INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Final version
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ICH HARMONISED GUIDELINE

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11(R1)

ICH Consensus Guideline

TABLE OF CONTENTS

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

1. INTRODUCTION

1.1 Objectives of the Guidance

The number of medicinal products currently labeled for pediatric use is limited. It is the goal of this guidance to encourage and facilitate timely pediatric medicinal product development internationally. The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.

1.2 Background

Other ICH documents with relevant information impacting on pediatric studies include:

- E2: Clinical Safety Data Management
- E3: Structure and Content of Clinical Study Reports
- E4: Dose-Response Information to Support Drug Registration
- E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6: Good Clinical Practice: Consolidated Guideline
- E8: General Considerations for Clinical Trials
- E9: Statistical Principles for Clinical Trials
- E10: Choice of Control Group in Clinical Trials
- M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Q1: Stability Testing
- Q2: Validation of Analytical Procedures
- Q3: Impurity Testing

1.3 Scope of the Guidance

Specific clinical study issues addressed include: (1) considerations when initiating a pediatric program for a medicinal product; (2) timing of initiation of pediatric studies during medicinal product development; (3) types of studies (pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD), efficacy, safety); (4) age categories; and (5) ethics of pediatric clinical investigation. This guidance is not intended to be comprehensive; other ICH guidances, as well as documents from regional regulatory authorities and pediatric societies, provide additional detail.

1.4 General Principles

Pediatric patients should be given medicines that have been appropriately evaluated for their use. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, often, the development of pediatric formulations of those products. Advances in formulation chemistry and in pediatric study design will help facilitate the development of medicinal products for pediatric use. Drug development programs should usually include the pediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the pediatric population. Obtaining knowledge of the effects

of medicinal products in pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

2. GUIDANCE

2.1 Issues When Initiating a Pediatric Medicinal Product Development Program

Data on the appropriate use of medicinal products in the pediatric population should be generated unless the use of a specific medicinal product in pediatric patients is clearly inappropriate. The timing of initiation of clinical studies in relation to studies conducted in adults, which may be influenced by regional public health and medical needs, is discussed in section 2.3. Justification for the timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities at an early stage and then periodically during the medicinal product development process. The pediatric development program should not delay completion of adult studies and availability of a medicinal product for adults.

The decision to proceed with a pediatric development program for a medicinal product, and the nature of that program, involve consideration of many factors, including:

- The prevalence of the condition to be treated in the pediatric population
- The seriousness of the condition to be treated
- The availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments
- Whether the medicinal product is novel or one of a class of compounds with known properties
- Whether there are unique pediatric indications for the medicinal product
- The need for the development of pediatric-specific endpoints
- The age ranges of pediatric patients likely to be treated with the medicinal product
- Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues
- Potential need for pediatric formulation development

Of these factors, the most important is the presence of a serious or life-threatening disease for which the medicinal product represents a potentially important advance in therapy. This situation suggests relatively urgent and early initiation of pediatric studies.

Information from nonclinical safety studies to support a pediatric clinical program is discussed in ICH M3, section 11. It should be noted that the most relevant safety data for pediatric studies ordinarily come from adult human exposure. Repeated dose toxicity studies, reproduction toxicity studies and genotoxicity tests would generally be available. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.

2.2 Pediatric Formulations

There is a need for pediatric formulations that permit accurate dosing and enhance patient compliance. For oral administration, different types of formulations, flavors and colors may be more acceptable in one region than another. Several formulations, such as liquids, suspensions, and chewable tablets, may be needed or desirable for pediatric patients of different ages. Different

drug concentrations in these various formulations may also be needed. Consideration should also be given to the development of alternative delivery systems.

For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate single-dose packaging.

The toxicity of some excipients may vary across pediatric age groups and between pediatric and adult populations, e.g., benzyl alcohol is toxic in the preterm newborn. Depending on the active substance and excipients, appropriate use of the medicinal product in the newborn may require a new formulation or appropriate information about dilution of an existing formulation. International harmonization on the acceptability of formulation excipients and of validation procedures would help ensure that appropriate formulations are available for the pediatric population everywhere.

2.3 Timing of Studies

During clinical development, the timing of pediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Since development of pediatric formulations can be difficult and time consuming, it is important to consider the development of these formulations early in medicinal product development.

2.3.1 Medicinal Products for Diseases Predominantly or Exclusively Affecting Pediatric Patients

In this case, the entire development program will be conducted in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults. Some products may reasonably be studied only in the pediatric population even in the initial phases, e.g., when studies in adults would yield little useful information or expose them to inappropriate risk. Examples include surfactant for respiratory distress syndrome in preterm infants and therapies targeted at metabolic or genetic diseases unique to the pediatric population.

2.3.2 Medicinal Products Intended to Treat Serious or Life-Threatening Diseases, Occurring in Both Adults and Pediatric Patients, for Which There Are Currently No or Limited Therapeutic Options

The presence of a serious or life-threatening disease for which the product represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of pediatric studies. In this case, medicinal product development should begin early in the pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit. Pediatric study results should be part of the marketing application database. In circumstances where this has not been possible, lack of data should be justified in detail.

