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Dockets Management Branch  
(HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
rm 1061  
Rockville, MD 20857

**Re: International Conference on Harmonisation; E11: Clinical Investigation of Medicinal Products in the Pediatric Population, Docket Number 00D-1223, 65 Federal Register 19777, April 12, 2000**

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing medicines allowing patients to lead longer, happier, healthier and more productive lives. Investing \$26 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for new cures.

I am writing on behalf of PhRMA to provide comments on the *International Conference on Harmonisation (ICH) E11 guidance on the Clinical Investigation of Medicinal Products in the Pediatric Population*. PhRMA believes the E11 guideline represents an important addition to the existing ICH guidelines in the area of pediatric clinical investigations. We would like to ensure that as this guideline is finalized, the following comments (presented in an edit-marked version of the draft E11 guideline), which constitute clarifications in the text, or raise concerns which may not have been addressed by the Expert Working Group (EWG), are taken into consideration.

The enclosed attachment summarizes PhRMA's comments on this document. We trust that these will be useful to the Agency as this draft guideline is revised.

Sincerely,

00D-1223

***Pharmaceutical Research and Manufacturers of America***

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS  
FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

**PhRMA COMMENTS ON E11 DRAFT CONSENSUS GUIDELINE**

**CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION**

Released for Consultation  
at Step 2 of the ICH Process  
on 7 October 1999  
by the ICH Steering Committee

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.*

**CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION**

**Draft ICH Consensus Guideline**

Released for Consultation, 7 October 1999, at *Step 2* of the ICH Process

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## CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

### 1. INTRODUCTION

#### 1.1 Objectives of the Guideline

The number of medicinal products currently labeled for pediatric use is limited. It is the goal of this guideline to encourage and facilitate timely pediatric medicinal product development internationally. The guideline 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:

- E-2: Clinical Safety Data Management
- E-3: Structure and Content of Clinical Study Reports
- E-4: Dose-Response Information to Support Drug Registration
- E-5: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E-6: Good Clinical ~~Practices~~Practice: Consolidated Guideline
- E-8: General Considerations for Clinical Trials
- E-9: Statistical Principles for Clinical Trials
- E-10: Choice of Control Groups in Clinical Trials
- M-3: Guideline for the ~~timing~~Timing of non-clinical Non Clinical safety Safety studies Studies for the conduct ~~Conduct of human Human clinical Clinical trials Trials for pharmaceuticals Pharmaceuticals~~
- Q-1: Stability ~~testing~~Testing
- Q-2: Validation of Analytical Procedures
- Q-3: Impurity Testing

#### 1.3 Scope of the Guideline

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

**[Should specific references to published documents referred to above be provided in this document?]**

#### 1.4 General Principles

Medicinal products used to treat pediatric patients ~~Pediatric patients should be given medicines which have been appropriately evaluated appropriately and adequately 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, at times, the development of ~~of~~ pediatric formulations for ~~of~~ those products. Major advances in formulation chemistry and in pediatric

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study design ~~ensure help facilitate that this goal can be achieved~~ the development of information supporting appropriate pediatric uses of medicinal products.

Drug development programs typically should include the pediatric patient population when a product is being developed for a disease ~~/ or condition in adults and it is anticipated the product also~~ will be used in the pediatric population. The ethical imperative to obtain knowledge of the effects of medicinal products in pediatric patients ~~has to~~ must be balanced against the ethical imperative to protect each pediatric patient in clinical studies. ~~This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole. Companies, regulatory authorities, health professionals and society as a whole share this responsibility.~~

## 2. GUIDELINES

### 2.1 Factors bearing on the initiation of ~~Issues when initiating a~~ pediatric medicinal product development programs

Where the sponsor intends for the product to be used on pediatric populations ~~Data to~~ support the appropriate use of medicinal products in the pediatric population should be available, unless the use of a specific medicinal product in pediatric patients is clearly inappropriate. The initiation of clinical studies in relation to studies conducted in adults is discussed in 2.3; initiation of clinical studies in either adult or pediatric populations, ~~which may be influenced by regional public health and medical needs, is discussed in 2.3.~~ In general, pediatric studies should not delay completion of adult studies and availability of a medicinal product for adults. Justification for timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities at an early stage and be reviewed as data are obtained.

