European Regulatory Authorities and Pediatric Labeling

Elisabeth Autret, MD

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN CHILDREN

The Need for Medicinal Product Testing in Children

Children should not be given medicines that have not been evaluated adequately for use in that age group. There is a responsibility, shared by applicants and the appropriate authorities, to ensure that children have timely access to safe and effective medicines that have accurate, scientifically justified prescribing information. Applicants are encouraged to investigate the safety and efficacy of a product in children, if it is likely to be of therapeutic benefit in this age-group, and to develop suitable formulation, even if use is likely to be small.

However important a clinical trial may be to prove or disprove the value of a treatment, individual members of one or both of the groups—subject or control—can suffer injury as a result of inclusion in the trial, even if the whole community benefits. As with adults who participate in clinical trials and who understand the issues involved in giving their informed consent, consent should be obtained from the legal guardian of children in accordance with national legislation. Children should be fully informed about the trial in language and terms they understand and, if able, should personally sign and date the written informed consent. The child should be made aware of his/her rights to decline to participate. The child’s wish to be withdrawn from a study must be respected.

These measures should be applied in conjunction with 1) part 4 of Directive 75/318/EEC, as amended, which requires “... details concerning patients who may be at increased risk”; the CPMP/ICH guideline for good clinical practice; and 3) the CPMP guideline on biostatistical methodology in clinical trials in applications for marketing authorizations for medicinal products.

These measures are intended to assist applicants with specific problems presented by medicinal product testing in children. The child should stand to obtain some direct benefit from the clinical trial, except under very specific conditions, although it is not appropriate to offer financial or other inducements to parents, guardians, or children to participate in clinical trials. However, they may receive reimbursement for their costs, including those for travel and subsistence.

Scientific Considerations

Adequate evaluation of medicinal products for use in children cannot be conducted in adult studies because there are physiologic differences between children and adults, and because children suffer from different diseases than adults or show a different natural history for the same disease.

The following are some specific age-dependent differences.

Pharmacokinetic Differences

These differences include reduced protein binding, slow elimination attributable to immaturity of both metabolic pathways and renal functions, and unpredictable absorption in both term and preterm infants at birth and in the first weeks of life. In later infancy and early childhood, faster rates of metabolism may necessitate the administration of higher doses per unit of body weight or surface area than in adults to obtain identical plasma levels and clinical effects (examples are phenytoin and digoxin). In addition, faster rates of elimination may necessitate more frequent administration.

Altered Pharmacodynamic Responses

At the early stages of development, some receptor functions, effector systems, and homeostasis mechanisms, although adequate for this age, are not developed sufficiently to permit the desired pharmacologically induced change of organ or tissue function.

Process of Growth and Development

Normal growth and development, both physical and mental, can be influenced adversely by medicinal products (eg, retarded growth with corticosteroids, impaired educational progress with anticonvulsant therapy). Outcomes depend on the timing and the duration of exposure and are not always reversible.

Specific Pathology

Children may need medicinal products for diseases that differ from those in adults because of increased frequency (eg, otitis media, invasive bacterial infections); increased severity (eg, diarrhea); or different natural history (eg, acute leukemia, nephrotic syndrome, or arteriosus, vitamin K deficiency bleeding, inborn errors of metabolism, growth hormone deficiency, pediatric tumors).

For all these reasons, the effects of many medicinal products on children may differ considerably from
effects observed in adults, even when dosage has been adapted to body weight or body surface area. Thus, the adult experience with the medicinal product may not predict accurately the minimal effective dose, maximum titrated dose, therapeutic effect, or adverse reaction in the child.

The Need to Minimize Risks

Every effort must be made to reduce known hazards, and investigators should be fully aware, before the start of a clinical trial, of all relevant preclinical and clinical toxicity that has been seen in the development of the medicinal products.