2.3.3 Medicinal Products Intended to Treat Other Diseases and Conditions

In this case, although the medicinal product will be used in pediatric patients, there is less urgency than in the previous cases and studies would usually begin at later phases of clinical development or, if a safety concern exists, even after substantial postmarketing experience in adults. Companies should have a clear plan for pediatric studies and reasons for their timing. Testing of these medicinal products in the pediatric population would usually not begin until Phase 2 or 3. In most cases, only limited pediatric data would be available at the time of submission of the application, but more would be expected after marketing. The development of many new chemical entities is discontinued during or following Phase 1 and 2 studies in adults for lack of efficacy or an unacceptable side effect profile. Therefore, very early initiation of testing in pediatric patients might needlessly expose these patients to a compound that will be of no benefit. Even for a

nonserious disease, if the medicinal product represents a major therapeutic advance for the pediatric population, studies should begin early in development, and the submission of pediatric data would be expected in the application. Lack of data should be justified in detail. Thus, it is important to carefully weigh benefit/risk and therapeutic need in deciding when to start pediatric studies.

2.4 Types of Studies

The principles outlined in ICH E4, E5, E6, and E10 apply to pediatric studies. Several pediatric-specific issues are worth noting. When a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors[1] that could impact on the extrapolation of data to other regions should be considered.

When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies.

When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older pediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of pediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for pediatric use.

An approach based on pharmacokinetics is likely to be insufficient for medicinal products where blood levels are known or expected not to correspond with efficacy or where there is concern that the concentration-response relationship may differ between the adult and pediatric populations. In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected.

Where the comparability of the disease course or outcome of therapy in pediatric patients is expected to be similar to adults, but the appropriate blood levels are not clear, it may be possible to use measurements of a pharmacodynamic effect related to clinical effectiveness to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies could provide increased confidence that achieving a given exposure to the medicinal product in pediatric patients would result in the desired therapeutic outcomes. Thus, a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies.

In other situations where a pharmacokinetic approach is not applicable, such as for topically active products, extrapolation of efficacy from one patient population to another may be based on studies that include pharmacodynamic endpoints and/or appropriate alternative assessments. Local tolerability studies may be needed. It may be important to determine blood levels and systemic effects to assess safety.

[1] In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors which may result in different drug responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

When novel indications are being sought for the medicinal product in pediatric patients, or when the disease course and outcome of therapy are likely to be different in adults and pediatric patients, clinical efficacy studies in the pediatric population would be needed.

2.4.1 Pharmacokinetics

Pharmacokinetic studies generally should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Relative bioavailability comparisons of pediatric formulations with the adult oral formulation typically should be done in adults. Definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in whom the medicinal product is likely to be used should be conducted in the pediatric population.

Pharmacokinetic studies in the pediatric population are generally conducted in patients with the disease. This may lead to higher intersubject variability than studies in normal volunteers, but the data better reflect clinical use.

For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may provide sufficient information for dosage selection. This can be corroborated, if indicated, by sparse sampling in multidose clinical studies. Any nonlinearity in absorption, distribution, and elimination in adults and any difference in duration of effect between single and repeated dosing in adults would suggest the need for steady state studies in the pediatric population. All these approaches are facilitated by knowledge of adult pharmacokinetic parameters. Knowing the pathways of clearance (renal and metabolic) of the medicinal product and understanding the age-related changes of those processes will often be helpful in planning pediatric studies.

Dosing recommendations for most medicinal products used in the pediatric population are usually based on milligram (mg)/kilogram (kg) body weight up to a maximum adult dose. While dosing based on mg/square meter body surface area might be preferred, clinical experience indicates that errors in measuring height or length (particularly in smaller children and infants) and calculation errors of body surface area from weight and height are common. For some medications (e.g., medications with a narrow therapeutic index, such as those used in oncology), surface-area-guided dosing may be necessary, but extra care should be taken to ensure proper dose calculation.

Practical considerations to facilitate pharmacokinetic studies

The volume of blood withdrawn should be minimized in pediatric studies. Blood volumes should be justified in protocols. Institutional Review Boards/Independent Ethics Committees (IRB's/IEC's) review and may define the maximum amount of blood (usually on a milliliters (mL)/kg or percentage of total blood volume basis) that may be taken for investigational purposes. Several approaches can be used to minimize the amount of blood drawn and/or the number of venipunctures.

- Use of sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample
- Use of laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies (blood counts, clinical chemistry)
- Collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis
- The use of indwelling catheters, etc., to minimize distress as discussed in section 2.6.5.
- Use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient. Techniques include:

- Sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall "population area-under-the-curve"
- Population pharmacokinetic analysis using the most useful sampling time points derived from modeling of adult data

2.4.2 Efficacy

The principles in study design, statistical considerations and choice of control groups detailed in ICH E6, E9, and E10 generally apply to pediatric efficacy studies. There are, however, certain features unique to pediatric studies. The potential for extrapolation of efficacy from studies in adults to pediatric patients or from older to younger pediatric patients is discussed in section 2.4. Where efficacy studies are needed, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. Measurement of subjective symptoms such as pain requires different assessment instruments for patients of different ages. In pediatric patients with chronic diseases, the response to a medicinal product may vary among patients not only because of the duration of the disease and its chronic effects but also because of the developmental stage of the patient. Many diseases in the preterm and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older pediatric patients and call for novel methods of outcome assessment.

