**Safety, Dosing, and Pharmaceutical Quality for Studies that Evaluate Medicinal Products (including Biological Products) in Neonates**

**Running Title: Study of Drugs in the Neonate**

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# ABSTRACT

The study of medications among pediatric patients has increased worldwide since 1997 in response to new legislation and regulations, but these studies have not yet adequately addressed the therapeutic needs of neonates. Additionally, extant guidance developed by regulatory agencies worldwide does not fully address the specificities of neonatal drug development, especially among extremely premature newborns who currently survive. Consequently, an international consortium from Canada, Europe, Japan and the United States was organized by the Critical Path Institute to address the content of guidance. This group included neonatologists, neonatal nurses, parents, regulators, ethicists, clinical pharmacologists, specialists in pharmacokinetics, specialists in clinical trials and pediatricians working in the pharmaceutical industry.  This group has developed a comprehensive White Paper to guide neonatal clinical trials of medicines – particularly early phase studies (available online). Key points include: the need to base product development on neonatal physiology and pharmacology while making the most of knowledge acquired in other settings; the central role of families in research; and the value of the whole neonatal team in the design, implementation and interpretation of studies. This paper should facilitate successful clinical trials of medicines in neonates by informing regulators, sponsors and the neonatal community of existing good practice.

# PURPOSE

This is a summary of a comprehensive document intended to assist investigators and sponsors of studies that evaluate medicinal products and biologics in neonates. The full document (with extensive references and illustrative figures) can be found online (Supplemental material, online). The focus of the document is on studies that will contribute to applications to regulatory authorities, but the same principles apply to other studies involving neonates. In addition, this document may be useful for regulators who will be reviewing these studies, because this document expands upon previous draft guidances (1 – 10). One goal of this document is to support the standardization and harmonization of approaches to studies in neonates worldwide in order to facilitate global development of new and existing medicinal products for this vulnerable population.

The scope of this document is clinical pharmacology information (e.g., pharmacokinetics (PK), pharmacodynamics (PD), and exposure-response (E-R) relationships) that supports findings of effect, efficacy, and safety and helps to identify appropriate dosages in term and preterm neonates. Because consideration of pharmaceutical quality and ethics influence most aspects of the design and implementation of clinical pharmacology studies, this document also discusses pharmaceutical quality, ethics and participant welfare during studies. The use of quantitative approaches (i.e., pharmacometrics) to employ knowledge about disease and E-R from relevant prior clinical studies is also described in order to design and evaluate future studies in term and preterm neonates.

# BACKGROUND

Worldwide efforts during the past two decades have dramatically increased the study of medicinal productsin children, but not in the neonate. Off label use of medicinal products for neonates is a universal problem. A review of submissions to the U.S. Food and Drug Administration (FDA) illustrates the omission of neonates from studies. From a total of 428 medicinal products studied in pediatric patients, only 28 (7%) were studied in the neonate. But even worse, in a population of 290 Newborn Intensive Care Units (NICUs) and 445,335 patients only 7 of these 428 medicines (1.6%) were actually used routinely (11).

To address the need for study of medicinal products in neonates worldwide, a group of individuals with a broad range of expertise described the issues that need to be addressed in such studies.

Neonates deserve particular attention because the immaturity, small size and rapid developmental changes in this high risk pediatric population complicate the measurement of beneficial and adverse effects of medications, especially with increasing survival of neonates at the borderline of viability (22-23 weeks gestation) (12-13).

## Definitions of the Neonate

Defining and classifying neonates is complex because different terms are used to reflect maturational ages (see Table) (14). As has been adopted by the European Medicines Agency (EMA), the optimal definition of a neonate is up to 44 completed weeks postmenstrual age (PMA). Infancy is from 44 completed weeks PMA to 1 year after the expected date of delivery (2).

A further complexity is that growth abnormalities, either large for gestational age (LGA, weight >90th centile) or small for gestational age or growth restricted (SGA, weight <10th centile), can affect neonatal developmental physiology and pharmacology (15). Trials that exclusively use birth weight as an inclusion criterion generally include a larger proportion of growth-restricted, more mature neonates compared to those that use gestational age. Trials should specify whether or not neonates born outside the normal growth range will be included. The assessment of growth should be based on growth charts or standards such as standard deviation scores that have been validated for the population under study. This means that a given study may have to use different growth charts or standards in different locations and for different populations within a single study.

