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Evaluation of Medicines for Human Use

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Committee for Medicinal Products for Human Use

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

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EXECUTIVE SUMMARY

To be added after finalisation of the Guideline

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 drug use 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).

The reasons why clinical trials of medicinal products have not been performed in neonates as in older age groups are multiple, and they include the age-related difficulties in feasibility as well as the small patient population, and especially the uniqueness of their diseases. The Regulation on Medicinal Products for Paediatric Use (Regulation (EC) 1901/2006) is creating obligations with regard to specially conducting clinical trials in order to meet the recognised need for authorised medicinal products and the availability of information on the use of medicinal products for paediatric patients including this age group. Clinical trials to investigate medicinal products in the neonatal population thus have to address the needs of this population (or subgroups thereof, refer to section 9.1) which, for example, arise from the following conditions that specifically affect the neonatal population.

However, neonatal studies encompass multiple difficulties, of which ethical issues, the high vulnerability, technical difficulties, lack of self assessment, immaturity, prematurity, and the need for specific formulations are examples of such complicating factors.

2 SCOPE

The guideline aims to provide guidance for the development of medicinal products for use in the neonatal population. 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 in this therapeutic area will require revisions of the guideline and, on behalf of the sponsor or applicant, consideration of current scientific knowledge.

As well as due to the complexity of how to investigate 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 Performed in Children – 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 (draft)
- 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 the age of 27 days
- Gestational age (GA): Time between first day of last normal menstrual period and date of birth, usually expressed in weeks; GA is defined at birth.
- Post-natal age (PNA) or chronological age: Age calculated from date of birth
- Post-menstrual age (PMA): Time between first day of last normal menstrual period and day of assessment, that is, gestational age plus post-natal age
- Corrected age (of preterm neonates): Age calculated from expected date of delivery
- Preterm neonate: < 37 weeks of gestational age
- 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 10^{th} 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 (time between day of conception and the date of assessment) 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 drug 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 drug administered to the neonate may affect the ongoing maturation processes. If possible, points in time of major developmental changes should be identified that could significantly influence drug exposure, safety and efficacy. 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, 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 drug 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 dramatic 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.

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 measuring, electrocardiogram [ECG], echocardiography, and Doppler sonography). Radiologic (e.g. X-ray, MRI) and laboratory (e.g., blood gases, haematocrit) assessment 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 2nd and 4th month 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.

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.

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 bilirubin levels, albumin binding capacity, blood brain barrier development and neuronal susceptibility to injury. Compounds with a presumed effect on any of these factors 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. Hyperoxemia and hypocapnia (especially when associated), hypoxia as well as vasoactive substances may have a dramatic impact on cerebral blood flow in the neonate during the first days of life.

Monitoring of brain function

Measures to monitor brain function include EEG (electroencephalography), amplitude-integrated EEG, ultrasonography, Doppler sonography, auditory and visual evoked potential measurements (AEP, VEP), cerebrospinal fluid (CSF) sampling, (functional) magnetic resonance imaging (MRI) and positron emission tomography (PET). 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 study purposes should occur in exceptional circumstances only, but should not prohibit the development of medicinal products for anaesthesia.

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 in utero, GFR is significantly reduced during fetal development. In addition, fetal 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.

Very low birth weight (VLBW) infants 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 very preterm baby has to be considered when estimating infant renal elimination capacity in such a group of babies and stratification may be 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 is generally more protracted 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 1 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 organic pathway undergoes more rapid maturation for anions than that for organic cations.

Additionally, certain adverse drug reactions affecting the renal system may only be seen in preterm infants (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 VLBW, 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 infants and after 4 weeks in very low birth weight infants. 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 (measuring nappy 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 development 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 pathway responsible for 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 comparing human safety data obtained in adults and older children. 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, barbiturates, glucocorticoids) and the potential to temporarily alter post-natal drug disposition need to be considered when planning a study in neonates and in the interpretation of data.

Monitoring of liver function

If the drug investigated is likely to be eliminated mainly through hepatic metabolism, markers of 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 tract

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

Gastrointestinal absorption is influenced by factors such as tissue perfusion, surface area, gastric and intestinal pH, intestinal mobility and 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.

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 levels are reached by approximately 2 years of age.

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

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

Reduced gastrointestinal motility may have unpredictable effects on drug availability 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 mobility that is 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.

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 fetal 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 fetal 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, are actively transported across the placenta before birth prevalently mainly in during the last 4 weeks of term gestation, and maternal secretory IgA are 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 sub-chorial 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 the volume of distribution, peak plasma concentrations and half-lives. For instance, total body water is highest in the newborn and decreases substantially in the first 4 months of life. On the contrary, the amount of body fat is low at birth and increases progressively in the first months of life.