2.4.3 Safety

ICH guidances on E2 topics and ICH E6, which describe adverse event reporting, apply to pediatric studies. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Unintended exposures to medicinal products (accidental ingestions, etc.) may provide the opportunity to obtain safety and pharmacokinetic information and to maximize understanding of dose-related side effects.

Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in pediatric patients. Because developing systems may respond differently from matured adult organs, some adverse events and drug interactions that occur in pediatric patients may not be identified in adult studies. In addition, the dynamic processes of growth and development may not manifest an adverse event acutely, but at a later stage of growth and maturation. Long-term studies or surveillance data, either while patients are on chronic therapy or during the posttherapy period, may be needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.

2.4.4 Postmarketing Information

Normally the pediatric database is limited at the time of approval. Therefore, postmarketing surveillance is particularly important. In some cases, long-term follow-up studies may be important to determine effects of certain medications on growth and development of pediatric patients. Postmarketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the pediatric population or additional information for the entire pediatric population.

2.5 Age Classification of Pediatric Patients

Any classification of the pediatric population into age categories is to some extent arbitrary, but a classification such as the one below provides a basis for thinking about study design in pediatric patients. Decisions on how to stratify studies and data by age need to take into consideration developmental biology and pharmacology. Thus, a flexible approach is necessary to ensure that studies reflect current knowledge of pediatric pharmacology. The identification of which ages to study should be medicinal product-specific and justified.

If the clearance pathways of a medicinal product are well established and the ontogeny of the pathways understood, age categories for pharmacokinetic evaluation might be chosen based on any "break point" where clearance is likely to change significantly. Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant. For efficacy, different endpoints may be established for pediatric patients of different ages, and the age groups might not correspond to the categories presented below. Dividing the pediatric population into many age groups might needlessly increase the number of patients required. In longer term studies, pediatric patients may move from one age category to another; the study design and statistical plans should prospectively take into account changing numbers of patients within a given age category.

The following is one possible categorization. There is, however, considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories. Ages are defined in completed days, months, or years.

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on region))

2.5.1 Preterm Newborn Infants

The study of medicinal products in preterm newborn infants presents special challenges because of the unique pathophysiology and responses to therapy in this population. The complexity of and ethical considerations involved in studying preterm newborn infants suggest the need for careful protocol development with expert input from neonatologists and neonatal pharmacologists. Only rarely will it be possible to extrapolate efficacy from studies in adults or even in older pediatric patients to the preterm newborn infant.

The category of preterm newborn infants is not a homogeneous group of patients. A 25-week gestation, 500-gram (g) newborn is very different from a 30-week gestation newborn weighing 1,500 g. A distinction should also be made for low-birth-weight babies as to whether they are immature or growth retarded. Important features that should be considered for these patients include: (1) gestational age at birth and age after birth (adjusted age); (2) immaturity of renal and hepatic clearance mechanisms; (3) protein binding and displacement issues (particularly bilirubin); (4) penetration of medicinal products into the central nervous system (CNS); (5) unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension); (6) unique susceptibilities of the preterm newborn (e.g., necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity); (7) rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; and (8) transdermal absorption of medicinal products and other chemicals. Study design issues that should be considered include: (1) weight and age (gestational and postnatal) stratification; (2) small blood volumes (a 500-g infant has 40 mL of blood); (3) small numbers of patients at a given center and differences in care among centers; and (4) difficulties in assessing outcomes.

2.5.2 Term newborn infants (0 to 27 days)

While term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles discussed above also apply to term infants. Volumes of distribution of medicinal products may be different from those in older pediatric

patients because of different body water and fat content and high body-surface-area-to-weight ratio. The blood-brain barrier is still not fully mature and medicinal products and endogenous substances (e.g., bilirubin) may gain access to the CNS with resultant toxicity. Oral absorption of medicinal products may be less predictable than in older pediatric patients. Hepatic and renal clearance mechanisms are immature and rapidly changing; doses may need to be adjusted over the first weeks of life. Many examples of increased susceptibility to toxic effects of medicinal products result from limited clearance in these patients (e.g., chloramphenicol grey baby syndrome). On the other hand, term newborn infants may be less susceptible to some types of adverse effects (e.g., aminoglycoside nephrotoxicity) than are patients in older age groups.

2.5.3 Infants and toddlers (28 days to 23 months)

This is a period of rapid CNS maturation, immune system development and total body growth. Oral absorption becomes more reliable. Hepatic and renal clearance pathways continue to mature rapidly. By 1 to 2 years of age, clearance of many drugs on a mg/kg basis may exceed adult values. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation.

2.5.4 Children (2 to 11 years)

Most pathways of drug clearance (hepatic and renal) are mature, with clearance often exceeding adult values. Changes in clearance of a drug may be dependent on maturation of specific metabolic pathways.

Specific strategies should be addressed in protocols to ascertain any effects of the medicinal product on growth and development. Children achieve several important milestones of psychomotor development that could be adversely affected by CNS-active drugs. Entry into school and increased cognitive and motor skills may affect a child's ability to participate in some types of efficacy studies. Factors useful in measuring the effects of a medicinal product on children include skeletal growth, weight gain, school attendance, and school performance. Recruitment of patients should ensure adequate representation across the age range in this category, as it is important to ensure a sufficient number of younger patients for evaluation. Stratification by age within this category is often unnecessary, but it may be appropriate to stratify patients based on pharmacokinetic and/or efficacy endpoint considerations.