The decision to proceed with a pediatric development program, and the nature of the program, for a medicinal product involves 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 and its effect on quality of life
- the availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy of those treatments; ~~and the adverse event profile~~ (with focus on including any unique pediatric safety issues identified in pediatric studies), palatability (for oral delivery), tolerability, ease of compliance and frequency of dosing.
- whether the medicinal product is novel or one of a class of compounds with known properties
- whether ~~there are~~ condition constitutes a unique pediatric indications or is one similar to that seen in adults for the medicinal product
- the age ranges of patients likely to be treated with the medicinal product
- whether there are unique pediatric (developmental) safety concerns about the medicinal product, based on available adult clinical and non-clinical safety data ~~including any non-clinical safety issues~~
- potential need for pediatric formulation development

~~Of these factors, the most important is the presence of a serious disease without good current therapy. This situation suggests relatively urgent and early initiation of pediatric studies.~~

Information from non-clinical safety studies to support a pediatric clinical program is discussed in the ICH M-3 guideline, section 11. It should be noted that the most relevant safety data for pediatric studies come ordinarily from adult human exposure. Repeat dose toxicology and reproductive toxicology/genotoxicology [clarification requested: does 'genotoxicology' refer to 'genotoxicity' studies as described in the ICH S2A and S2B guidelines?] would generally be required; repeat dose

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toxicology may not be applicable for some biotechnology products. The need for juvenile animal studies should be considered on a case by case basis, and based on developmental toxicology concerns that cannot be addressed in the studies already conducted. If juvenile animal studies are performed, appropriate toxicokinetic assessments should ordinarily be considered in conjunction with those studies.

The timing of the initiation of pediatric studies in relation to those conducted in adults is discussed in 2.3. In general, pediatric studies should not delay completion of adult studies and the availability of a medicinal product for adults. The presence of a serious disease without good current therapy suggests the need for relatively urgent and early initiation of pediatric studies. However, significant improvement in therapy for a common but less serious disease may suggest the need for similar urgency. In all cases, the timing of, and the approach to, a pediatric clinical program should be clearly addressed with regulatory authorities at an early stage.

## **2.2 Pediatric formulations**

For some medicinal products ~~There is a need for the development of a~~ pediatric formulations ~~that permit facilitates~~ accurate dosing and enhances patient compliance. For oral administration, different types of formulations (suspensions, "sprinkles", chewable tablets), and different 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 may be desirable for pediatric patients of different ages. Different concentrations of these various formulations may also be necessary. Consideration should be given to the development of alternative approaches for delivery of medicinal products such as patches or suppositories.

For injectable formulations, the concentration of the medicinal product ~~should~~must be compatible with the doses to be administered, including doses for small premature infants if the drug is to be used in that population. This may require a more dilute solution to allow accurate administration of the dose using available syringes and administration pumps, or a more concentrated solution where fluid restriction imposed for very small patients is a concern. For medicinal products supplied as single use vials, consideration should be given to dose-appropriate single dose packaging, conditions for safe multiple use of preservative-free vials, or addition of preservatives. The toxicity of some excipients may vary across age groups and between pediatric and adult patients~~Some excipients (e.g., benzyl alcohol) may be toxic, particularly in the pre-term 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 will help assure that appropriate formulations are available for the pediatric population everywhere (see ICH Q-1-3).

## **2.3 Prioritization of medicinal products for pediatric clinical programs**

Timing of studies  
During clinical development, the timing of pediatric studies should ~~be flexible and will depend on the medicinal product, the type of disease or conditions it being treated~~treats, safety considerations, and the efficacy and safety of alternative treatments, including non-medicinal therapies. Because~~Since~~ development of pediatric formulations can be difficult and time consuming, it is important to consider formulation development~~this~~ early in a medicinal product development.

### **2.3.1 Medicinal products for diseases predominantly or exclusively affecting pediatric patients**

In this case, ~~t~~The entire development program for medicinal products to treat diseases predominantly or exclusively affecting pediatric patients will be conducted in the pediatric populations 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 and/or expose them to inappropriate risk. Examples include surfactant for respiratory distress syndrome in pre-term infants, and therapies targeted at metabolic/genetic diseases unique to the pediatric population.

