effort should be made to administer isotonic solutions. It is advantageous if the medicinal product is compatible with glucose solutions (50-100 mg/ml).

Displacement values of dry powder formulations should be taken into consideration when dosing is critical, in order to calculate appropriate volume of reconstitution and dosing. The volume of the dose to be administered should be as small as possible and as compatible with these requirements.

Environmental conditions of the neonatal unit, for example temperature, humidity and phototherapy may affect medicinal product stability and should be investigated, as appropriate.

Oral use

Oral administration should be used when possible and appropriate in the neonatal population, but there is still lack of data on absorption and safety (see also section 2.5). The way of enteral feeding (e.g., feeding tube, sucking), the time intervals (e.g. continuous, hourly feeds) and amounts of feeding have to be considered and specified.

Preparations for oral administration are most likely to be liquid dosage forms. For such products the volume to be administered should be kept as small as possible. As liquid preparations more often contains excipients like preservatives and antioxidants, special care should be taken regarding the choice of excipients as some may have toxic effects. Sterile and/or single use oral dosage forms may be considered in order to avoid the use of preservatives and to avoid or to reduce antioxidants.

If the product is likely to be administered via an enteral (e.g. nasogastric, nasojejunal) tube, issues such as viscosity of formulation (to permit flow of the product through neonatal tubes [e.g., 6FR/8FR] and avoid blockage), size of particles, adsorption to commonly used enteral tubes and interaction with common formula/breast milk should be investigated.

The osmolality of the preparation has to be taken into account (cf. 2.5).

In case of possible solid dosage forms, e.g. granules, powders etc., unit dose presentations would be preferable. When microbial contamination is an issue, the product should be presented as a sterile product. If the solid dosage forms are likely to be administered via an enteral tube the considerations mentioned above also apply.

Taste issues should be considered as in older children.

Rectal use

Rectal administration is not commonly used in this age group, and it is associated with erratic absorption. If considered it must be fully evaluated for safety and efficacy in addition to the appropriate bioavailability studies.

Topical use

Topical administration may be necessary or suitable for local or systemic effect. Account must be taken of skin immaturity, especially in preterm neonates, and the large and more permeable and moisturised surface area to weight ratio which all predispose to an increased systemic absorption that could lead to toxicity.

Intramuscular (IM) use

Intramuscular administration is not usually a route of choice for neonates because absorption may be slow and unpredictable, varying with postnatal age and clinical state; injections may be painful and cause tissue damage. If the intramuscular route is considered its use must be justified.

Other routes

Other routes of administration may be required or may be suitable (e.g., endotracheal, inhalation etc). Their use should be justified.

The above text highlights the main principles, which should be kept in mind prior to the conduct of clinical trials in neonates. However, it is not intended to provide exhaustive information on formulation aspects to be considered when developing products to be used in clinical trials in neonates.

If a formulation is significantly changed during development for neonatal use, comparison of bioavailability may be required (see section 8).

7 DOSE-FINDING

In general, most drugs are developed for adults and older children before they are developed for the neonatal population. All relevant pre-clinical and clinical data in adults and children, or in adults and juvenile animals, should be taken into consideration to find a safe starting dose in neonates. PK / PD modelling techniques, using age appropriate and validated biomarkers, need to be considered to find the optimal dose. For a new medicinal product, the optimal dose has to be clinically verified. Existing physiologically based pharmacokinetic models to predict pharmacokinetic characteristics in the neonatal population may be considered if appropriate.

The modelling of the influence of maturation on PK and on the PK / PD relationship may be considered to predict the changes in dosing as a function of age. Applicability of these models would need to be justified and new models might need to be developed. Where the medicinal product belongs to a chemical / pharmacological class including products already studied in neonates or older children, all relevant data should be considered.

Body weight, particularly in linearly or exponentially transformed values, and BSA should be investigated for best correlation with PK data; taking into account that body weight is likely to be more user friendly and that various covariates have to be considered (see following section). Depending on the duration of treatment, the individual maturation of a patient may be extensive and the dose may need to be adjusted over time (see section 9.4).

Allometric scaling should be considered for drug clearance when it is predicted from sparse data in neonates or extrapolated from data in older infants. The appropriate scaling factor will depend on the postnatal age (in particular, during or after the first 7 to 10 days of life) and potentially also on the medicinal product.

8 PHARMACOKINETIC STUDIES AND PK/PD STUDIES

Reference is made to the “Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population”, especially section 4.1.

