DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00D–1223]

International Conference on Harmonisation; E11: Clinical Investigation of Medicinal Products in the Pediatric Population

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guidance entitled ''E11: Clinical Investigation of Medicinal Products in the Pediatric Population.'' The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guidance sets forth critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population. The draft guidance is intended to encourage and facilitate the timely development of pediatric medicinal products internationally.

DATES: Submit written comments by May 30, 2000.

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Copies of the draft guidance are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573. Single copies of the draft guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852, or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: M. Dianne Murphy, Center for Drug Evaluation and Research (HFD–2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In October 1999, the ICH Steering Committee agreed that a draft guidance entitled ''E11: Clinical Investigation of Medicinal Products in the Pediatric Population'' should be made available for public comment. The draft guidance is the product of the Efficacy Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Efficacy Expert Working Group.

In accordance with FDA's good guidance practices (62 FR 8961, February 27, 1997), this document is being called a guidance, rather than a guideline.

The draft guidance sets forth critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population. The draft guidance addresses the following clinical study issues: (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, efficacy, safety); (4) age categories for studies; and (5) ethics of pediatric clinical investigation. The draft guidance is not comprehensive, but is intended to be used in conjunction with other ICH guidances and documents from regional regulatory authorities and pediatric societies. The draft guidance is intended to encourage and facilitate the timely development of pediatric medicinal products internationally.

This draft guidance represents the agency's current thinking on clinical investigation of medicinal products in the pediatric population. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft guidance on or before May 30, 2000. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm or at http://www.fda.gov/cber/publications.htm.

The text of the draft guidance follows:

E11: Clinical Investigation of Medicinal Products in the Pediatric Population [1]

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

[1] This draft guidance represents the agency's current thinking on clinical investigation of medicinal products in the pediatric population. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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 on the following topics include relevant information impacting on pediatric studies:

- 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
- 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 for studies; 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. Major advances in formulation chemistry and in pediatric study design ensure that this goal can be achieved.

Drug development programs should include the pediatric patient population when a product is being developed for a disease/condition in adults and it is anticipated the product will be used in the pediatric population. The ethical imperative to obtain knowledge of the effects of medicinal products in pediatric patients has to 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.

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 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, which may be influenced by regional public health and medical needs, is discussed in section 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.

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
- 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 age ranges of patients likely to be treated with the medicinal product
- Unique pediatric (developmental) safety concerns about the medicinal product, including any nonclinical safety issues
- Potential need for pediatric formulation development

Of these factors, 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 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 come ordinarily from adult human exposure. Repeat-dose toxicology and reproductive toxicology/genotoxicology 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 (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 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 needs to 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 compatibility 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. Some excipients (e.g., benzyl alcohol) may be toxic, particularly 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 will help ensure that appropriate formulations are available for the pediatric population everywhere (see ICH guidances on topics Q1 through Q3).

2.3 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 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 from 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

In this case, medicinal product development should begin early in the pediatric population, following initial safety data and reasonable evidence of potential benefit. Pediatric study results should be part of the marketing application data base. 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 the medicinal product will be used in pediatric 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 postmarket experience in adults. Companies should have a clear plan for pediatric studies and reasons for their choice of when to initiate them. 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 application submission, but more would be expected after marketing. Even for a nonserious disease, if the medicinal product represents a major therapeutic advance for the pediatric population, studies should begin as early in development as possible, and the submission of pediatric data would be expected in the application. Lack of data should be justified in detail. As the development of many new chemical entities is discontinued 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 that will be of no benefit. Thus, it is important to carefully weigh risk/benefit and therapeutic need in deciding when to start 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 that could impact the extrapolation of data to other regions should be considered.

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 all 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. 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. 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 pharmacokinetic 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 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 use 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. A PK/PD approach could avoid the need for clinical efficacy studies.

For certain products, it may be useful 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 need to be conducted. Similarly, in situations where a pharmacokinetic approach is not applicable, such as for topically active products, studies may need to include clinical endpoints or appropriate alternative assessments.

2.4.1 Pharmacokinetics

Pharmacokinetic studies generally should be performed to support formulation development, determine pharmacokinetic parameters in different age groups to support dosing recommendations, and 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.

Pharmacokinetic studies in the pediatric population differ from most adult PK studies in that they are generally conducted in patients with the disease. This may lead to higher intersubject variability, 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 often be sufficient to ascertain correct dosing. This can be corroborated, if indicated, by sparse population sampling in multidose clinical studies. Any nonlinearity 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. 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 milligrams (mg)/kilograms (kg) up to a maximum adult dose. While dosing on a mg/square meter 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., medications with a narrow therapeutic index, such as those used in oncology), surface-area-guided dosing may be necessary, but with extra care to ensure 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 (IRB's/IEC's) generally establish the maximum amount of blood (usually on a milliliters (mL)/kg or percentage of total blood volume basis) that may be taken for 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 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
- 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 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

— The use of indwelling catheters, etc., to minimize distress as discussed in section 2.6.5.

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 unique features 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. 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 preterm and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older pediatric patients and calling for novel methods for outcome assessment.

2.4.3 Safety

Reporting requirements for adverse events, as described in ICH guidances on E2 topics and ICH E6, apply to pediatric studies. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Unexpected 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 than matured adult organs, 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 needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.

2.4.4 Postmarketing Experience

Normally the pediatric data base is limited at the time of approval. Therefore, postmarketing and long-term followup 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 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. Thus, a flexible approach is necessary to ensure that studies reflect current knowledge of pediatric pharmacology.

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 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 the age groups might not correspond to the categories 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 should prospectively take into account changing numbers of patients within a given age category.

The following is suggested as a possible categorization. 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 to 18 years (dependent on region))

2.5.1 Preterm Newborn Infants

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

The category of preterm 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. Essential features to be considered in this age range 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/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 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., digoxin-induced arrhythmias, aminoglycoside nephrotoxicity).

2.5.3 Infants and Toddlers (28 days to 23 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 pathways continue to mature rapidly. Clearance of many drugs on a mg/kg basis may exceed adult values by 1 to 2 years of age. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable interindividual 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. 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 ensure 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 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 to 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. 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). 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 should 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

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 obtain some direct or indirect benefit from the clinical study except under the special circumstances discussed in ICH E6 (''Good Clinical Practice,'' 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 noncoercive manner. While reimbursement and subsistence costs may be covered in the context of a pediatric clinical study, coercive inducements (financial or other), either to the parents or to the child, are not appropriate.

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

Pediatric study participants are dependent on their parents or guardians who take legal responsibility for the participants' welfare and safety; fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants 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's/IEC's). 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. A 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 a pediatric patient would be jeopardized by his or her failing to participate in the study; the patient's agreement or assent may be waived under such circumstances. Emancipated or mature minors (as 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 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 where 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 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 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, andfood appropriate for age
- Conducting studies in a familiar environment such as the hospital or clinic where participants normally receive their care
- Using 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.

Dated: April 5, 2000.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 00–9064 Filed 4–11–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Cardiovascular and Renal Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration