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GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS IN INFANTS AND CHILDREN

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Comments on the contents of this publication are invited and should be addressed to the following office:

Martha M. Freeman, M.D.
Assistant to the Associate Director
for New Drug Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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ABSTRACT

This comprehensive guideline for "General Considerations for the Clinical Evaluation of Drugs in Infants and Children" has been excerpted from the report prepared under contract to the FDA by the American Academy of Pediatrics through its Committee on Drugs and entitled "General Guidelines for the Evaluation of Drugs To Be Approved for Use During Pregnancy and for Treatment of Infants and Children." (1974) The initial discussion pertains to factors affecting both safety and efficacy of investigational drugs in immature subjects in general. The second portion details the age specific factors which require particular consideration according to developmental state, from the fetus through 18 years of age.

Emphasis is placed on the need to elucidate unexpected toxicities which may result from immature physiologic and metabolic mechanisms, as distinct from those predictable from the drug's known pharmacologic properties. Research needs are identified in terms of special techniques required to study drugs adequately in young subjects. Flexibility in approach is essential to permit the necessary modification according to the nature of the drug and its intended use, and the age of the patient.

FOREWORD

This booklet, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children," is excerpted from the more expansive report, "General Guidelines for the Evaluation of Drugs To Be Approved for Use During Pregnancy and for Treatment of Infants and Children" which was prepared, under contract to the FDA, by the Committee on Drugs of the American Academy of Pediatrics (AAP). The Committee's report was published by the AAP in July 1974 and has been widely circulated.

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS IN INFANTS AND CHILDREN

I. GENERAL PRINCIPLES

A. INTRODUCTION AND OVERVIEW

The booklet entitled "General Considerations for the Clinical Evaluation of Drugs" contains much information which is applicable to drug testing in children and it should be considered a companion piece to this booklet.

To facilitate approval of new drugs for use in children testing should be related to the anticipated duration of usage and to the size and age of the pediatric population likely to be exposed to the new drug. Emphasis should be placed on elucidation of unexpected toxicity, not simply collecting examples of the types of toxicity predictable from knowledge of the pharmacologic properties of the drug. New and innovative forms of in vitro and in vivo testing should be employed because new agents developed today, which may exhibit some of the same forms of toxicity responsible for therapeutic catastrophies of the past, may not be identified as such by current testing procedures.

The design of studies must be flexible to recognize the need for evaluation of a new drug or substance for the treatment of rare diseases or diseases which are unique to the pediatric age group. In these circumstances, special considerations may include an abridgement of the usual requirements for safety and efficacy. Such abridgement should be considered when the use of the drug is limited to a few patients, particularly patients suffering from a disease for which no alternate therapy is available. In addition, an investigator concerned with such patients should be allowed considerable latitude to administer various substances, particularly naturally occuring amino acids, cofactors, and vitamins without extensive preclinical studies. Furthermore, if no appropriate animal model for a disease condition exists, and if efficacy is readily demonstrable (e.g. certain seizure patients), early efficacy studies in children are appropriate.

B. FACTORS AFFECTING BOTH SAFETY AND EFFICACY

1. Methods

Adequate methods for determination of the drug and its major metabolites (especially those which are pharmacologically active) in biologic fluids (especially serum and optimally in tissues) should be developed during preclinical or early clinical (phase I and II) testing. The particular method obviously will depend on the chemical nature of the drug, expected concentrations in serum, etc., but it should not require administration of radiation emitting substances. Assays based on techniques such as radioimmunoassay, gas-liquid chromatography, and competitive protein binding are at present the most likely to achieve the desired degree of accuracy, sensitivity, and reproducibility. Use of stable isotopes is a method of great promise, although the initial cost of equipment may be prohibitive except in research centers and the National Center for Toxicologic Research. The administration of radioisotopes to children is not to be generally condemned, but it should be avoided except

under special circumstancs. Such techniques are of great value and entirely appropriate for special studies under appropriate circumstances. For example, use of tracer amounts of labeled (^{14}C, ^{3}H) amino acids, glucose, or other intermediary metabolites may be invaluable for defining metabolic diseases, and similar employment of labeled drugs could conceivably be employed. Use of isotopes, other than ^{14}C and ^{3}H, which have short half-lives and low-energy emission equivalent to a conventional chest- x-ray offer considerable promise and should be employed whenever possible.