The onset of puberty is highly variable and occurs earlier in girls, in whom normal onset of puberty may occur as early as 9 years of age. Puberty can affect the apparent activity of enzymes that metabolize drugs, and dose requirements for some medicinal products on a mg/kg basis may decrease dramatically (e.g., theophylline). In some cases, it may be appropriate to specifically assess the effect of puberty on a medicinal product by studying pre- and postpubertal pediatric patients. In other cases, it may be appropriate to record Tanner stages of pubertal development or obtain biological markers of puberty and examine data for any potential influence of pubertal changes.

2.5.5 Adolescents (12 to 16-18 years (dependent on region))

This is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development. In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate.

This is also a period of rapid growth and continued neurocognitive development. Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and, by changing the pattern of growth, may affect final height. Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies.

Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.

2.6 Ethical Issues in Pediatric Studies

The pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk. The purpose of this section is to provide a framework to ensure that pediatric studies are conducted ethically.

To be of benefit to those participating in a clinical study, as well as to the rest of the pediatric population, a clinical study must be properly designed to ensure the quality and interpretability of the data obtained. In addition, participants in clinical studies are expected to benefit from the clinical study except under the special circumstances discussed in ICH E6, section 4.8.14.

2.6.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The roles and responsibilities of IRB's/IEC's as detailed in ICH E6 are critical to the protection of study participants. When protocols involving the pediatric population are reviewed, there should be IRB/IEC members or experts consulted by the IRB/IEC who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

2.6.2 Recruitment

Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant. Reimbursement and subsistence costs may be covered in the context of a pediatric clinical study. Any compensation should be reviewed by the IRB/IEC.

When studies are conducted in the pediatric population, an attempt should be made to include individuals representing the demographics of the region and the disease being studied, unless there is a valid reason for restricting enrollment.

2.6.3 Consent and Assent

As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a study (age of assent to be determined by IRB's/IEC's or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent. In all cases, participants should be made aware of their rights to decline

to participate or to withdraw from the study at any time. Attention should be paid to signs of undue distress in patients who are unable to clearly articulate their distress. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

Information that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one in which the patients are unable to provide individual consent. Studies in handicapped or institutionalized pediatric populations should be limited to diseases or conditions found principally or exclusively in these populations, or situations in which the disease or condition in these pediatric patients would be expected to alter the disposition or pharmacodynamic effects of a medicinal product.

2.6.4 Minimizing Risk

However important a study may be to prove or disprove the value of a treatment, participants may suffer injury as a result of inclusion in the study, even if the whole community benefits. Every effort should be made to anticipate and reduce known hazards. Investigators should be fully aware before the start of a clinical study of all relevant preclinical and clinical toxicity of the medicinal product. To minimize risk in pediatric clinical studies, those conducting the study should be properly trained and experienced in studying the pediatric population, including the evaluation and management of potential pediatric adverse events.

In designing studies, every attempt should be made to minimize the number of participants and of procedures, consistent with good study design. Mechanisms should be in place to ensure that a study can be rapidly terminated should an unexpected hazard be noted.

2.6.5 Minimizing Distress

Repeated invasive procedures may be painful or frightening. Discomfort can be minimized if studies are designed and conducted by investigators experienced in the treatment of pediatric patients.

Protocols and investigations should be designed specifically for the pediatric population (not simply re-worked from adult protocols) and approved by an IRB/IEC as described in section 2.6.1.

Practical considerations to ensure that participants' experiences in clinical studies are positive and to minimize discomfort and distress include the following:

- Personnel knowledgeable and skilled in dealing with the pediatric population and its age-appropriate needs, including skill in performing pediatric procedures
- A physical setting with furniture, play equipment, activities, and food appropriate for age
- The conduct of studies in a familiar environment such as the hospital or clinic where participants normally receive their care
- Approaches to minimize discomfort of procedures, such as:
    - Topical anesthesia to place IV catheters
    - Indwelling catheters rather than repeated venipunctures for blood sampling
    - Collection of some protocol-specified blood samples when routine clinical samples are obtained

IRB's/IEC's should consider how many venipunctures are acceptable in an attempt to obtain blood samples for a protocol and ensure a clear understanding of procedures if an indwelling catheter fails to function over time. The participant's right to refuse further investigational procedures must be respected except as noted in section 2.6.3.

3. ADDENDUM to ICH E11

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Scope and Objective of the ICH E11 Guideline Addendum (R1)

Pediatric drug development has evolved since the original ICH E11 Guideline (2000), requiring consideration of regulatory and scientific advances relevant to pediatric populations. This addendum does not alter the scope of the original guideline which outlines an approach to the safe, efficient, and ethical study of medicinal products in the pediatric population. ICH E11 (2000), including the present addendum (R1) is not intended to be comprehensive; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and pediatric societies, provide additional detail.

The purpose of this addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development. The use of the word "should" means that something is suggested or recommended, but not required, unless specific regulatory or statutory requirements are specified as advised by regulatory authorities worldwide.