In general, safety studies should be conducted first in animals as a part of the routine preclinical development, then in adults and, finally, in younger patients. The possibility of polymorphic metabolism of the medicinal product should be considered. This sequential approach should identify most toxicity problems, but children of certain ages may have adverse reactions not seen in adults (eg, retinopathy of prematurity, kernicterus, gray syndrome of the newborn with chloramphenicol, tooth discoloration with tetracycline). However, there are circumstances in which parallel evaluation in adults and children is acceptable or even preferable.

As is the case for trials in adults, studies should be designed efficiently using the minimum numbers required to provide statistical significance, especially in pivotal studies. A poorly designed trial is unethical. It may provide uninterpretable results and may require additional studies, thereby exposing more children.

All staff should be aware of the usual procedure to stop the study at the earliest possible time if a hazard arises. In a blinded, controlled study, there must be no delay in breaking the code.

Children should not be exposed knowingly to doses of unneeded products. However, before the start of any investigation of a medicinal product in children, the sponsor and the investigator(s) should agree to emergency protocols so that appropriate studies (eg, pharmacokinetic) can be initiated promptly in the unusual circumstances of accidental overdose or intoxication, or when unusual administration or dose of a medicinal product is required by a child, although such use and dosage schedules have not been evaluated fully.

Pharmaceutics companies are encouraged to provide facilities for such emergency assay of the medicinal product, and clinicians should report the results promptly to the appropriate authorities.

The Need to Minimize Distress

A widespread concern exists that trials may involve repeated invasive procedures that may be painful or frightening to a child. This is unlikely if the trials are designed and conducted by investigators experienced in the treatment of children. Trials should not be designed or conducted by those inexperienced in working with children.

Protocols and investigations should be adapted for children and approved by a responsible research ethics committee, which should ensure that trials are designed and conducted in a manner that minimizes pain, discomfort, and fright, and that includes only the number and extent of examinations and invasive procedures scientifically and clinically essential.

Classification of Children by Age and Maturity

Children respond to medicinal products differently, depending on their physiologic and anatomic stage of development. There is wide variation among individuals in terms of weight, surface area, and stage of development (maturity in the preterm infant, stage of puberty in the adolescent) for a given age. Nonetheless, classification of children by age group is useful for evaluation of medicinal products, because age is almost accurately known and, for a given population, an adequate sample defined by age is likely to be sufficiently representative for extrapolation of trial results to prescribing information for that population.

Because of the variation among individuals, standardization of age groups is inevitably arbitrary. However, the definition of generally accepted, easily memorable, age groups provides important advantages in terms of assessment and monitoring of efficacy and safety for applicants, appropriate authorities, prescribers, dispensers, and patients.

When a clinical trial is to be performed in children, it is usually desirable to begin with older children before extending the trial to younger children and then to infants. Evaluation should be made in the appropriate age group(s) depending on expected use. The extent and type of the studies needed depend on the current knowledge of the medicinal product and the possibility of extrapolation from other age groups.

Appropriate formulations are required for different age groups. For example, oral suspensions are preferable for younger children. Also, younger children need special devices when taking medicinal products by inhalation.

The following age groups are intended as a guide, considering that individual growth and development will vary from the norm. They represent the development of a so-called average child. Additional consideration must be given to sex differences and to the need to correlate data relating to medicinal product plasma levels, therapeutic dose, adverse reactions, weight, surface area, and maturity/stage of development. Ages are defined in completed weeks, months, or years.

Preterm Newborn Infants (<36 Weeks’ Gestation)

Note that the definition is based on estimated gestational age (maturity) at birth, and not birth weight. A distinction should be made for low birth weight infants as to whether they are immature or growth-retarded. If immature, dosage may require modification according to gestational age.

Term Newborn Infants (0–27 Days)

Newborn infants, both term and preterm, show an increased sensitivity to pharmacological agents. The newborn body composition differs from that of older
infants (eg, more water, limited energy stores), particularly in the case in preterm infants. The newborn period is characterized by rapid renal, hepatic, enzymatic, and homeostatic development. Significant changes occur, affecting glomerular filtration and tubular secretion. Preterm infants have poorly developed regulatory mechanisms and are at risk for respiratory depression.