The small sample volume obtainable, particularly from small infants, is a critical factor in the development of appropriate methods, particularly when multiple samples are required. This is not a prohibitive requirement and should not be used as an excuse to avoid development of appropriate assay procedures. Radioimmunoassays for drugs such as digoxin or diphenylhydantoin have been developed which utilize as little as 20 to 100 microliters of serum. The development of appropriate methods for determination of serum levels is particularly important for those drugs in which serum levels can readily be related to pharmacologic or therapeutic effects. In these instances, determination of serum levels is the key to studies of dose, dose interval, bioavailability (when coupled with urinary excretion), apparent volume of distribution, etc.

Methods should be continually reviewed, revised, and updated with the goal of developing methods appropriate for routine use in laboratories cooperating with the investigator, and such assays should become sufficiently standardized and simplified so they are within the practical capability of the clinical laboratory of any large hospital. Moreover, modifications should be directed toward identification and quantification of the principle metabolites of the drug, so comparison may be made with the elimination pattern of adults. If major differences exist, such studies would serve as a warning of possible adverse effects and should lead to attempts to identify the unique pathway of metabolism in the immature patient.

With certain categories of drugs - the so-called "hit and run" agents, such as the cytotoxic drugs, certain enzyme inhibitors, storage granule depletors, etc. - assays of serum levels are of little or no value. Therefore, requirements for assay methodology may be relaxed or waived. Other appropriate assays of biologic effect should be developed for these agents. For example, inhibition of incorporation of tritiated thymidine into white blood cells might be used as a measure of the effect of certain cytotoxic agents. Antibiotics and certain other chemotherapeutic agents have special requirements and methods for estimation of effective serum levels. Bioassay techniques are entirely appropriate as long as the method is scaled down to the small sample volume of pediatric patients. Techniques employing the patient's own pathogen as the test organism should be available for the use of clinical laboratories engaged in phase II and III trials.

2. Studies of Absorption, Distribution, Metabolism and Excretion (ADME)

Studies with varying degrees of depth and completeness, appropriate to the drug and its intended use, are essential for each age group and are described in detail in the respective sections. In general, the preclinical and early clinical phases should lead to accumulation of data which account in a major way for the disposition of the drug. Not every metabolite may be identified, and the intimate details of each of the ADME phases will not be elucidated. Judgment must be exercised about requirements for data which are clinically relevant, and not all drugs should be subjected to full investigation. However,

the following data should be available for drugs which will be administered orally in divided doses for courses of one week or longer:

a. Absorption: From the physical nature of the drug and its pKa the influence of changes in pH of the stomach and intestine on the ionization and thus the absorption of the drug can be predicted and verified. When appropriate, the approximate percentage of a single oral dose absorbed should be determined. If easily studied and when of possible clinical importance, the area of the gastrointestinal tract where the drug is absorbed (i.e., stomach, terminal ileum, etc.) may provide useful information in predicting drug interactions and alterations in absorption in disease states.

b. Distribution: Binding to plasma proteins (affinity and percent bound at therapeutic blood levels), whether albumin, globulins, or special carrier proteins, and the percent of total serum concentration which is "free" should be determined. Distribution and particular propensity for accumulation or fixation to certain tissues (for example, tetracycline in bone and teeth) in developing and mature animals should alert reviewers of possible forms of toxicity so appropriate additional studies can be requested. Apparent volume of distribution may be useful in designing dosage regimens. Studies of dialyzability may be useful in developing recommendations for the management of overdoses and accidental ingestions.

c. Metabolism: The pattern of metabolites and the biotransformation reactions involved - that is, hydroxylation, demethylation, glucuronidation, etc. - should be known from studies in man. Requirements for toxicity studies in immature animals (especially rodents) should be limited, if possible, to a species for which experimental evidence has established a similarity by immature humans to the handling of the agent being tested.

3. Bioavailability

An important influence on studies of safety and efficacy is the bioavilability of different formulations and of different manufacturers' products. When the dosage form constitutes a new chemical entity, appropriate studies must be conducted in adults before children are exposed. The exact and total constituents of the final dosage form should be known. Studies of bioavailability should include, but not be limited to, determination of serum levels and the time of peak levels after a single dose. Total absorption is usually best determined by quantitative determination of the urinary excretion of the drug and its principal metabolites. Because of differences in pH, gastric emptying time, intestinal motility, etc., differences in bioavailability, especially between newborn infants and adults, should be duly considered and investigated when appropriate. Moreover, when changes in gastric or intestinal pH, flora, or motility might be reasonably anticipated to differ from normal because of disease or other factors, additional studies are indicated. Studies of bioavailability often may be sufficiently covered in conjunction with studies of absorption, efficacy, etc., and need not demand independent investigations.