Pharmacokinetic information is important to support adequate dosing in subpopulations of the clinically studied population and to assess the potential for clinical relevance of toxicity findings in the preclinical studies. However, pharmacokinetics alone is of limited value for extrapolating efficacy and safety from other patient groups, and extrapolation of efficacy will in general need pharmacodynamic data and PK/PD monitoring.

A population PK approach is preferable due to the importance of finding covariates related to dose-individualisation between individuals and over time in the maturating individual. The analysis can be made on rich and/or sparse data depending on the number of patients available and the possibility of developing highly sensitive analytical methods where very small sample volumes could be used. The initial model could be based on rich data of a limited number of individuals and/or on data available in older children, as well as on other prior information, followed preferably by a population PK approach.

It should be noted that population PK and modelling of oral administration require extra cautious consideration in the neonatal population as there may be marked absorption differences in neonates as compared to other age groups as well as very prolonged absorption in a subgroup of individuals.

In cases where C_{max} is clinically important for safety or efficacy reasons, efforts should be made to characterise this parameter satisfactorily due to the differences in volume of distribution between neonates and older children. If possible, the protein binding of highly protein bound active substances should be assessed to enable the measurement of free plasma concentrations. Immature expression of carrier proteins should also be considered. Special consideration should be given to drugs which are

highly protein bound and fast metabolized in adults, since major differences can be assumed in newborns. Depending on the characteristics of the medicinal product, there may be a need for differentiation between a loading dose (large Vd) and smaller or more spaced maintenance doses (low total body clearances).

Effort should be made to include the determination of potential covariates in the studies (PNA, PMA, GA, weight, BSA, renal function, concomitant use of drugs, S-bilirubin, repeated feeding and feeding patterns, concomitant medication etc.) for allowing covariates to be identified, which may allow satisfactory dose individualisation. Adjustments of the dose by covariates (e.g. bodyweight, BSA) should usually be based on the covariate with the highest correlation to the relevant PK parameters. However, the difficulties in determining the covariate should be taken into account. The determination of BSA is difficult in neonates and other covariates should be considered if their use gives an adequate dosing. Titration based on plasma concentration or a clinical safety or efficacy marker should also be considered. This is further described in the Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population.

Potential factors confounding and altering PK data should be recognised, such as blood transfusions and use of plasma expanders or serum albumin, which impact intravascular volume and alter protein binding of highly bound medicinal products.

Neonates treated in hospital and especially on NICUs often receive multiple drugs to treat different conditions. Therefore, any known or potential interactions of the medicinal product investigated should be carefully considered when planning a clinical study as well as during data analysis. Concomitantly used drugs should be included in the population pharmacokinetic analysis. In general, formal interaction studies should be performed in adults. However, if there are quantitative or qualitative differences in the contribution of enzymes to the elimination of a medicinal product between neonates and adults, results of adult interaction studies investigating effects of other drugs on the investigated medicinal product can not be directly extrapolated to neonates. In these cases, estimations based on *in vitro* metabolism data as well as other sources of information should if possible be performed. If a dosing recommendation is needed for a commonly used medicinal product combination and if an interaction is expected, specific pharmacokinetic interaction studies might need consideration.

8.1 Comparisons of different formulations

If a formulation is significantly changed during development for neonatal use, comparison of bioavailability may be required. Such studies will usually be performed in adults or possibly in older children but, if not representative for neonates, additional (e.g., population) PK studies may be needed in neonates to ensure appropriate systemic exposure to the medicinal product. For example, lipid formulations may require such studies in neonates due to differences in pancreatic lipase activity and low biliary output. Multiple-dose studies may be required to ensure appropriate treatment and the approach used should be carefully considered and justified depending on the clinical situation and medicinal product characteristics. Urine sampling to accurately characterise systemic exposure to parent compound and potentially, to active metabolites, could be used as a partial replacement of blood sampling (see also section 9.6) and, if a precise C_{max} estimation is not needed, potentially as a complete replacement, provided the neonate already has an indwelling bladder catheter and reliable quantitative samples can be obtained. A similar approach should be taken in situations where a completely new neonatal formulation has been developed with little or no clinical efficacy and safety data using the specific formulation. Data on local tolerability should also be collected if the route of administration is changed or if there are major changes in formulations administered by the same route.