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**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**

~~In this case, when a manufacturer chooses to develop its product for pediatric use medicinal-product development in the pediatric population should begin early in the pediatric population clinical development program, following assessment of initial safety data and reasonable evidence of potential benefit. In most instances pediatric studies will be conducted in a logical progression that includes assimilation of data from studies in adults as a pre-requisite. When conducted, pediatric study results should ordinarily 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, where if the medicinal product has a will be used in pediatric use patients but there is less urgency than in the previous cases, studies might begin at various phases of clinical development; or if a safety concern exists, even after substantial post-market experience in adults. If a manufacturer chooses to develop its product for pediatric use the company Companies should have a clear plan for pediatric studies and reasons for their choice of when to initiate them. Testing of such these medicinal products in the pediatric population would usually not begin until Phase 2 or 3. In most cases, only limited pediatric data, if any, would be available at the time of application submission, but more would be expected after marketing, unless the pediatric study experience directed otherwise. Even if for a non-serious disease, if the medicinal product represents a major therapeutic advance for the pediatric population, the sponsor should give consideration to conducting studies should begin as early in development, as possible, and the submission of pediatric data would be expected in the application. As the development of many new chemical entities is discontinued following in Phase 1 and 2 adult trials for lack of efficacy or an unacceptable side effect profile, very early initiation of testing in pediatric patients might needlessly expose these patients to a compound which will be proved subsequently of no benefit. Thus, it is important to carefully weigh benefit/risk/benefit and therapeutic need in deciding when to start pediatric studies, especially when anticipated pediatric use is limited or not critical.~~

**[Clarification: a more specific title for sections 2.3.1, 2.3.2 and 2.3.3 would be useful to prevent mis-interpretation. A fourth section as outlined below would complete this section:]**

**2.3.4 Medicinal products intended to treat other diseases and conditions in adults where significant pediatric usage is not anticipated**

This category addresses medicinal products where the nature or frequency of the illness, the characteristics of the drug and/or the dosage form, or the anticipated therapeutic advantages of the product are such as to pose no demonstrable need for the product in the pediatric population. Examples of such cases involve conditions where pediatric usage is infrequent and effective alternatives are available, where the product has only marginal advantages over current therapy and/or exists only in strengths or dosage forms inappropriate to pediatric usage.

In such cases pediatric study is optional, except where post-marketing surveillance demonstrates a clear patter of pediatric use. In such cases investigations to provide adequate evidence of safety and appropriate instructions in the observed usage should be undertaken as soon as a pattern of pediatric usage of the product is demonstrated.

**2.4 Types of studies**

The principles outlined in ICH E-4, E-5, E-6, and E-10 apply to pediatric studies. **[Note: should the evolving E12 series on specific therapeutic categories be mentioned here?]** Several pediatric-specific issues are worth noting. For example, wWhen a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors that could impact the

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extrapolation of data to other regions should be considered. Typically, any such differences do not significantly affect the ability to extrapolate findings to other regions.

When the 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 ~~at~~ the age ranges of pediatric patients likely to receive the medicinal product, together with safety or other studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. **[Clarification requested: 'other studies' needs clearer definition in the light of the preceding information and the non-homogeneity of this population]** If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies. Where efficacy is correlated with a range of plasma concentrations, a PK approach that demonstrates a dose/plasma concentration range relationship may be appropriate. It may be appropriate to obtain safety information for the pediatric population in a single indication, even when multiple indications have been studied and approved for adult use of the medicinal product.

When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older ~~pediatric~~ patients, and 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. This approach may be necessary where assessment of outcome variables is particularly difficult in younger patients (e.g., forced expiratory volume (FEV1) below the age of 6 years). In such cases, pharmacokinetic studies in all 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.

~~A~~ PK ~~studies alone~~ approach may not be sufficient for medicinal products where blood levels are not known to correspond with efficacy, or where there is concern that the concentration-response relationship may differ between the adult and pediatric populations. Where the comparability of the disease course and/or outcome of therapy in pediatric patients is expected to be similar, but the appropriate blood levels are not clear, it may be possible to utilize measurements of a pharmacodynamic effect to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies would provide increased confidence that achieving a given exposure to the medicinal product in pediatric patients will result in the desired therapeutic outcomes. This could avoid the need for clinical efficacy studies.