The possible toxicity or influence on the pharmacologic properties of the drug by the vehicle and/or other components of the formulation (stabilizers, excipients, etc.) must be considered. This results from the fact that many drugs tested in the form of tablets or capsules in adults will be administered as suspensions, solutions, or elixirs to infants and children. Moreover, the vehicle or solubilizing chemicals in parenteral preparations must be considered as a possible source of uniquely toxic agents, particularly for newborn infants.

4. Drug Interactions

Interactions between drugs occur in a variety of ways, ranging from physiochemical incompatibilities to opposing or synergistic pharmacologic effects. Preclinical and in vitro testing can be expected to detect most interactions, particularly when coupled with phase I and II testing in adults. However, especially in neonates, age-dependent differences in pharmacokinetics may result in unique interactions. For appropriate review of a new agent, the types of drugs which may be used in conjunction with the proposed agent for the same disease or condition at different ages should be considered to completely evaluate possible drug interactions.

Physicochemical interactions will probably be detected in early work with the new drug. Of particular concern in pediatric usage would be interactions which might interfere with the absorption or action of vitamins, trace minerals, essential amino and fatty acids, or other constituents of infant formulas and other dietary sources.

Physiologic or pharmacologic actions which might further impair the normally limited capacity of the neonate to metabolize and/or excrete drugs would be of particular concern. Specifically, inhibition of or competition for hepatic biotransformation reactions occurring via the mixed-function oxidase system and/or the glucuronide conjugating system, or decreases in glomerular filtration rate or tubular secretion can be predicted to have important consequences for the newborn.

Further interactions of particular concern to newborn infants relate to bilirubin, particularly with drugs administered near term, at delivery, or directly to the newborn. Binding to albumin with displacement of bilirubin and enhanced neurotoxicity is known to occur with a number of anionic compounds. Other factors (e.g., hypoxemia and acidosis) have also been reported to increase the potential toxicity of bilirubin. Moreover, binding by drugs might interfere with the transport and action of endogenous substances other than bilirubin (cortisol, thyroxin, fatty acids, etc.) and with the binding of other drugs.

5. Enzyme Induction

The importance in pediatrics of the induction of hepatic drug-metabolizing enzyme activity by exposure to drugs and chemicals is unclear at present. Three hundred or more drugs and chemicals are known to produce marked increases in liver size, proliferation of smooth endoplasmic reticulum, and increases in the specific activity of mixed-function oxidase and glucuronyl transferase enzymes in experimental animals. In clinical studies, small changes in serum concentrations and half-life for a few drugs have been reported in adults, although some negative reports have appeared.

Almost nothing is known about "inducibility" at various ages in man. Decreases in serum bilirubin levels have been reported in congenital nonhemolytic jaundice and in normal infants with "physiologic" jaundice treated with phenobarbital, nikethamide, and DDT. Increased smooth endoplasmic reticulum in hepatocytes and increased NADPH cytochrome c reductase (a microsomal enzyme) activity have been shown in infants treated with phenobarbital. Similarly, increased glucuronidation of salicylamide has been reported. Thus, the infant can respond to exogenous "inducing" agents although the details of the process and the extent and the clinical importance of this reponse remain unclear.

When induction is considered relevant, noninvasive types of studies, such as antipyrine half-life as determined by salivary concentrations or urinary excretion of the hydroxylated metabolite, may be undertaken. The urinary excretion of 6-hydroxycortisol or D-glucaric acid may also be used as monitors. Invasive techniques - such as direct determination of serum half-life or, rarely, liver biopsy obtained adventitiously - may yield more direct data.

C. EFFICACY

Because of ethical considerations, reasonable evidence of efficacy generally should be known before infants and children are exposed to the agent. Testing against the best known agent will be the preferable method for establishing efficacy with many drugs. A drug may be useful for only a certain percentage of the population diagnosed as having a general broad category of disease. For example, it is entirely possible that only a relatively small percentage of the "disease" population with bronchial asthma (a disorder probably of multicausal etiology resulting in similar clinical manifestations) may benefit from a particular therapeutic agent. In contrast, evaluations of efficacy at times may deal with an extremely small population. For example, a useful agent might demonstrate efficacy after study in only a few patients with a rare aminoacidopathy. Therefore, the requirement for demonstration of efficacy must not deal with fixed numbers. Again, flexibility must underline decisions about the number of subjects in each phase.