9 SPECIAL ASPECTS OF CLINICAL TRIAL DESIGN IN NEONATES

As for all clinical trials all measures to avoid bias should be included in trials performed in neonates. Therefore uncontrolled trials should be avoided in principle for demonstration of efficacy. They have limited usefulness for the demonstration of safety. On the other hand for randomised trials, in particular those using a placebo, there should be equipoise (genuine uncertainty) at the beginning of the trial and no participants should receive care known to be inferior to existing treatments.

The size of a trial conducted in neonates should be as small as possible to demonstrate the appropriate efficacy with sufficient statistical power. Adaptive, sequential, Bayesian or other designs may be used to minimise the size of the clinical trial. However, a balance between the need to stop recruitment early and the need to obtain reliable safety information should be aimed at.

In neonatal studies measures to reduce and prevent invasive procedures and pain are needed, but non-invasive measures or surrogate markers require careful validation.

In addition, clinical trials in neonates should be carried out in experienced neonatology centres with relevant expertise and with appropriate resources, in order to ensure optimum professional conditions for the protection and medical support of the neonates. This is also important for generalising the trial results. Normally, an independent data safety and monitoring board should be in operation for a clinical trial in neonates. For further guidance, refer to the document on ethical considerations for clinical trials on medicinal products with the paediatric population.

9.1 Age and further stratification criteria

Taking into account age classes is of particular importance when recruiting patients within the clinically relevant age interval to optimise the evidence the potential influence of maturation. However, during data analysis, the use of age as a continuous co-variable is recommended whenever possible for the same reason.

Depending on the medicinal product concerned and the disease to be treated, stratification of the trial population might be appropriate or necessary. Frequently, stratification by term gestation is needed in clinical trials, as PK and PD properties differ between preterm and full-term neonates. The same applies to age and post-menstrual age (PMA). For instance, stratification regarding neonatal nephrogenesis should be before and after 34 weeks of PMA (see 2.3). However, PK and PK/PD data should be analysed for association with size-related covariates (age, weight etc) as continuous covariates. Stratification of some analyses may be considered, in conjunction with measures to quantify the homogeneity of a treatment effect.

The following subgroups within the neonatal population should be recognised as distinct, and the use or not-use of these criteria for stratification should be justified accordingly.

- SGA or not; hypertrophy or not
- ELBW, VLBW, and LBW
- GA (for example, < 26 weeks, 26 - 29 weeks, 30 - 33 weeks, 34 - 36 weeks, >= 37 weeks)

Additionally, the importance of further criteria (e.g., from the course of medical treatment) such as the following may need to be identified.

- Ventilation (if any, days and type of ventilation, inspired oxygen fraction) and interventions such as pulmonary or cardiopulmonary resuscitation or assistance
- Existence and haemodynamic significance of patent ductus arteriosus Botalli or other cardiac problems
- Hypothermia
- Antenatal treatment (e.g., with glucocorticosteroids, antibiotics, or blood products); intrauterine and perinatal exposure to medicinal products administered to the mother
- Maternal diseases (diabetes mellitus, autoimmune diseases etc.)
- Use of medicinal products with haemodynamic effect (e.g., catecholamines), medicinal products with effect on apnea-bradycardia (e.g., caffeine, theophylline), and drugs for muscle relaxation, pain treatment, or sedation (e.g., morphine)
- Ethnicity
- Number and type of infections, days of incubator care and incubator / warming device environment, temperature adjustments, course of enteral feeding

- Blood transfusion(s)
- Parenteral nutrition or tube feeding.
- Apgar score
- Congenital anomalies
- Volume and time of blood sampling

In addition, some of the conditions affecting neonates are associated with profound changes in body function, such as about 20 % larger energy requirements in bronchopulmonary dysplasia (BPD), which may require consideration in a trial.

9.2 Endpoints and outcome measures

For use in clinical trials in neonates, there is a need to elaborate clinically relevant primary endpoints, linked to the conditions and prospects specific to preterm and term neonates. In addition, the need for establishing age appropriate surrogate endpoints should be considered.

For the distinct diseases in neonatology, stringent and harmonised definitions should be detailed in the protocol and used within a trial, especially when used as an endpoint. The method to determine the GA should be clearly described. Endpoints should be assessed using validated procedures for measurement or judgement.

The known complications and sequelae of prematurity (e.g. intracerebral/intraventricular haemorrhage [IVH], NEC, ROP, BPD) as well as survival should be evaluated at least as secondary endpoints in trials that include the neonatal population. In general, additional endpoints related to long-term physical and psychosocial development should be studied.