It may be useful for certain products to determine blood levels for purposes of safety assessment (e.g.; to determine relative systemic exposure for topically applied agents).

When novel indications are being sought for the medicinal product in pediatric patients, or where 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 ordinarily need to be conducted~~still be required~~. Similarly, in situations where PK is not applicable, such as with most topically active products, studies may need to include clinical endpoints or appropriate alternative assessments.

#### **2.4.1 Pharmacokinetics**

Pharmacokinetic studies generally will be needed to: support formulation development; determine pharmacokinetic parameters in different age groups to support dosing recommendations; understand PK/PD relationships where these may differ from adults. Bioequivalence comparisons of pediatric formulations with the adult oral formulation typically should be done in adults. Definitive pharmacokinetic studies for dose selection across age-ranges where the medicinal product is likely to be used should be conducted in the pediatric population.

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Pharmacokinetic studies in the pediatric population ~~may be differ from adult studies in that they are generally~~ conducted in patients with the disease ~~or in healthy pediatric patients~~. Studies conducted in pediatric patients with the disease This may lead to higher result in higher intersubject variability, but the data better reflect clinical use. This does not indicate that a larger number of subjects or data points are required to adequately define the pharmacokinetic profile of the medicinal product in the pediatric population(s).

For medicinal products ~~that~~ which exhibit linear pharmacokinetics in adults, single dose pharmacokinetic studies in the pediatric population may often be sufficient to ascertain correct dosing. This can be corroborated, if indicated, by sparse population sampling in multi-dose clinical studies. Any non-linearity in absorption, distribution, and elimination in adults, and any duration-of-effect-related changes would suggest the need for steady state studies in the pediatric population. ~~Each of~~All these approaches ~~is~~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 mg/kg up to a maximum adult dose. While dosing on a surface area (mg/m<sup>2</sup>) basis might be preferred, clinical experience indicates that errors in measuring height or length (particularly in smaller children and infants), and calculation errors of surface area from weight and height are common. For some medications (e.g., those with a narrow therapeutic index, such as drugs those used in oncology), surface area-guided dosing may be necessary, but with extra care to assure proper dose calculation.

*Practical considerations to facilitate pharmacokinetic studies*

The volume of blood withdrawn should be minimized in pediatric studies; Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) generally establish the maximum amount of blood (usually on ml/kg or % of total blood volume basis) that can be taken for investigational ~~experimental~~ purposes. Several approaches can be used to minimize the amount of blood drawn.

- use of sensitive assays (gas chromatography/mass spectroscopy, tandem mass spectroscopy) for parent drugs and metabolites to decrease the volume of blood required per sample
- use of laboratories experienced in handling small volumes of blood, both for pharmacokinetic analyses, as well as to minimize the amount of blood necessary 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
- use of population pharmacokinetic approaches to minimize the number of samples obtained from each patient. Techniques include:
  - sparse sampling approaches where each patient contributes as few as 2-4 observations at pre-determined times to an overall "population area-under-the-curve"
  - population PK analysis utilizing the most useful sampling time points derived from modeling of adult data
  - the use of indwelling catheters, etc. to minimize distress as discussed in 2.6.5

**2.4.2 Efficacy**

The principles in study design, statistical considerations and choice of control groups detailed in ICH E-6, E-9, and E-10 **[E-12?]** in general apply to pediatric efficacy studies. There are, however, certain unique features to pediatric studies. The potential for extrapolation of efficacy from studies in adults to pediatric

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patients or from older to younger pediatric patients is discussed in section 2.4. Where efficacy studies are required, 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 in patients of different ages. Responses of chronic diseases may vary in patients with early stages of disease and in patients with years of disability and organ dysfunction. Many diseases in the pre-term and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older pediatric patients, and requiring novel methods for outcome assessment.

### **2.4.3 Safety**

Reporting requirements for adverse events, as described in ICH E-2 and ICH E-6, apply to pediatric studies. Age appropriate normal laboratory values and clinical measurements should be utilized in adverse event reporting. Unexpected exposures to medicinal products (accidental ingestions, etc.) may provide anecdotal safety information in individual cases, but the spontaneous safety reporting system should not be relied upon for extensive clinical safety data or for a clear opportunity to obtain safety and pharmacokinetic information, and to maximize understanding of dose-related side effects.