During long-term follow-up it is important to account for expected developmental status. This can be done using Corrected Gestational Age (CGA). During studies that are conducted over relatively short time periods (i.e. up to 3 months after the expected date of delivery), it may be more convenient to refer to PMA than CGA

Inclusion of specific age groups should reflect the aims of the study and may benefit from a narrow population to generate a clear signal of efficacy (or lack thereof). In contrast, detailed understanding of PK and PD will benefit by recruiting a broader population, since the thorough assessment of PK/PD relationships hinges on the identification and quantification of sources of variability. It should be noted that the results of clinical pharmacology studies may suggest that age-stratifications for dosage used in prescribing information (e.g. the label) or the summary of a medical product’s characteristics are not the same as the stratifications used in a study.

# CLINICAL PHARMACOLOGY CONSIDERATIONS

## General Considerations

The team should develop a clear concept of the treatment goal, identify knowledge gaps required to attain the treatment goal, design studies to fill the information gaps, conduct the studies and review the information continuously. When possible, information gaps should be filled from other sources, or at least narrowed before clinical studies are conducted.

Early in the planning for a neonatal clinical trial, it is wise to involve neonatal nurses. They can provide valuable advice about the practicality of a study design and are pivotal in communication with families. Another important aspect of planning clinical trials involves input from parents/guardians and children (potentially former preterm neonates) (16). They often provide valuable input not previously considered by investigators and their perspective on acceptable levels of risk may differ from that of investigators or even Ethics Committees (16 – 18).

Modeling and simulation through pharmacometrics, physiologically-based PK/PD modeling, as well as systems pharmacology modeling provide an ideal framework for knowledge synthesis, study design (including trial simulation) and analysis. Pharmacometric methods can inform decisions about the number of participants, times of sample collection, covariates, phenotypic analyses and population analyses.

Traditionally, there is an expectation that each application for licensing/marketing authorization contains a self-sufficient body of data about the product ranging from pre-clinical data through a sequence of phases or exploratory/confirmatory studies. This approach is difficult to apply to neonates because of the issues identified in the Background. Instead, information about a medicinal product may come from a number of sources including bridging from pre-clinical and extrapolation from other clinical populations (19 – 25).

The timing of clinical studies in neonates should be appropriate to the condition and the medicinal product. The traditional approach has been to wait until Phase III clinical trials have been completed in adults. This approach is not appropriate in most situations. As increasingly required by regulatory authorities, pediatric medicinal product development should proceed as soon as “proof of concept” for the likelihood of direct benefit for neonates is established in adult studies, unless the disease is unique to newborns (in which case product development usually involves neonates from the early stages) (26). Delay in the initiation of neonatal studies will deprive this population of a new and potentially more beneficial therapy.

## Pharmacokinetics (PK)

In the neonate, body weight and maturation (gestational and postnatal age (PNA)) are important determinants of medicinal product absorption, distribution, metabolism, and excretion (ADME) and explain a substantial amount of exposure variability and changes in PK parameters. These determinants are described in detail in the full document (27 – 43). In addition, other factors such as physiologic derangements (e.g. organ dysfunction, body cooling); concomitant or prior medication exposure; feeding status and type of feedings; and pharmacogenomics influence ADME in term and preterm neonates. Therefore, the PK of a medicinal product is typically evaluated over a wide gestational age and PNA spectrum in which the agents will be used.

*Physiologically Based Pharmacokinetics (PBPK)*

When data are available to describe the developmental changes in pathways of medicinal product disposition, physiologically based PK (PBPK) may be a useful approach for integration of developmental changes in specific processes that determine ADME. Unanticipated differences in medicinal product clearance in neonates must be identified based on a careful PK study. For example, the clearance of daptomycin and micafungin is faster in the neonate than older infants and adults, thus requiring higher dosages (44, 45). Although this is unusual in neonates, it emphasizes how inadequate PK studies could lead to inappropriate dosing of therapeutics in the neonate thereby limiting their efficacy.

## Pharmacodynamics

Investigators should collect and analyze both PK and whenever possible PD data in neonatal studies to determine how the two are linked (i.e., the PK-PD or exposure-response relationship). PD may include the effect of the medicinal product on biomarkers or clinical endpoints for both safety and effectiveness provided that the biomarkers have been validated. These measurements may allow a better understanding of whether the PK-PD relationships of the medicinal product in neonates are similar to those observed in older children or adults and may aid in deriving rational dosing strategies.