In this addendum, section 2 on ETHICAL CONSIDERATIONS**,** section 4 on AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS INCLUDING NEONATES**,** and section 7 on PEDIATRIC FORMULATIONS, supplement the content in ICH E11 (2000). Section 3 on COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS addresses issues to aid scientific discussions at various stages of pediatric drug development in different regions. Section 5 on APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT includes enhancement to the topic of pediatric extrapolation, and introduces modelling and simulation (M&S). Section 6 on PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS includes discussion of feasibility, outcome assessments, and long-term clinical aspects. These sections describe essential considerations intended to provide high level guidance on the implementation of these important approaches in pediatric drug development, reflecting the evolving nature of these topics. This harmonized addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions for the acceptance of data generated in pediatric global drug development programs and ensure timely access to medicines for children.

2. ETHICAL CONSIDERATIONS

ICH E11 (2000) Section 2.6 addresses relevant principles for the ethical conduct of pediatric studies, including the roles and responsibilities of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), recruitment of study participants, parental (legal guardian) consent/permission and child assent (See Glossary), and minimization of risk and distress. These ethical principles are also defined in the current legal and regulatory framework of health authorities worldwide responsible for ensuring safeguards for the protection of children participating in research.

A fundamental principle in pediatric drug development requires that children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need. When clinical studies are required to obtain information relevant to the use of a medicinal product, such studies should be conducted in pediatric populations having the disease or condition for which the investigational product is intended, unless an exception is justified. Without a prospect of direct clinical benefit from an experimental intervention or procedure, the foreseeable risks and burdens to which pediatric participants would be exposed must be low, i.e., comparable to those risks and burdens encountered in their routine clinical care. The burden of trial-related activities

should also be minimized. Experimental interventions or procedures that present greater than low risk to participants must offer a sufficient prospect of clinical benefit to justify or outweigh exposure of a pediatric population to such risk. Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments, such that the child is not disadvantaged by enrollment in the research study. There should be a reasonable expectation that knowledge resulting from the clinical study will contribute to the health of the pediatric population.

The general principles of ethical considerations for parental (legal guardian) consent/permission and child assent are outlined in ICH E11 (2000) Section 2.6.3 and continue to apply. Information regarding participation in the clinical study and the process of parental (legal guardian) consent/permission and child assent must be clearly provided to the parent (legal guardian) and as appropriate to the child participant, at the time of enrollment. When obtaining child assent, relevant elements of informed consent should be provided that are appropriate to the child's capability to understand. Refusal to assent or withdrawal of assent by a child should be respected.

Over the course of a clinical study, it may be necessary to reassess the assent of a child in recognition of their advancing age, evolving maturity and competency, especially for long-term studies or studies that may require sample retention. During clinical studies there is a requirement for obtaining adequate informed consent for continued participation from pediatric participants once a child reaches the age of legal consent. Local regulations related to confidentiality and privacy of pediatric participants must be followed.

The transparency of clinical research in pediatric drug development includes the registration of clinical trials on publicly accessible and recognized databases, and the public availability of clinical trial results. Objective and unbiased information thus made available can benefit pediatric populations through enhancing clinical research, reducing unnecessary clinical trials, and informing clinical decisions in pediatric practice.

3. COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS

General principles outlined in ICH E11 (2000) Sections 1.4 and 2.1 continue to apply. Pediatric drug development programs are increasingly multiregional, and these programs face specific challenges due to regional differences in pediatric regulatory requirements, operational practicalities, standards of care, and cultural expectations. These regional differences in some instances limit the ability of health authorities to align requirements for pediatric product development. To address such differences, timely and efficient drug development requires a common scientific approach for which the following questions should be considered:

- What is the medical need in one or more pediatric populations that the drug could address?
- Who are the appropriate pediatric populations or subgroups that could be considered? (See Section 4)
- What are the key issues in the drug development program that need to be addressed based on the intended pediatric use of the drug?
- Based on the existing knowledge, including developmental physiology, disease pathophysiology, nonclinical data, data in adult or pediatric populations, or data from

related compounds, what are the knowledge gaps that should be addressed to establish the safe and effective use of the drug? (See Section 5.1)

- What specific nonclinical studies could be considered?
- What clinical studies and/or methodological approaches could be considered? (See Section 5)
- What pediatric-specific clinical study design elements could be considered? (See Section 5)
- What practical and operational issues should be considered? (See Section 4 and Section 6)
- Are there different formulations/dosage forms or delivery devices that will be needed for specific pediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of pediatric patients in different subgroups? (See Section 7)

A common scientific approach should consider input from stakeholders (e.g., clinicians, patients, experts from academia), and should be based on scientific advances and up-to-date knowledge.

Early consideration of pediatric populations during drug development planning, along with early interactions between drug developers and regulatory authorities worldwide can facilitate agreement on a common scientific approach to a pediatric development program. When differences are identified, established regulatory pathways to minimize the impact of these differences can be utilized. Therefore, a common scientific approach, not common regional requirements, is at the cornerstone of efficient pediatric drug development and timely delivery of safe and effective medicines for children.

4. AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS, INCLUDING NEONATES

General principles outlined in ICH E11 (2000) Section 2.5 continue to apply. A rationale for the selection of the pediatric population to be included in clinical studies should be provided. Chronological age alone may not serve as an adequate categorical determinant to define developmental subgroups in pediatric studies. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, available treatment options, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies. Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study. Depending on factors such as the condition, the treatment, and the study design, it may be justifiable to include pediatric subpopulations in adult studies (See Section 6) or adult subpopulations in pediatric studies.

Advances in medical care have led to better survival of high risk newborn infants, especially preterm newborn infants, which makes drug development research in newborn infants or “neonates” increasingly important for certain conditions. Neonates include term, post-term and preterm newborn infants. The neonatal period for term and post-term newborn infants is defined as the day of birth plus 27 days. The neonatal period for preterm newborn infants is defined as the day of birth through the expected date of delivery plus 27 days. As the neonatal population represents a broad maturational range, the conditions that affect this population can vary considerably; therefore, it is important to carefully consider the rationale for the selection of a neonatal population or subpopulation to be studied.

5. APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT

The concepts presented in ICH E11 (2000) Section 2.4 continue to apply. The principles outlined in ICH E4, E5, E6, E9, and E10 should be consulted. The number of pediatric studies and knowledge in the field of pediatrics has increased since ICH E11 (2000). Respective regulations for pediatric drug development worldwide have also evolved. However, drug development in pediatrics continues to present challenges and opportunities. In some cases, there are difficulties with generating data across a pediatric population due to a variety of ethical considerations and feasibility issues. Alternative approaches may provide opportunities to address these issues when structured and integrated into the drug development program as per the principles outlined in this addendum. Proactive multi-disciplinary dialogue regarding the acceptability of such approaches with regulatory authorities is recommended. The planning for pediatric development of the drug should be integrated into overall product development. Waiting to begin planning until adult development has concluded can limit the opportunity to generate meaningful data for pediatric drug development.

5.1. The Use of Existing Knowledge in Pediatric Drug Development

To better inform the design of a pediatric drug development program, there is an opportunity to utilize existing knowledge. Existing knowledge about a drug under development includes evidence already or concurrently generated in adult and pediatric populations with similar or other relevant diseases or conditions. Existing knowledge also integrates nonclinical data, data about related compounds, disease pathophysiology, consideration of the developmental physiology, and clinical data from the pediatric population or subgroup. Use of such information may optimize pediatric drug development programs without reducing standards for pediatric authorization. Safety and risk considerations based on existing knowledge should guide the decision whether specific risk mitigation, such as staggered enrollment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge must be identified and managed prospectively. As data are generated through the drug development cycle, it is possible that the assumptions behind the parameters that have gone into the development strategy and methodology may need to be revisited to take new information into account. This new information will continue to inform the strategy and present an opportunity to further address uncertainties.

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S (see Glossary) that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups). The following subsections provide general considerations on the use of extrapolation and M&S in pediatric drug development.

5.1.1. The Use of Extrapolation in Pediatric Drug Development

The concept of “extrapolation” is used in different ways in drug development. “Pediatric extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

When a drug is studied in a pediatric population, one should consider all factors which may result in different drug responses, such as intrinsic (e.g., developmental) and extrinsic (e.g., geographic) factors that could impact on the extrapolation of data from one population to the other.

The process of pediatric extrapolation examines several factors that support the assumptions of similarity of disease and similarity of response to therapy between the pediatric and the reference populations, including disease pathogenesis, criteria for disease diagnosis and classification, measures of disease progression, and pathophysiological, histopathological, and pathobiological characteristics. A thorough understanding of the differences between pediatric and reference populations is required relative to the pathophysiology of the disease, available biomarker/endpoints, organ systems physiology (i.e., renal, hepatic, central nervous system, skeletal, and immune systems), as well as clinical context of available therapeutics, the mechanism of action of the drug and its pharmacological behavior. As new information is generated, the process of pediatric extrapolation should be reviewed and confirmed.

Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship and prediction of an effective dose and regimen for the intended population, may be derived from existing data about the use of the drug; published literature; expert panels and consensus documents; or previous experience with other products in the same therapeutic class. All data and information gathered can either confirm the extrapolation approach or inform how it might be improved. Ultimately, the exercise should identify if there are sufficient data to support pediatric extrapolation, or if additional clinical information is needed.

When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as existing data may only provide some information about potential safety concerns related to the use of a drug in the pediatric population [See ICH E11 (2000) Section 2.4].

When pediatric extrapolation is considered in a pediatric drug development strategy, the following framework of questions should be assessed to identify what additional supportive data are needed:

1. What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?

2. What is the strength of the evidence of efficacy in the reference populations?

3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population?

4. What evidence supports a similar exposure-response between the reference and intended populations?

5. What uncertainties and/or limitations do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?

6. If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

As evidence builds, the acceptability of the proposed extrapolation approach should be reassessed and it may be appropriate to change the extrapolation approach.

5.1.2. The Use of Modelling and Simulation in Pediatric Drug Development

Advancement in clinical pharmacology and quantitative M&S techniques has enabled progress in utilizing model-informed approaches (e.g., mathematical/statistical models and simulations based on physiology, pathology and pharmacology) in drug development. M&S can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy. Considering the limited ability to collect data in the pediatric population, pediatric drug development requires tools to address knowledge gaps. M&S is one such tool that can help avoid unnecessary pediatric studies and help ensure appropriate data are generated from the smallest number of pediatric patients. The usefulness of M&S in pediatric drug development includes, but is not limited to, clinical trial simulation, dose selection, choice and optimization of study design, endpoint selection, and pediatric extrapolation. With M&S, quantitative mathematical models are built with all available and relevant sources of existing knowledge. Well conducted M&S can inform on the pharmacokinetics, pharmacodynamics, efficacy and safety of a drug.