9.3 Pharmacogenetics and -genomics

The relationship between phenotype and genotype may be completely different in the neonate as compared to other patient groups. Genetic testing like other tests is subject to prior informed consent. If target genes of interest can be identified, pharmacogenetic analyses of these genes are encouraged. If there are important pharmacogenetic differences affecting pharmacokinetics, efficacy and safety of the medicinal product in the adult populations, pharmacogenetic analysis of the target genes is recommended in neonates. In such cases, the time-dependency (maturation) of the relationship between genotype and phenotype may need to be described.

9.4 Dosage adjustment over time

Within days in the life of preterm and term neonates, there may be large physiological and / or pathological changes in body weight, BSA, and body composition, as indicated above. For example, physiological post-natal weight loss may be more than 10 % of birth weight, and body weight in preterm neonates may increase rapidly, up to threefold during post-natal medical care.

Consequently, there is a need to continuously re-calculate and adjust dosages of investigational medicinal products on the basis of actual weight (or other relevant covariates) or on the basis of results from therapeutic drug monitoring, because fixed or perpetuated dosages are most probably inadequate in terms of efficacy and safety.

9.5 Placebo and active comparator

Use of placebo in neonates is more restricted than in adults and older children, as neonates are even more vulnerable. Placebo can be used on top of best standard of care, as placebo use does not imply the absence of treatment. The use of placebo may be needed for scientific reasons, for example to quantify variability and to determine treatment effects. Placebo may be warranted in children as in adults when evidence is lacking. As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases. In all cases, placebo use should be accompanied by measures to minimise its use and to avoid irreversible harm, especially in serious or rapidly evolving diseases.

As the number of medicinal products approved for the neonatal population is limited, a comparator may have to be chosen that is not approved for the indication. Medicinal products that do not have a marketing authorisation may be considered suitable as controls if they represent evidence-based standard of care.

As appropriate, a rescue treatment to be used in case of insufficient efficacy should be employed whenever possible in a pre-specified manner, and the rescue treatment and removal of participants from the trial should occur according to pre-specified criteria.

Reference to the document on ethical considerations for clinical trials on medicinal products with the paediatric population is made in this regard.

9.6 Blood sampling

Preterm and term neonates have very limited blood volume, are often anaemic due to age and frequent sampling related to pathological conditions. The fact that they receive blood transfusions (or iron or erythropoietin supplementation) must not be used as a convenience for increased volume or frequency for blood sampling. The number of samples and/or sample volume should be kept to a minimum.

To limit volume of the blood for samples, microanalytical methods and microassays should be developed and used. Alternative methods may be non-invasive techniques and microdialysis, which measure drug levels in saliva, urine etc., if reliably shown to reflect systemic exposure and as long as bias related to maturation is not an issue. However, the burden associated with some alternative methods (such as repeated skin taping of urine collection bags) should be recognised and weighed against expert blood sampling.

Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected blood loss is to be detailed in the trial protocol. Sampling should be performed by trained staff. The number of attempts for sampling should be limited. Techniques to minimise blood loss due to sampling should be used, and re-administration of void blood can be considered if acceptable under local healthcare provisions. Timing of sampling and number of sampling attempts should be defined in the protocol. Timing of sampling should be co-ordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimise pain and distress, and the risk of iatrogenic complications.

The following blood volume limits for sampling are recommended (not evidence-based). If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time. The actual situation of the neonate (sleep/activity, severity of anaemia, and haemodynamic state) should permit such blood sampling. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3 % corresponds to about 2.4 to 2.7 ml blood per kg body weight.

9.7 Study analysis

As in any clinical trial, the study analysis should be carefully planned in advance, taking into account the limited amount of data that may be available with this patient population. The Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005) is fully applicable to studies with term and preterm neonates, and it therefore needs to be taken into consideration for the planning of the study and of the analysis.

9.8 Pain and distress

As most investigations and procedures carry the risk of pain for the neonates, pain should be prevented, and if unavoidable evaluated, monitored and treated appropriately. Evaluating and monitoring the level of pain may be difficult in the neonate, as scales are based on physiological parameters that can be affected by concomitant diseases and procedures. However, the development and / or use of validated scales is recommended, for example, the Premature Infant Pain Profile (PIPP) or the Neonatal Infant Pain Scale (NIPS) scale for the assessment of pain.