**Biomarkers**

A large number of neonatal biomarkers and clinically important outcomes have been described in several systematic reviews (46, 47). Biomarkers may have some utility in clinical practice, but insufficient high-quality data are available to support their use in most neonatal medicinal product development. In many cases, biomarkers are first evaluated in adults. The use of a biomarker in a neonate requires evidence to support a neonatal use. This may be relatively easy if the disease pathophysiology and pharmacologic response in children are similar to adults. Sufficient similarities are not always present: e.g., low blood pressure is a useful biomarker in adults for systemic underperfusion and shock; but it has not been a useful biomarker in neonates for evaluation of organ perfusion. In neonates, clinically meaningful surrogate outcomes or biochemical biomarkers borrowed from older age groups or therapeutic contexts may not reflect biological events (the combination of disease and ontogeny) with sufficient precision to predict a lasting effect for a medicinal product. If sufficient evidence to support the use of a biomarker in neonates is not available, then the medicinal product development program should include work to develop evidence that supports the use of that biomarker in neonates.

The pathophysiology of many neonatal conditions frequently involves multiple organ systems, so analysis of a single biomarker may not be sufficient. Despite these limitations, biomarkers can have utility in medicinal product development (e.g., population enrichment strategies).

**Outcomes**

When selecting outcomes, it is important to note that neonates may be uniquely susceptible to medicinal products that cross the blood brain barrier and to other physiologic changes that may impact neurologic development (e.g. hypoxemia and/or acidosis). In addition, the immaturity of organ systems in neonates mean that safety signals may not manifest until long after the product is administered. It is necessary to include the assessment of safety in the study objectives and it is usually necessary to follow neonates beyond the period of safety surveillance of 30-90 days that is typically used in adults. While longer-term surveillance of safety and efficacy may help define more accurate endpoints, surrogate outcomes such as reduced length of hospital stay, the incidence of co-morbidities, biomarkers, and health care costs should be important factors in neonatal medicinal product development.

Long-term outcome studies currently pose major challenges due to problems with patient dropout and relocation, quality control (including validation of testing instruments), diagnostic accuracy, interpretation of the measures themselves, underlying medical conditions, and potential environmental effects post-discharge. Parental socioeconomic status and education must be measured in the assessment of developmental outcomes. Short-term outcomes do not always correlate with long-term outcomes.

Long-term outcomes studies may be best conducted as part of a post-marketing risk management plan rather than as part of the initial dossier that leads to the availability of the product on the market.

## Pharmacogenetics

Genetic differences that clinically affect both exposure and response have been increasingly documented, but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in neonates. Some of the difficulties in obtaining specific pharmacogenetic information in pediatric patients, including neonates have been reviewed (48, 49). Nevertheless, if medicinal product exposure in a neonatal clinical pharmacology study is dependent on a well-known pharmacogenetic biomarker (e.g., Cytochrome P450 2D6 (CYP2D6)) (50), obtaining DNA may provide additional information for the interpretation of the PK and PD results. In particular, if there are important pharmacogenetic differences affecting PK, efficacy and safety of a medicinal product in the adult population, pharmacogenetic analysis of the target genes is recommended in neonates, given that the relationship between phenotype and genotype may be completely different in the neonate compared to other patient groups (51, 52). DNA collection may be performed on scavenged blood samples after PK analyses are performed or on buccal swabs.

# POINTS TO CONSIDER FOR NEONATAL CLINICAL TRIALS

The pediatric plan should outline the neonatal study or studies that the applicant plans to conduct unless a waiver is granted (53, 54).The submission of the initial neonatal plan is intended to encourage sponsors and investigators to consider neonatal studies early in product development and begin planning for these studies when appropriate.

The neonatal plan is a living document and it is expected that the plan will evolve with time. The plan is useful for directing the process for the sponsor as well as meeting regulatory requirements. Early and frequent discussion of the neonatal plan between sponsors and regulators is extremely valuable and highly recommended. Families, investigators and networks can add considerable value at all stages of the development and implementation of a plan.