Other potential hazards include enhanced medicinal product penetration to the brain; the possibility of rapid transdermal medicinal product absorption; a very high body surface area to weight ratio; a rapid variation with age of protein binding of medicinal products and changes in bilirubin kinetics; and difficulty in identifying the nature and mechanisms of toxicity.

Infants and Toddlers (28 Days–23 Months)

This is a period of CNS maturation associated with the completion of myelination. During this time immune systems develop, and both overall growth and brain growth are rapid. Potential for drug metabolism cannot be extrapolated directly from body weight because of differences in the proportions of different tissues in relation to weight (for example, the ratio of liver volume to unit body weight).

Children (2–11 Years)

Children in this age group reach several important milestones of psychomotor development that could be affected adversely by CNS-active drugs. Somatic growth and development proceed at a constant rate. In this age group, a number of factors can be useful in determining the effects of a medicinal product on such areas as skeletal growth, weight gain, school attendance, and school performance.

There are important pharmacokinetic differences in this group that must be considered to avoid therapeutic failures. Although absorption, distribution, and excretion rates in this age range can be extrapolated more confidently from adult data, metabolism per unit weight continues to differ from that seen in adults.

Adolescents (12–17 Years)

This is a period of sexual maturation when a medicinal product may interfere with the actions of sex hormones and impede development. Pregnancy testing and, in relevant trials, review of sexual activity and contraceptive use become necessary.

This also is a period of rapid growth. Drugs or illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt by changing the pattern of growth that may affect final height.

Many diseases also are influenced by the hormonal changes that occur in puberty (eg, insulin resistance increases in diabetes mellitus; seizures may recur around menarche; migraine and asthma may change in frequency and severity), and thus may influence the results of clinical trials.

Within this age group, children are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when drugs, such as steroids, affect appearance. In clinical trials, compliance checks are important, and investigators must be aware of and prepared for the possibility of intentional overdose. Children involved in recreational use of unprescribed drugs need to be specifically excluded.

Children of the same age display wide variations in height, weight, and psychosocial and sexual development, and there are significant differences between the sexes in these factors.

Categorization of Evaluation of Medicinal Products in Children

There are four principal categories of medicinal products in which pediatric testing is necessary. The categories of clinical trial methodology should be adapted specifically to the disease and to the therapeutic class. Note should be taken of guidelines that already exist for certain therapeutic classes and/or for medicinal products intended for long-term use in adults. These can be adapted for pediatric use where appropriate, taking into account the features of the disease in childhood. Clinical trials also should demonstrate that the dosage form is appropriate for administration to the child.

Medicinal Products for Diseases Affecting Children Exclusively

Trials in children are essential to demonstrate efficacy and show the safety profiles of the product.

Medicinal Products to Treat Diseases That Primarily Affect, are of Particular Gravity, or Have a Different Natural History in Children

Clinical trials in children are needed at an early stage in clinical development to confirm the efficacy of the product and to determine the appropriate conditions of use.

Medicinal Products to Treat Disease Occurring in Adults and Children, for Which no Treatment Exists

Clinical trials in children are needed at an early stage in clinical development, usually as soon as there is evidence of efficacy in adults. The purpose of pediatric trials is to determine a safe and effective dosage schedule in the different age groups and to detect unforeseen and unique effects in childhood.

Medicinal Products to Treat Disease Occurring in Adults and Children, for Which Treatment Exists

These medicinal products will already have a background of exposure in adults. The purpose of pediatric trials is to demonstrate comparable efficacy, safety, or convenience in children compared with existing treatment; to determine safe and effective dosage schedules in the different age groups; and to detect unforeseen and unique effects in childhood.

Timing of Clinical Trials in Children in Relation to Studies Conducted in Adults

General Principles

The pediatric dosage regimen may be determined at different stages in the evaluation of a medicinal
product in adults, according to the disease (severity, specificity), the degree of innovation of the medicinal product, potential risks, and therapeutic alternatives.