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 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 non-terminally differentiated cells or cell cultures (fetal or neonatal) 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., diaplacentar exposure) and local tolerance studies. In addition to these conventional nonclinical studies, juvenile animal data should be provided if feasible. The limitations of species specificity should be taken into account. Finding adequate juvenile animal models with similar organ maturation is challenging. Available options should be investigated in depth, including whether relevant data can be obtained from peri-/post-natal studies, e.g. by optimising the design of such studies. Juvenile toxicity studies will be necessary if available data are insufficient, and if feasible. If not, a scientifically data based

justification should be provided. 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 should depend on the condition to be treated and the clinical state of the neonate. Age-appropriate formulations 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 requiring calculation and measurement of very small volumes or multiple dilutions. Prescribing software 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.

In general, the IV route will normally be used in clinically unstable term and preterm neonates.

When developing protocols for neonatal trials, devices designed for IV administration to neonates must be selected and specified. Account must be taken of the potential lag time between injection and delivery of the drug to the blood circulation. Administration of the complete dose must be ensured.

Drug preparations must allow accurate measurement and administration. The need for additional dilution and/or flushing of devices may be important for effective administration and in avoiding thrombophlebitis and acute systemic effects but must take account of fluid and electrolyte balance. Local tolerance and toxicity of the drug preparation must be investigated (see also section 5.2) and every effort should be made to administer isotonic preparations. The volume to be administered should be as small as possible and as compatible with these requirements.

Sick neonates may receive multiple drug infusions and bolus injections with limited opportunity for physical separation. IV feeding is common and there may be high concentrations of macro- and micronutrients, especially calcium and phosphate. There is significant risk of physical and/or chemical incompatibility with the investigational preparation. Potential incompatibilities must be studied and strategies developed to avoid problems during administration. Conversely, positive recommendations with regard to compatibilities would be most helpful to the user of the product.

Environmental conditions of the neonatal unit, for example temperature, humidity and ultraviolet light may affect drug stability and should be investigated.

Other routes of administration may be required or may be suitable. Their use should be justified.

Oral administration may be appropriate for some medications for use in the neonatal population, but there is still lack of data on absorption and safety (see also section 2.5). Such preparations are most likely to be liquid dosage forms and the following considerations might apply:

- The volume to be administered should be kept as small as possible.
- In order to avoid such excipients as preservatives, antioxidants etc and eliminate microbial contamination, a sterile product should be considered.

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. For oral administration, the way of feeding (e.g., feeding tube), the time intervals and amounts of feeding (i.e., the actual feeding patterns) have to be considered and specified.

Rectal administration is not commonly used in this age group. If considered it must be fully evaluated for safety and efficacy.

Topical administration may be necessary or suitable for local or systemic effect. Account must be taken of skin immaturity and maturation, especially in preterm neonates, and the large surface area to weight ratio which all predispose to systemic toxicity. There may be increased systemic absorption and toxicity from eye, nasal and other preparations intended for local effect.

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

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 older children but, if not representative for neonates, additional PK studies may be needed in neonates to ensure appropriate systemic drug exposure. 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 drug characteristics. Urine sampling could be used as a partial or complete replacement of blood sampling (see also section 9.6). 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.

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 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. 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.

Both body surface area and weight need to be investigated for best correlation with PK data and for best use as dosing reference; 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).

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. In neonates, however, pharmacokinetics alone is of limited value in neonates for extrapolating efficacy and safety from other patient groups and extrapolation of efficacy will in general need 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 on other prior information, followed 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, as synthesis of binding proteins such as albumin could be lower in the neonate with consequences on drug binding and free bilirubin. The need for differentiation between a loading dose (large Vd) and smaller maintenance doses (low total body clearances) as important, e.g., for methylxanthines, aminoglycosides, and anticonvulsants, has to be identified.

Effort should be made to include the determination of potential covariates in the studies (PNA, PMA, GA, weight, body surface area [BSA], renal function, concomitant use of drugs, S-bilirubin, repeated feeding and feeding patterns 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.

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 the main enzymes involved in the elimination of the drug are different in the neonate, 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 drug combination and if an interaction is expected, specific pharmacokinetic interaction studies should be considered.

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 neonatology experienced centres with relevant expertise and with appropriate resources, in order to ensure optimum professional conditions for the protection and medical support of the neonates.

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).