## Approaches to Neonatal Studies

Clinical pharmacology studies assess PK (i.e., medicinal product exposure), PD (i.e., effect on biomarker or clinical endpoint), and E-R relationships. It is essential to study these topics in neonates because neonates often differ from adults. For example, it is not unusual to make incorrect estimates of key parameters such as clearance. For this reason it is important to include early assessments of clearance after 5 or 10 patients are studied in each neonatal age group. If an inaccurate initial estimate of clearance is not identified early in the study, then conclusions of the study may be erroneous.

## Extrapolation

Extrapolation is a well-recognized approach to providing sufficient evidence to support the safe and effective use of medicinal products in pediatric populations (55 – 58). As described by Dunne and associates at the FDA (24) and the EMA Committee for Medicinal Products for Human Use (CHMP) (25), extrapolation of efficacy findings from studies in older populations can be successful. This means that a development program can be devised for neonates that minimizes the burden of the research on the participants and allows development of medicinal products for rare conditions. Note that minimizing the burden on the neonate does not make the development program “easier” for the Sponsor. The prerequisite for extrapolation is a well-justified case that reasonable similarity can be assumed between source and target population of both disease progression and response to intervention. It is important to use extant data systematically although regulatory agencies have different ways to structure the case for extrapolation (24, 25).

## PK Sampling Procedures

## Conventional PK studies with intensive blood sampling are rarely performed in neonates because of the limited circulating blood volume (59). Conducting PK sampling during times of routine laboratory sampling (opportunistic sampling) is an approach that reduces the number of blood draws for PK sampling only. This approach can yield similar PK models to study-specific samples taken at optimized time points (60). Scavenged sampling, by using blood or other fluid leftover in the laboratory after clinical studies have been completed, is another non-invasive approach as is the use of residual dried blood spots.

## Neonatal Dose Selection for Clinical Pharmacology Studies

This section presents some general principles, acknowledging that experts in this field must be included in the study team: the full document provides a more detailed discussion. Since there may be limited information on the safety of the dose of medicinal product to be administered, the dose range in first-in-age group studies requires careful consideration. When there is significant uncertainty about the dose, cautious approaches will often be appropriate, including initial titration of an intentionally low dose or use of therapeutic drug monitoring during the trial.

In neonates, clinical trial simulations can be particularly helpful to assess sample size considerations and design a trial that’s both feasible and can adequately evaluate medicinal product exposure, safety and effectiveness.

Where PK/PD studies are designed, the dose range should account for observed differences in response between older children and adults with the neonatal population, both in terms of exposure and response (61). For example, there is evidence that pediatric populations are on average less sensitive to antihypertensive medicinal products than the adult population. Therefore, neonatal studies may include exposures greater than the highest medicinal product exposure associated with the approved adult dose, provided that prior data about the E-R relationship and safety information justify such an exposure.

## Neonatal Dosage Forms and Formulations

There are challenges associated with any route of administration in neonates, as recently summarized by the EMA CHMP (62). Formulations that permit accurate dosing and enhance adherence or accuracy in dosing (i.e., dose accuracy without manipulation) in neonates are a crucial part of clinical pharmacology studies and subsequent pharmacotherapy. If there is a neonatal indication, an age-appropriate dosage formulation must be made available on the market (62).

Excipients with known toxicity in neonates should be avoided (e.g. ethanol, propylene glycol or benzyl alcohol), if possible (63 – 66). Intravenous administration has specific issues (e.g. dead space, flow rate, flush volume, medicinal product volume) as recently summarized by Sherwin et al (67). Study medicinal products should be administered separately from other medicinal products if possible. If the medicinal product is administered as a prolonged, continuous infusion then co-administration with other products will be necessary when the product is used in clinical practice, due to limited vascular access. Prior to co-administration, compatibility of the medicinal product with total parenteral nutrition and other relevant intravenous medicinal products needs to be examined.

If the sponsor demonstrates that all reasonable attempts to develop a stable, specific and safe formulation have failed, the sponsor should develop and validate an age-appropriate formulation that can be prepared by a pharmacist in a licensed pharmacy using an approved medicinal product and commercially available ingredients. If the sponsor conducts the neonatal studies using such a formulation, the information listed in the full document should be provided in the study report.