Medicinal products may have effects on physical and cognitive growth and development, and the adverse event profile may differ in pediatric patients. Because developing systems may respond differently from the matured adult organ, some adverse events 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, either while patients are on chronic therapy or during the post-therapy period, may be necessary to determine possible effects on skeletal, behavioral, cognitive, sexual and immune maturation and development. This is a circumstance where it may be appropriate to consider animal studies rather than clinical studies.

### **2.4.4 Post-marketing experience**

Normally the pediatric database is limited at the time of approval. Therefore, postmarketing and long-term follow-up studies and surveillance are particularly important. They 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 arbitrary, but a classification provides an initial basis for thinking about study design in pediatric patients. As discussed below, decisions about how to stratify studies and data by age need to consider developmental biology and pharmacology. Age group distinctions may have less meaning, particularly in serious diseases, such as certain solid tumors which only occur in the pediatric to young adult populations. Thus, a flexible approach is necessary to assure that studies reflect current knowledge of pediatric pharmacology. Selection of categories for study should be compound-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 the "break point" where clearance is likely to change dramatically. 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 these age groups might not correspond to those age groups presented below. Dividing the pediatric population into too many small 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 need to account prospectively for changing numbers of patients within a given category.

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The following ~~are~~ are suggested for consideration as a possible age categorization, but selection should be justified for each compound studied. Ages are defined in completed days, months, or years.

- Pre-term newborn infants
- Term newborn infants (up to 0-287 days)
- Infants and toddlers (28 days up to 243 months)
- Children (2 years up to 124 years)
- Adolescents (12 years up to 16-18 years ~~{dependent on region}~~) (The use of Tanner stages to make distinctions among maturation of adolescents may be appropriate in the study of certain diseases and conditions.

**[Note: without the clarification above the age ranges are not clear]**

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**2.5.1 Pre-term newborn infants**

The study of medicinal products in pre-term newborn infants presents specific challenges because of the unique pathophysiology and responses to therapy in this population. The complexity and ethical considerations of studying pre-term 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 pre-term infant.

The category of pre-term infants is not a homogeneous group of patients. A 25 week gestation 500 g newborn is very different from a 30 week 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. Essential features to be considered in this age range include: gestational age at birth and age after birth (adjusted age); immaturity of renal and hepatic clearance mechanisms; protein binding and displacement issues (particularly bilirubin); penetration of medicinal products into the central nervous system; unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension); unique susceptibilities of the pre-term newborn (e.g., necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity); rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; transdermal absorption of medicinal products and other chemicals. Study design issues to be considered include: weight/age (gestational and postnatal) stratification; small blood volumes (a 500 g infant has 40 ml of blood); small numbers of patients at a given center and differences in care among centers; and difficulties assessing outcomes.

**2.5.2 Term newborn infants (0 up to -287 days)**

While term newborn infants are developmentally more mature than pre-term newborn infants, many similar of the physiologic and pharmacologic principles to those discussed above need to be considered in the design of studies in term newborns also apply to the term infant. Volumes of distribution of medicinal products may be different from those in older pediatric patients because of different body water and fat content, and a 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 central nervous system with resultant toxicity. Oral absorption of medicinal products may be less predictable than in older pediatric patients. Hepatic and renal clearance is 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, newborns may be less susceptible to some types of adverse effects (e.g., digoxin-induced arrhythmias, aminoglycoside nephrotoxicity).

**2.5.3 Infants and toddlers (28 days up to 243 months)**

This is a period of CNS maturation associated with completion of myelination. During this time, the immune system is rapidly developing, and both total body growth and brain growth are rapid. Oral absorption becomes more reliable. Hepatic and renal clearance continue to mature rapidly. Clearance of many drugs on a mg/kg basis may exceed adult values by 1-2 years of age. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation that needs to be taken into consideration in the design of clinical trials in this age group.

*Clinical Investigation of Medicinal Products in the Pediatric Population*

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**2.5.4 Children (2 years up to -124 years)**

While ~~M~~most pathways of drug clearance (hepatic and renal) have matured in this age group, with clearance often exceeding adult values, ~~E~~changes in clearance of a drug may be dependent on maturation of specific metabolic pathways.