Based on ethical considerations, sick children rather than well ones will be the principal source of the experimental population, therefore, placebo groups cannot always be employed. Obviously, therapy cannot be withheld or an inactive drug cannot be administered by injection or other painful procedure. A number of alternative methods to the classical double-blind placebo experimental design can be suggested. In many instances, a standard drug can be used for comparison. Historical group controls may be utilized. "No drug" crossover can be used if the patient can tolerate a "no drug" period without serious compromise of his health. At times, the patient may serve as his own control, either as a personal historic control or in a "crossover drug/no drug" or "drug/standard drug" design. The drug may be most importantly compared to other therapeutic modalities, for example, behavioral modification, psychotherapy, dietary manipulation, and so forth.

Specific types of diseases where efficacy is likely to be tested are described for each age group in Section II.

D. EXPERIMENTAL DESIGN

Ethical, practical, and legal considerations may preclude studies by the most theoretically ideal experimental approach. This fact need not be viewed as an insurmountable obstacle because drugs should optimally be tested under conditions of actual clinical use, whether administered to hospitalized patients or in office practice. Such considerations do not obviate the need to establish a rigid protocol, including appropriate controls of whatever type, evaluating dose response phenomnena, and adhering to sound experimental design.

Study design must: (1) account for adequate control of variables and include appropriate statistical procedures, (2) detail methods and provide validation for assessment of benefit, (3) allow for handling of adverse or side effects, and (4) demonstrate awareness of the placebo response, both for beneficial and for adverse effects.

Perhaps the single most important variable to be assessed and controlled is the comparability of the study populations. This must be assessed in terms of a variety of parameters appropriate to the study, at times including but not limited to disease, social, physical, intellectual, and behavioral equivalence.

The mechanism(s) for evaluating adverse effects, whether by means of volunteered or elicited reports, questionnaires, or other means must be clearly stated and appropriate for the age group(s) under study.

Provision should be made for the management of accidental or intentional overdosage and severe, acute toxic reactions. Dialysability, specific antidotes, and other therapeutic measures should be assessed, and such information should be included in the protocol which is available to all involved in the study.

There should be safeguards to ensure that any study can be terminated at the earliest possible moment if danger to the subjects arises.

Studies of blood, liver, and renal function should be selective and appropriate for known modes of action and toxicity, rather than the accumulation of a mass of laboratory data from samples obtained by venipuncture or other painful procedures which are then run through the autoanalyzer. Initially, a wide base of studies may be used; but, if these studies are negative, only a few highly selective parameters should be monitored. A similar approach is suggested for the use of ECG, EEG, and other time-consuming and expensive studies.

II. SPECIFIC AGE-DEPENDENT FACTORS INFLUENCING SAFETY AND EFFICACY

Growth from conception to adult life involves complex changes in anatomy, physiology, bichemistry, and behavior which vary considerably from one state of development to another. Therefore, the action and adverse actions of pharmacological agents will vary as absorption, distribution, metabolism and excretion, and receptor sensitivity are altered by the changes associated with growth and development.

In recognition of these developmental changes, this portion has been written in sections; periods of childhood have been divided into stages which share characteristics distinguishing each stage from the other stages. In each stage, factors which may influence the disposition and action of a drug and the major immediate, delayed, and adverse actions are related to the major biologic events of the stage.

By introducing these age groups, it is not suggested that each drug be tested in each age group; rather, this is an attempt to ensure that the important biologic characteristics of the age(s) in which the drug eventually will be used therapeutically will be considered in evaluating both its beneficial and its undesirable effects.

Each age group will be evaluated as follows:

1. A General Statement of the biochemical, physiologic, and behavioral characteristics of the age group; specific ways in which the child is unique at the stage will be given.

2. Safety Considerations of particular importance to the age group. These are divided into three subgroups relating to the type of toxicity encountered and the temporal relationship of these effects to the initiation of therapy.

    a. Immediate Toxicity: Signs and symptoms occur soon after the initiation of therapy.

    b. Delayed Toxicity: Toxic effects occur only after a period of chronic administration. Certain adverse effects which occur in the immediate period of administration but manifest themselves later (such as tetracycline staining of the teeth) are also included in this category.

c. Late Onset Toxicity: Toxicity which becomes apparent months to years later, e.g., adenocarcinoma of the vagina in girls born to mothers who received diethylstilbestrol during pregnancy.

3. Efficacy

Means of establishing the beneficial effects of a drug and particular forms of desirable therapeutic activities.

4. Problems in Drug Evaluation

Special problems which may arise in the evaluation of drug action in a given age group.

5. Ethical Considerations

Special ethical considerations pertinent to each age group are delineated.