## Study Design including Sample Size

For clinical investigators working to improve the treatment of neonatal diseases with low incidence rates (e.g. rare diseases), traditional sample size requirements for clinical research may impede the conduct of the trial. Innovative trial designs that have been used in rare disease populations may be applicable to neonates, including adaptive designs. Prior knowledge of the disease, exposure, and response from adult and other relevant pediatric data, such as that related to variability, can be used to derive sample size for ensuring precise parameter estimation.

**Number of Patients**

Precision of PK and E-R parameters in the sample size calculation is critical for neonatal studies. Prior knowledge of the disease, exposure, and response from adult and other relevant pediatric data, such as that related to variability, can be used to derive sample size for ensuring precise parameter estimation. The sponsor should account for potential sources of variability, including inter-subject and intra-subject variability, and differences between adults and older children in the final selection of the sample size for each age group.

*Number of Samples Per Patient*

The number of blood samples collected in a clinical pharmacology study to estimate PK measures and parameters for each patient in the study should be carefully considered. The number of samples is often very limited in neonates. Blood volume limitations for PK sampling will vary by gestational and PNA and this can affect the number of PK samples for medicinal products requiring >0.5 mL of whole blood per sample. Newer microsampling techniques can provide measurements of multiple analytes (e.g. electrolytes, blood glucose, blood gases) on a single 0.3 mL sample of blood. Accelerator mass spectrometry can use samples as small as 7 microlitres.

## PK Sample Collection

Given the difficulty in collecting blood samples in neonates, special approaches to allow optimal times of sample collection may be useful. Sampling windows may need to be wider than is typical for an adult study to account for difficulty in sampling. The sampling scheme should be planned carefully to obtain the maximum information using the minimum number of samples.

Participant welfare is of paramount importance during clinical trials. Trial planning needs to account for the availability of experienced staff, techniques for analgesia (e.g. topical anesthetics), pacifiers or oral sucrose, and applicability across different units. The pros and cons of sampling routes have been summarized (68).

## Covariates and Phenotype Data

The sponsor should obtain, at a minimum, the following covariates for each neonate: gestational age at birth, birth weight, length and head circumference, PNA, current weight, race, ethnicity, sex, diagnoses, concomitant and recent medications or intravenous fluids (including blood transfusions), and relevant laboratory tests that reflect the function of the organs responsible for medicinal product elimination. The sponsor should examine the relationship between the covariates and the PK of the medicinal product of interest.

## Analysis

An analytic method that is readily adaptable and that uses only minimum sample volumes should be chosen.

Two basic approaches for performing the PK analysis in neonates can be used; a non-compartmental PK approach and a population PK approach.

**Non-compartmental Analysis**

The non-compartmental analysis PK approach involves administering either single or multiple doses of a medicinal product to a relatively small group of patients with relatively frequent blood and urine sample collection. Samples are collected over specified time intervals chosen on the basis of absorption and disposition half-lives (predicted from other studies with modification based on known maturation of the route(s) of disposition). Data are usually expressed as the means of the relevant measure or parameter and inter-individual variances. This approach should include a sufficient number of neonates to give a precise estimate of the mean: standard approaches can be applied to neonates. If medicinal product administration and sampling are repeated within a PK study, some understanding of intra-individual variability in PK parameters can be obtained. A non-compartmental approach is often not feasible in neonates.

**Population Analysis**

An alternative approach for analysis in pediatric clinical pharmacology studies is the population approach to PK analysis. Population PK accommodates infrequent (sparse), but informative, sampling of blood or plasma from a larger patient population than would be used in a compartmental or non-compartmental analysis PK approach to determine PK parameters. Sparse sampling of blood or plasma is considered more acceptable for neonatal studies, because the total volume of blood sampled can be minimized. Sampling can often be performed concurrently with clinically necessary blood or urine sampling. Because relatively large numbers of patients are studied and samples can be collected at various times of the day and repeated over time in a given patient, estimates of both population and individual means, as well as estimates of intra- and inter-subject variability, can be obtained if the population PK study is properly designed.

## Adverse and Serious Adverse Event Reporting

It is crucial to capture safety data in all neonatal clinical pharmacology studies (69, 70). This need is particularly acute in neonates because of the limited number of participants in clinical studies – particularly if an extrapolation approach is used. Safety must be included in the objectives of all studies of medicinal products in neonates. Maturing organs may be damaged in the neonatal period, but that damage may only become manifest as the child develops.

# ETHICAL CONSIDERATIONS

Treatment of neonates with medical products without the benefit of comparable evidence provided for adults through appropriate clinical trials is unethical (71, 72). Not only do clinical trials in neonates present special medical and pharmacologic challenges that have been outlined above, they also present ethical challenges (73). Neonates are a vulnerable population for a variety of reasons such as the inability to comprehend the risks of a study, to express their views about those risks or to choose whether or not to participate (26, 74). Uncertainties about the effects of medicinal products, the optimal dose and the long-term consequences of administering medicinal products to neonates make a benefit-risk balance more difficult. Variations among nations and among local Institutional Review Boardsor Ethics Committees within countries in the interpretation and implementation of guidelines for studies in neonates can present challenges to any international clinical trial.

International guidelines such as the International Conference on Harmonisation (ICH) E6 state that “before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks”. In most guidelines, the level of acceptable risk is indexed to the likelihood of direct benefit (75). It is essential to recognize that neonates face significant risks because of exposure to medicinal products that have not been adequately evaluated (76, 77). Once new, improved medicinal products are approved for adults and older children, they will be used in neonates even if they have not been studied adequately in this population. In this context, the risks and potential harms arising from research studies may not add substantively to the burdens borne by neonates. For each study the recognition of acceptable risks and burdens should be based on an explicit balance with the benefits of research in a way that takes into account the views of families.

Before initiation of a clinical trial, a duly appointed, independent Ethics Committee must approve the proposed trial. The Ethics Committee must have access to sufficient expertise in neonatal research. Given the limited number of relevant experts and the need for consistent decision-making arrangements, federated Ethics Committees or a single Ethics Committee for each country will work particularly well for neonatal clinical trials (similar to current models for cancer trials) as long as it includes appropriate expertise.

An Independent Data, Safety and Monitoring Board (separate from the local Ethics Committee) may be needed to oversee the trial (78, 79). This committee should be comprised of Pediatricians and/or Neonatologists, Biostatisticians, community members, and other appropriate personnel with sufficient expertise to be able to examine the safety and efficacy of the trial and stop a trial if there are significant concerns about safety or if it becomes apparent (through interim analyses) that the medicinal product is not efficacious.

Permission for the participation of a neonate in a clinical trial can be challenging. This permission must be free of undue influence and coercion, although the parents or legally appointed guardian(s) of a sick neonate are likely to be in a state of heightened anxiety. When it is appropriate for the study, the process of continuous consent allows families to extend the decision-making process (80).

Sponsors and investigators need to be mindful of variation in ethical approaches while aiming to develop a consistent global approach and avoid locating studies in outside countries where the regulatory agencies will be most flexible and provide limited oversight.

# CONCLUSIONS

Neonatal clinical pharmacology studies are unique. There is an ethical imperative to minimize the number of participants in neonatal clinical studies and a need to study new and existing medicinal products as efficiently as possible. These drivers promote an approach to clinical pharmacology that starts with a broad search for existing knowledge and uses pharmacometric tools to integrate existing knowledge in order to plan and analyze clinical studies.

It is important to plan neonatal studies early in the medicinal product development process. Important data to support the application of a medicinal product to neonates may need to be gathered during the adult phases of clinical medicinal product development. Pre-clinical studies may need to include juvenile animal studies.

Multiple stakeholders must work well together to insure the successful development and regulation of neonatal medicinal products, and the International Neonatal Consortium (INC) was established to help promote that collaborative process. Establishing and maintaining relationships among the key stakeholders of a neonatal development plan need special attention. Teams including regulators need to be open-minded about study design and focused on filling information gaps using the most appropriate approach. Sponsors and investigators need to develop better ways to share information relevant to all neonatal studies in a pre-competitive way. For example, pooling adverse event rates in the placebo arms of neonatal trials will inform all clinical development programs by identifying the rates of anticipated adverse events in neonates in different parts of the world who have not been exposed to novel treatments.

Many neonatal conditions have a major public health impact but involve rare diseases and have relatively few patients. This means that a global development pathway is needed for most medicinal products used in neonates. While sponsors need to work closely with multiple regulatory agencies and investigators, regulators need to develop processes to reach agreement as often as possible during the development and implementation of neonatal programs to develop medicinal products.

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