If a product is being developed initially for the treatment of a childhood-specific illness, the clinical development may start in children before any previous adult exposure. In other circumstances, relevant safety and tolerability data from previous adult exposure are needed before proceeding with studies in children. In most cases, reasonable evidence of efficacy in adults also is needed to justify these studies in children. In all cases, pediatric studies nevertheless should be conducted as soon as the medicinal product profile allows, to avoid an excessive delay in obtaining marketing authorization for children compared with adult marketing authorization.

Timing of Specific Categories of Medicinal Products

Medicinal Products for Diseases Affecting Exposure to Adults

Trials in children can start before any previous adult human exposure.

Medicinal Products to Treat Diseases That Primarily Affect, Are of Particular Gravity, or Have a Different Natural History in Children

Clinical trials in children are needed at an early stage in clinical development, after demonstration of safety and reasonable (phase I/II) evidence of efficacy in adults.

Medicinal Products to Treat Disease Occurring in Adults and Children, for Which There is No Current Treatment

Clinical trials in children are needed at an early stage in clinical development, after demonstration of safety and reasonable (phase I/II) evidence of efficacy in adults.

Medicinal Products to Treat Disease Occurring in Adults and Children, for Which Treatment Exists

Clinical trials in children will follow completion of adult phase III trials.

Nature of Clinical Trials in Children

As indicated above, trials are considered necessary in children for at least four categories of medicinal products. The kind of trials and the extent of information needed for registration depend on the category and the information already available.

Pharmacokinetic Studies

Objectives

Medicinal product blood levels can provide the basis for determination of the dosage schedule, in particular for those medicinal products for which serum levels can be readily related to the pharmacologic or therapeutic effects. Initial titrating doses may be estimated based on body weight/surface area from an extrapolation of adult data. Radiolabeled studies are not appropriate in children.

All studies should lead to an accumulation of data that account for the absorption, distribution, metabolism, and excretion of the medicinal products. Identification and quantification of the principal metabolites of the medicinal product permit comparison with the elimination pattern of adults. If major differences exist, such studies serve as a warning of possible adverse effects and should lead to attempts to identify the unique or unusual pathway of metabolism in the immature patient. Plasma protein binding should be studied, at least in newborns and infants.

Each age group requires studies of varying degrees of depth and completeness appropriate to the medicinal product and the intended use. Not all medicinal products need to be subject to full investigations, but judgment should be exercised about requirements for clinically relevant data.

Methods Appropriate for Trials in Children

The development of appropriate methods for using small blood volumes (eg, radioimmunoassay, high performance liquid chromatography, mass spectrometry, all of which use as little as 20–100 μL) is particularly important. Urinary determinations also are useful (eg, for assessment of biologic half-life and exploration of metabolism); however, collections are not easy (incomplete emptying of the bladder and loss of urine). Determinations of medicinal substances in saliva have been used, but do not always provide accurate information and require the cooperation of the patient for collection. Nevertheless, this can be a useful noninvasive method of sample collection provided there is a good relationship between salivary and plasma/blood concentration. Population pharmacokinetic methods may provide a means to acquire pediatric data and reduce the burdens on individual patients.

Clinical Studies

These studies demonstrate or confirm that the medicinal product is effective and without unforeseen toxicity, and that the proposed dosage schedule is appropriate in terms of efficacy and safety.

An essential requirement is that pediatricians and/or pediatric pharmacologists must be involved in the trial design and conduct. Clinical trial methodology is children is not fundamentally different from that in adults in design, statistical analysis, or trial management. Protocols should be adapted to 1) the therapeutic class; 2) the clinical situation; 3) the stage of maturity of the child; and 4) the proposed objectives of treatment (eg, relief of symptoms, prevention of death).

Design

Controlled Studies

Absolute efficacy can only be established reliably by demonstrating superiority to placebo in a placebo-controlled trial. This is justifiable if a suitable reference medicinal product is not available, if information on the absolute effect is needed (eg, pertussis vaccine), or if the efficacy of existing therapies is in doubt. Placebo-controlled trials may also be necessary in cases in which the placebo effect is known to be high or very variable (eg, pain control, hay fever).