The incorporation of M&S into pediatric drug development should be based on a strategic plan established through multidisciplinary discussions outlining objectives, methods, assumptions, deliverables and timelines.

When building a model, it is important to consider several elements, including the context of use of the model, the quality and the extent of the existing data, and the assumptions made. Assumptions are usually structured around five main areas: pharmacology, physiology, disease considerations, existing data, as well as the mathematical and statistical assumptions underpinning the model.

Complexity in M&S requires a careful assessment of the impact of each of the above assumptions because the impact of each one on model building can vary between populations. In pediatrics, it is particularly critical to consider the maturation of organ systems with the understanding that data from older subgroups may not necessarily be informative for the younger subgroups. Once assumptions are set, different scenarios should be defined and tested to support the analysis of the impact of potential uncertainty in existing knowledge.

Emerging knowledge is incorporated into the model in an iterative approach to revisit and improve the model. A series of “learn and confirm” cycles should be used for model building and simulation/prediction, and be confirmed as soon as new information is generated. Several models may be needed to support a given pediatric drug development program depending on the question(s) to be addressed, the credibility of the model, and the emerging data generated.

Risk assessment is a critical part of M&S. The clinical and statistical consequences of a specific approach should be discussed with experts to define the risks to be handled. The risks associated with accepting the model depend on the relative contribution of the model in making a decision during product development and its consequences. These risks should be assessed and weighed against the credibility of the model for the context of use.

6. PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS

Before deciding which types of methodological approaches are to be used in clinical trial design and execution, one should consider several practical factors that influence the design and

execution of pediatric clinical trials. Three key practical factors to consider are feasibility, outcome assessments, and long-term clinical aspects, including safety.

6.1. Feasibility

Pediatric drug development faces unique feasibility issues, including a small number of eligible children for clinical research, limited pediatric specific resources at research centers, and the scarcity of dedicated pediatric trial networks. Consideration should be given to the available centers that are willing to participate, have access to eligible pediatric participants, and are appropriately staffed in research and clinical care of pediatric patients. When studying pediatric conditions, it may be necessary to consider implementing clinical trial operational strategies, including, but not limited to, the use of pediatric research coordinating centers; the development of master protocols for pediatric clinical trials or registries, planned and conducted in a collaborative manner to evaluate multiple therapies for the same disease or condition with a common control arm; and the enhancement of pediatric clinical research networks. These operational strategies and adherence to Good Clinical Practice (ICH E6) should result in improved feasibility and increase timely and efficient pediatric drug development.

The foreseeable experience of children and their parent(s)/legal guardian should be considered, including the emotional and physical burden and the convenience of participation. Current standards of care can influence physician/patient treatment choices that may impact the design and conduct of pediatric clinical trial. Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study.

6.2. Outcome Assessments

As stated in the ICH E11 (2000) Section 2.4.2, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. The relevant endpoints and outcome measures for the pediatric population should be identified as early as possible. The standardized measurement, collection, analysis, and reporting of outcome assessments are encouraged to optimize pediatric drug development [See ICH E11 (2000) Section 2.4 and ICH E11 (R1) Section 5]. It is important to include protocol design features that allow pediatric participants at appropriate ages to contribute directly in these measures when possible. Where relevant, it may be prudent to initiate the evaluation of potential pediatric endpoints as part of the adult development program prior to their incorporation into the pediatric program.

6.3. Long-term Clinical Aspects

The concepts on safety presented in ICH E11 (2000) Section 2.4.3 and Section 2.4.4; ICH E6 and ICH E2 topics continue to apply. It is acknowledged that rare events may not be identifiable in pre-registration development, and that pediatric-specific adverse events are unlikely to be detected in development programs that are limited in size and duration. Planned collection of safety data in nonclinical studies, adult clinical studies regardless of dose or indication, or information from other sources (e.g., M&S), should serve to improve the design of pediatric studies and pharmacovigilance activities to address specific pediatric safety concerns.

Long-term effects of drug treatment in children can include impacts on development, growth, and/or maturation of organ/system function. Therefore, adequate baseline assessments of growth/development and organ function, and regular follow-up measurements should be planned and discussed with regulatory authorities, as appropriate. Early planning for follow-up in a drug

development program offers the opportunity to systematically capture and evaluate long-term effects in a disease or condition, and increase data interpretability.

7. PEDIATRIC FORMULATIONS[2]

Principal considerations for the development of age-appropriate pediatric formulations to allow for safe and accurate use of pediatric medicines as outlined in ICH E11 (2000) Section 2.2 continue to apply. Additional considerations for pediatric formulations to optimize efficacy and reduce the risk for medication and dosing errors should include age-appropriate dosage forms, ease of preparations and instructions for use for caregivers, acceptability (e.g., palatability, tablet size), choice and amount of excipients, as well as use of alternative delivery systems and appropriate packaging.