Specific strategies may need to 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. Similarly, entry into school and increased cognitive and motor skills may affect a child's ability to participate in some types of efficacy studies (e.g., FEV1, pain assessment scales). Among factors useful in determining the effects of a medicinal product on children are skeletal growth, weight gain, school attendance, and school performance. Recruitment of patients should ensure adequate representation across the age range in this category. This is important to assure a sufficient number of younger patients for evaluation. Stratification by age within this category often is unnecessary, but, it may be appropriate to stratify patients based on either pharmacokinetic and/or efficacy end-point 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 post-pubertal pediatric patients. In other cases, it may be appropriate to record Tanner stages of pubertal development or obtain biologic markers of puberty, and examine data for any potential influence of pubertal changes. Pregnancy testing and review of sexual activity may be required for post-pubertal children.

**2.5.5 Adolescents**

This is a period of sexual maturation and rapid growth; medicinal products may interfere with the actions of sex hormones and impede development or have an effect on the pubertal growth spurt. Pregnancy testing and, in relevant studies, review of sexual activity and contraceptive use become necessary.

~~This is also a period of rapid growth. 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., insulin resistance increases in diabetes mellitus, seizures may recur around menarche, frequency and severity of migraine and asthma change) and may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Non-compliance may be a special problem, particularly when medicinal products affect appearance, for example, steroids. In clinical studies, compliance checks are important. Tobacco and alcohol use and recreational use of unprescribed drugs and other substances needs to be specifically considered and monitored.

The upper age limit was arbitrarily set, and may vary 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 skillful in the care of this special population.

**2.6 Ethical Issues in Pediatric Studies**

*Clinical Investigation of Medicinal Products in the Pediatric Population*

The pediatric population represents a potentially vulnerable subgroup. Special measures ~~–should be taken–~~ are therefore needed to protect their rights of pediatric participants and to shield them from undue risk. The purpose of this section is to provide a framework to assure that pediatric studies are conducted ethically.

To be of benefit to those participating in a clinical study, as well as the rest of the pediatric population, a clinical study must be properly designed to assure the quality and interpretability of the data obtained. In addition, participants in clinical studies are expected obtain some direct or indirect health benefit from the clinical study except under very special circumstances as discussed in ICH E-6 (GCP; section 4.8.14).

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

The roles and responsibilities of IRBs/IECs as detailed in ICH E-6 are critical to the protection of study participants. When protocols involving the pediatric population are reviewed, ~~there should be~~ IRB/IEC must either include members, or experts consulted by the IRB/IEC, who are knowledgeable in pediatric ethical, clinical, and psychosocial issues or consult with experts who have such expertise.

**2.6.2 Recruitment**

Recruitment of study participants should occur in a non-coercive manner. While reimbursement and subsistence costs may be covered in the context of a pediatric clinical study, ~~other coercive inducements (financial or other) either to parents or the child must be reviewed and approved by the IRB/IEC are not appropriate.~~

**[Clarification requested if ‘coercive’ remains - what constitutes coercive?]**

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**

Pediatric study participants typically are legally dependent on their parents or /guardians who ~~take~~ have legal responsibility for their welfare and safety. No child should be enrolled in a clinical trial unless the parent(s) or guardian(s) of the child provides and fully informed written consent, should be obtained from the legal guardian in accordance with local regional laws and/or regulations and the elements of informed consent described in ICH E-6 (GCP - Consolidated Guideline) section 4.8. All participants and their parent(s) or guardian(s) should be fully informed about the study in language and terms they are able to understand. Participants should assent to enroll in a study (age of assent to be determined by IRB/IECs). 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, p~~ Participants and their parent(s) or guardian(s) should be apprised/made aware of their his/her rights to decline to participate or to withdraw from the study at any time. The participant’s wish to withdraw from a study must be respected. There may be circumstances in therapeutic studies where, in the opinion of the investigator; parents, and IRB/IEC, the welfare of the pediatric patient would be jeopardized by his or her failure their failing to participate in the study. In those circumstances the participant’s patient’s agreement or assent may be waived if the parent(s) or guardian(s) do not withdraw their consent under such circumstances. 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 capable of providing assent should not be obtained in a ~~more vulnerable~~ population or one unable to provide such assent/individual consent. For example, S studies in handicapped or institutionalized pediatric populations typically should be limited to diseases or conditions found principally or exclusively in these populations, or where the conditions in these pediatric patients would be expected to alter the disposition or pharmacodynamic effects of a medicinal product.