Exposure to pain and in particular repeated pain may trigger both an altered hypothalamic-pituitary-adrenal-axis reactivity and an increase in NMDA/excitatory amino acid activation resulting in damage to developing neurons. Most clinical parameters, as required for study purposes, should be measurable using preferably non-invasive techniques such as ECG cardiac monitoring, brain function monitoring, oxygen saturation (from pulse oximetry), urine collection, non-invasive blood pressure measurement, ultrasonographic assessment of the heart and lung circulation. For instance, transcutaneous measurement of PO_2 or PCO_2 is easily performed using a single sensor in preterm and term neonates; however, it entails the risk of skin burns associated with heating temperature and change intervals.

Blood sampling should be limited in number of samples and volume, and standard clinical care and sampling should if possible be coordinated (see also section 9.6). Pain due to unavoidable blood sampling should be pre-emptively treated whenever possible, using oral glucose or possibly topical anaesthesia, if evaluated in the age group.

Also refer to the respective sections of the document on ethical considerations for clinical trials on medicinal products with the paediatric population.

9.9 Safety monitoring

As a general recommendation for hospitalised neonates in a trial, vital signs should be monitored continuously, and related events should be registered according to neonatal definitions (apnea-bradycardia; sustained bradycardia, tachycardia, desaturation, hypotension; fever, hypothermia etc.). Specific age and/or gestation appropriate (e.g., laboratory) reference values and ranges should be used.

When there are no biochemical correlates that have been established to reflect investigational medicinal product safety, and when the trial does not require more extensive tests for pharmacological investigations, the function of the important and metabolically highly active organs like bone marrow, liver, and kidney should be monitored using blood sampling for respective laboratory values (for example, full manual differentiated blood count including normoblasts and reticulocytes; glucose, AST, ALT, bilirubin; creatinine, electrolytes).

Assessment of trial participants at entry / end of trial and long-term follow-up

In the neonatal population, adverse reactions, long-term effects, as well as general health-related problems may not be obvious, but should be searched for and may become evident by thorough clinical examination. Depending on the type of investigation and on the medicinal products, it is also recommended to consider that all trial participants be examined using age-appropriate neurodevelop-mental (e.g., Dubowitz neonatal assessment at discharge, later Griffith test, Hammersmith scales, Prechtl qualitative assessment of general movements, Bayley scales) and auxiological (weight, length, head circumference) scales, at least at the beginning and at the end of the trial, and during follow-up visits, where appropriate. Also, non-invasive and non-burdening examinations such as objective hearing tests (otoacoustic emissions and distortions spectra analysis), amplitude-averaging EEG recordings and laboratory parameters as mentioned in the following sections should be documented. The trial protocol could include specific measures for long-term follow-up and monitoring of the neurodevelopment of trial participants. Patients should at least be followed up until school age (e.g., 6-7 years). Evaluations of physical and psychosocial development should be provided. Any deviation from this approach should be clearly justified.

10 PHARMACOVIGILANCE AND LONG-TERM FOLLOW UP OF SAFETY

The challenging task of pharmacovigilance and follow-up in terms of duration and type depends on the product itself, the target organs, the duration of exposure and other risk factors for sequelae. The potential for adverse drug reactions occurring later in life should be monitored as neonates may have been exposed to medicinal products at a sensitive period in terms of organ maturation. Only a small number of neonates is likely to be included in rather short term trials, thus long-term adverse reactions may not be detected and would require additional appropriate pharmacovigilance approaches and particularly pharmacoepidemiological studies.

The difficulty to obtain data on short-and long-term effects of medicinal products on the developing brain, as effects may become apparent only later in life, increases the level of requirements for trials of medicinal products in neonates. Therefore, long-term monitoring for medicinal products affecting the CNS may be required.

Further important tools to evaluate pharmacovigilance aspects in neonates are:

- Access to epidemiological databases
- Case definitions for expected rare ADRs in neonates or paediatrics
- Description of standard of care and consequently standards of diagnostic and observation as a supplement to the study design.
- Evaluation of potential risks according to knowledge from preclinical studies in juvenile animal models or early phase clinical trials and post-marketing experience if available in adults.
- Attempt to define expected ADRs based on the knowledge of the proposed potential risk.
- Enhanced ADR reporting environment (educating parents when considering long term, delayed onset ADRs)
- Postmarketing trial as cohort or case control setting

However, a multidisciplinary approach is required to increase the awareness to a more proactive involvement of physicians in Pharmacovigilance aspects in neonates and consequently to enhance the safety profile of drugs at all stages of development covering the clinical challenges of the whole paediatric population.

Reference is made to the Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population.

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