Adult dosage forms are not always appropriate for use in the pediatric population, and if a product for adults is used, it may pose a safety risk. When pediatric considerations are not addressed early during drug development, the final medicinal product(s) may require such modification for use in children that the risk is increased for inaccurate dosing, changes in stability, bioavailability, or suboptimal patient acceptability. Examples of this include multiple small volume acquisitions from a vial designed for a single adult use; use of an opened adult capsule formulation or crushed tablets to mix with food for administration of a pediatric dose; and breaking tablets for dose reductions that do not have a functional score line. When modifications of the available preparations are unavoidable, measures to minimize the impact on dose accuracy, stability, bioavailability and safety must be addressed.

Planning for development of age-appropriate dosage forms for pediatric populations should be incorporated into the earliest stages of drug development. If modifications to the available forms are necessary to allow earlier inclusion of pediatric patients in clinical trials during drug development, an age-appropriate product and the applicable bridging studies in support of its use should be planned.

7.1. Dosage and Administration

In order to achieve the targeted drug exposure, more than one dosage form of the active pharmaceutical ingredient (API) and/or strengths may be needed to cover the range of pediatric populations intended to receive the medicinal product. For pediatric drugs, the setting where the product is likely to be administered should be considered when selecting the formulation for development. For example, long acting formulations may be beneficial in settings where the caregiver is not always available (e.g., school, nursery). Further, certain dosage forms that reduce the requirements for handling and storage may be more appropriate than others.

In developing a formulation for pediatric use, considerations should include the ease of accurate dose measurement and the capability to deliver small volumes of liquids to minimize the risk for dosing errors, especially in neonates, infants and young children. Such approaches could include clearly marked administration devices, and/or devices with scaling capability designed for accurate measurement of the smallest dose volume and dose increments.

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[2] For purposes of this document, the term "pediatric formulations" includes design considerations for the dosage form, route of administration, packaging, measuring or administration device of a pediatric medicine (drug).

7.2. Excipients

Excipients may lead to adverse reactions in children that are not observed (or not to the same extent) in adults. Thus, the use of excipients in pediatric medicines should take into account factors such as age, weight, maturity (e.g., term and preterm newborns related to their physiologic development), frequency of dosing, intended duration of treatment, and potential for additional excipient exposure from commonly co-administered medicines. The use of excipients and their quantity in a formulation should minimize risk and ensure product performance, stability, palatability, microbial control, and dose uniformity. Alternatives to excipients that pose a significant risk to children should always be considered, and the risk posed by the excipient weighed against the severity of the disease and availability of alternative treatments. When selecting excipients, one should always consider the potential impact on absorption and bioavailability of the API.

7.3. Palatability and Acceptability

Orally administered pediatric medicines must be palatable to ensure dose acceptance and regimen adherence. A formulation strategy for developing palatable drug preparations includes minimizing/eliminating aversive attributes of the API and considering favorable flavor attributes. Taste masking is often needed to improve the palatability of the API. As pediatric drug development can benefit global populations, the target for taste masking should not only be focused on ensuring that the preparation does not taste unpleasant. Ideally, the preparation should have a neutral taste or a taste with broad cultural acceptance.

Alternative dose administration strategies should be considered for pediatric populations who cannot be accommodated by the intended dosage form (e.g., segmenting or crushing tablets, co-administration with food or liquids). Appropriateness of the alternative strategy for a pediatric population, including patient and caregiver aspects (e.g., taste/palatability, ease and accuracy of modification, and potential changes in bioavailability due to a variety of factors) should be investigated prior to selection of the final market image formulation. Understanding real-world use behaviors in administering pediatric drugs and the mitigation of associated risks will contribute to the development of a drug product that allows for safe dose administration.

7.4. Neonates

Formulation requirements for neonates warrant special attention, such as its effects on electrolyte, fluid or nutritional balance. Intramuscular preparations should be avoided where possible due to pain, risk of over-penetration (e.g., bone, vasculature), and unpredictable drug absorption. Likewise, the tolerability of subcutaneous and intravenous preparations should be evaluated. For neonates, environmental conditions (e.g., temperature, light) and equipment used for drug administration (e.g., enteral feeding tubes) may have an effect on drug delivery and bioavailability. When developing a parenteral dosage form, compatibility with other commonly administered parenteral medicines or parenteral nutrition should also be considered and investigated as necessary, since intravenous access is often limited in neonates. While parenteral formulations may be used in neonates, it should be considered that their use often necessitates careful monitoring to minimize the risk of fluid and electrolyte disturbance.

8. GLOSSARY

Parental (legal guardian) consent/permission:

Expression of understanding and agreement by fully informed parent(s) or legal guardian to permit the investigator/sponsor of a clinical study to enroll a child in a clinical investigation. The choice of the terms parental consent or parental permission in different regions may reflect local legal/regulatory and ethical considerations.

Child assent:

The affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of agreement or disagreement must not be interpreted as assent.

Modelling and Simulation (M&S):

A range of quantitative approaches, including pharmacometrics/systems pharmacology and other mathematical/statistical approaches based on physiology, pathology and pharmacology to quantitatively characterize the interactions between a drug and an organ system which could predict quantitative outcomes of the drug and/or system's behavior in future experiments. In modelling and simulation, existing knowledge is often referred to as "prior" knowledge.