*Clinical Investigation of Medicinal Products in the Pediatric Population*

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**2.6.4 Minimizing Risk**

~~The protection of pediatric participants from undue injury should not be sacrificed simply because the~~  
~~However important a study may be to prove or disprove the value of a treatment, to society as a whole,~~  
~~participants may suffer injury as a result of inclusion in the study, even if the whole community benefits.~~  
Every effort must be made to anticipate and reduce known hazards. Investigators should be fully aware before the start of a clinical study of all relevant pre-clinical and clinical toxicity of the medicinal product. Minimizing risk in pediatric clinical studies requires that those conducting the study be properly trained and experienced in studying the pediatric population, including the evaluation and management of potential pediatric adverse events in the population under study.

In designing studies, every attempt should be made to minimize the number of participants, consistent with good study design, and the number of procedures. Mechanisms must be in place to assure 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 the studies are designed and conducted by investigators experienced in the evaluation and treatment of pediatric patients.

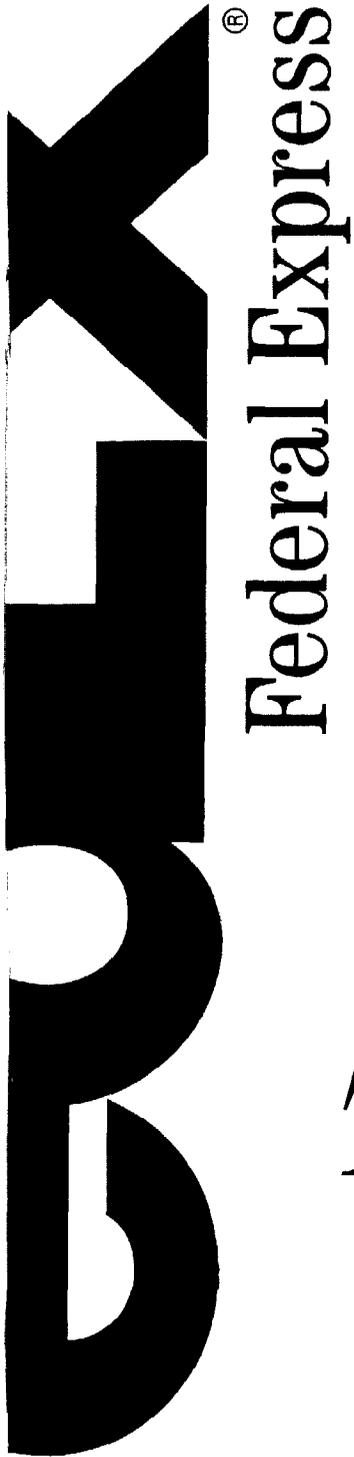
~~Protocols and investigations should be specifically designed for the pediatric population (not simply re-worked from adult protocols)~~  
should be designed to minimize discomfort and be reviewed and approved  
by a competent and experienced IRB/IEC.

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

- 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 and medical condition
- conducting studies in an familiar environment such as the hospital or clinic where they normally receive their care
- use of approaches to ~~minimizing~~ minimize discomfort of procedures, e.g.
  - topical anesthesia to place IV catheters
  - in-dwelling catheters rather than repeated venipunctures for blood sampling
  - collection of ~~PK some blood~~ PK some blood samples when routine clinical samples are obtained, as appropriate, based on dosing regimen and study design.

IRB/IEC's should consider how many venipunctures are acceptable in an attempt to obtain blood samples for a protocol, and to assure 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.

**[Clarification - is this last sentence consistent with the statement of 'waived refusal' in section 2.6.3?]**



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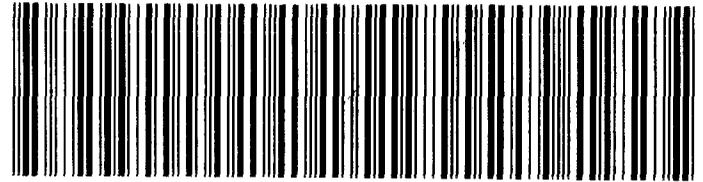
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