When placebo-controlled trials are considered unethical, one acceptable alternative is to demonstrate superiority to an established therapy. The demonstration of comparable efficacy to an established standard therapy also may be acceptable when no other options are available, provided the trials con-
form to the rigorous standards required under the circumstances.

**Uncontrolled Studies**

In certain cases (eg, rare diseases), controlled studies may not be possible. However, the reason for conducting uncontrolled studies should be justified. After initial exposure of an age group to the medicinal product on a trial-and-error basis, a suitable dosage schedule should be confirmed using objective criteria. Initially, such studies will rely on historical comparisons.

**Selection of Subjects**

As much as possible, the groups should be homogeneous with respect to 1) the state of maturity; 2) weight/height/surface area; and 3) other factors such as nutritional status or concurrent therapy.

Whether studies should be limited to specific age groups or should include several age groups and stratify for each will depend on whether the natural history of the disease under study and the expected response to the test compound are different in the different age groups. As in all clinical trials, the numbers of patients to be included in each age group will be determined by the study’s statistical design, taking into account the disease incidence in each age group.

**Criteria for Efficacy**

Current clinical and nonclinical data should be considered with reference to accepted norms for the age groups (eg, profile of blood pressure levels in children). Other supportive criteria also may be useful, such as the need for additional therapy, as well as participation in activities, school performance, growth and weight gain, provided their assessment is standardized during long-term treatments.

Efficacy endpoints may differ between adults and children. For example, small children with asthma cannot be assessed by measurements of peak flow rate or FEV₁.

**Safety**

Premarketing studies should include reports of adverse reactions manifested at the time of the study. The method of reporting of adverse effects, whether by spontaneous or elicited reports, by questionnaire, or by other means, must be stated clearly and appropriate for the age groups being studied.

Depending on the nature of the medicinal product and its indications, long-term studies also may be required to determine possible product-related effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development. Postmarketing studies will confirm the safety profile of the medicinal product.

**Scientific Data Required Before Medicinal Product Trial**

**Testing in Children**

When pediatric patients are included in clinical trials, results from previous adult human exposure would usually represent the most relevant safety data and, except in unusual circumstances, generally should be available before pediatric clinical trials are begun. In all cases, in addition to appropriate repeat-dose toxicity studies, all reproductive toxicity studies and the standard battery of genotoxicity tests should be completed before the initiation of trials in pediatric populations. Juvenile animal safety studies should be considered on an individual basis.

The need for carcinogenicity testing should be addressed before long-term exposure in pediatric clinical trials, taking into account the duration of treatment and/or cause for concern.

**Presentation of Clinical Trials in Children to Appropriate Authorities**

Unless the use of the medicinal product in children is clearly inappropriate, appropriate authorities will expect the presentation of clinical trials in children. Data should be generated before marketing authorization, not only when a medicinal product is to be used wholly or primarily in children, but also, for reasons of public health, when 1) a new medicinal product is likely to be used in children because of its uniqueness (a novel therapeutic effect that is particularly applicable to a pediatric disease or a convenient dosage form); and 2) a medicinal product represents a major therapeutic advance and is likely to be used in children.

Lack of data in children in any of the circumstances noted above should be justified by the applicant at the time of submission for marketing authorization. In assessing such justification, the appropriate authorities will take into account the timing of clinical trials in children in relation to studies conducted in adults and any ongoing or planned trials in children.

In other circumstances, there should be a recommendation that the medicinal product should not be used in children until additional data become available. The reason for the advice should be stated in the product specifications, together with any information that may be available on use in children.

Any such statement(s) regarding children in the product specifications should be transparent and reflect the available data.

**Postmarketing Experience**

Medicinal products that are used in children should undergo postmarketing surveillance according to the existing guidelines. The postmarketing period provides an opportunity to address the problem of variations in terms of efficacy and safety, both intra- and interindividual, in the different age groups, particularly in preterm and term newborns and in older infants.
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