The following subgroups within the neonatal population should be recognised as distinct, and criteria for stratification should be considered accordingly. 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.

- SGA or not; hypertrophy or not
- ELBW, VLBW, and LBW
- GA: < 26 weeks, 26 - 29 weeks, 30 - 33 weeks, 34 - 36 weeks, 37 - 40 weeks, > 40 weeks

Additionally, the importance of further criteria (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
- Antenatal treatment (e.g., with glucocorticosteroids, antibiotics, or blood products)
- Maternal diseases (diabetes mellitus, autoimmune diseases etc.)
- Use of drugs with haemodynamic effect (e.g., catecholamines), drug with effect on apnea-bradycardia (e.g., caffeine), and drugs for relaxation, pain treatment, or sedation (e.g., morphine)
- Number and type of infections, days of incubator care and incubator temperature adjustments, course of enteral feeding
- Volume and time of (all) blood sampling

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. Endpoints should be assessed using validated procedures for measurement or judgement.

The known complications and sequelae of prematurity (e.g. 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 mental development should be considered.

9.3 Pharmacogenetics

The relationship between phenotype and genotype may be completely different in the neonate as compared to other patient groups.

If feasible, blood may be collected for future pharmacogenetic analysis.

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 drug 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, body surface area, 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 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. However, the use of placebo is often needed for scientific reasons, including in paediatric trials with neonates. 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. Placebo use is not equivalent to absence of treatment, for example placebo could be used on top of standard care. In all cases, its use should be assorted with measures to minimise exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases.

As the number of approved drugs for the neonate population is limited, a comparator may have to be chosen that is not approved for the indication. Medicinal products devoid of 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 planned manner.

Reference to the draft 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.

To limit the need for blood samples, the use or special development of microassays, of non-invasive techniques, and of alternative methods is encouraged, like microdialysis, measuring drug levels in saliva, urine etc., if shown to reflect systemic exposure. 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. 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) must 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

When there is a limited number of data, it is imperative that the most efficient and informative analytical methods should be used. Many of these methods involve 'statistical modelling'. Such models usually make assumptions about the data or the form of the treatment effect. With few data, these assumptions may not be testable or verifiable. However, assumptions add to the data so that more complex statistical models give us more information than simple descriptive statistics. Hence, sensitivity analyses consisting of various analyses/models should be presented, which may make different assumptions abut the data. Such sensitivity analyses should be pre-planned. Then it can be seen if the conclusions are heavily reliant on the model assumptions or if, in fact, they are robust to a variety of plausible assumptions.

Adjustment for baseline variables may greatly improve the efficiency of an analysis. Factors used to stratify the randomisation in a study should be used to stratify the analysis. Including prognostic variables in a model can greatly enhance the precision of a treatment effect. Also refer to section 9.1 on age, stratification and confounding criteria.

Repeated measurements over time - or in different body locations - may also improve the efficiency of an analysis. A commonly encountered problem in the analysis of such data is the non-independence between observations. Non-independence occurs when data fall into groups or clusters, e.g. in different body locations or in longitudinal studies. There are different methods available to analyse clustered dependent data e.g. the Generalized Estimated Equations (GEE) method, Hierarchical Linear Models or Mixed-effects models. These modern statistical approaches take the correlation within subjects into account and can also allow an unequal number of observations per subject (e.g. caused by missing values) so that valid inferences can be assured.

Bayesian methods are a further means of 'adding assumptions' to data. They are a way to formally combine knowledge from previous data or prior 'beliefs' with data from a study. Such methods may be advantageous when faced with small datasets, although introducing prior beliefs is often a concern in drug regulation. As with sensitivity analyses mentioned above, a variety of reasonable prior distributions should be used to combine with data from studies to ensure that conclusions are not too heavily weighted on the prior beliefs. Reference is made to the Guideline on Clinical Trials in Small Populations.

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 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 draft document on ethical considerations for clinical trials on medicinal products with the paediatric population. Sponsors are advised to also refer to the Recommendations of the Working Group on Implementation of the Clinical Trials Directive 2001/20/EC.

9.9 Safety monitoring

As a general recommendation for hospitalised infants 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.).

When there are no satisfactory blood safety data on the investigational medicinal product available, and when the trial does not require more extensive tests for pharmacological investigations, the function of the important and highly metabolically active organs 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

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 neurodevelopmental (e.g., Dubowitz neonatal assessment at discharge, later Griffith test, Bayleys 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.

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 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 (e.g., cognition assessment at school age).

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 trials in juvenile animal model or early phase clinical trial 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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