A. INTRA-UTERINE (CONCEPTION TO BIRTH)

1. General

The administration of drugs to the pregnant woman presents a unique problem to the physician. He must consider maternal pharmacologic mechanisms, and he must be aware of the fetus as a recipient of the drug. In therapeutic endeavors directed toward maternal disease, consequences of drug usage have often been unexpected; and adverse effects have appeared in the developing fetus, for whom the drug was not intended. On the other hand, the possibility of development of drugs for the treatment of fetal disease diagnosed in utero should be considered, and guidelines should be developed for the evaluation of both efficacy and safety of this type of compound when it is administered either via the maternal route or directly to the fetus. Drugs may also be administered to women who are not aware they are pregnant.

2. Safety and Efficacy

Adverse effects of drugs on the fetus vary depending on the stage of intra-uterine development. Before implantation, drugs may appear in high concentrations in tubular fluid and lead to the death of the fertilized ovum. Drugs which cause an adverse effect during organogenesis may result in anatomic malformations. Drugs given beyond the period of organogensis may affect the fetus and cause a functional disorder which is not associated with any known anatomic malformation.

Suggested methods of procedure to evaluate drugs which may be given to the mother during intra-uterine development are given in the following paragraphs. A prerequisite to intra-uterine studies for any new drug is evaluation (phase I and II) in adult men and in nonpregnant women of childbearing age.

Organogenesis--To evaluate drugs which will be used in pregnant women during the period of organogenesis, pharmacokinetic studies should be conducted in animals, including a subhuman primate. Localization of the drug within the fetus may be readily accomplished using isotopic techniques. At the same time, although not mandatory, studies of drug metabolism and disposition within the human fetal-placental unit should be considered.

The next stage of intra-uterine development to be considered for drug evaluation is from the completion of organogenesis to the onset of labor. This

separation from the other periods of intra-uterine life is arbitrary because there will be drugs used throughout pregnancy for the management of maternal or fetal diseases. In addition to preclinical ADME tests, studies are suggested to delineate pharmacokinetics within the maternal-fetal-placental unit.

Effects on uterine blood flow should be assessed because of the importance of this parameter for considerations of safety. A current method which permits this assessment uses chronically catheterized sheep. Studies of drugs designed for direct administration to the fetus should be conducted in animals with the development of distribution and dose-response interrelationships. For clinical studies, evaluation should be carried out in those instances in which maternal or fetal disease warrants use of the drug. The first patients who undergo this phase III type of study should have careful evaluation of fetal heart rate via continuous electronic monitoring. Other physiologic parameters of the fetus should be followed during the period of drug administration insofar as technology permits. These pregnancies should be carefully followed, and the outcome should be meticulously ascertained - irrespective of whether the drug is administered for the duration of pregnancy or not. The infant should be carefully followed after birth until psychologic and physiologic development can be satisfactorily assessed. The state of fetal well-being should be assessed throughout pregnancy after the drug has been administered, whether singly or on multiple occasions, by measurement of urinary estriol excretion. Intrauterine growth should be assessed via noninvasive techniques, such as ultrasound. Pregnancy should be monitored by whatever means are technically available, commencing with the initiation of drug administration. This will permit determination of the time at which adverse effects occur, should such events take place. Evaluation of drug disposition will be greatly aided during this stage of development if advantage can be taken of pregnancies terminated by abortion by purposefully administering the drug just prior to termination.

Evaluation of drugs to be used for the management of labor and delivery--At this stage of development, direct assessment of effects of the drug on fetal physiologic processes (heart rate, respiration, activity) are possible, as is determination of concentrations of the drug and possible biochemical alterations (pH, glucose, etc.) in the fetus via sampling of scalp blood. Infants should be intensively evaluated at birth and throughout the neonatal period, with particular attention paid to their adaptation to extra-uterine life. This includes examination of acid-base status, weight gain, feeding ability and general activity, assessment of behavior by direct observation and through the use of psychometric tests which are valid for the neonatal period, and electroencephalography (EEG). Pharmacokinetic studies regarding drug disposition, metabolism and elimination should also be undertaken in these infants because they will have received the drug transplacentally shortly before birth. Determination of biologic half-life, excretion of the drug and its metabolites (including identification of the major metabolites in urine), and assessment of pharmacodynamic effects of the drug, if present, may be important for certain agents. Since most agents used at this stage of development are analgesics or anesthetics, careful examination of the functioning of the central and automic nervous systems is indicated. By intensive and comprehensive investigation of a few infants, followed until assessment of drug effects on psychologic and physiologic development can be made with validity, a determination can be made about the advisability of continuing trials of the drug during labor and delivery.

In the pregnant human female, studies at this stage of development can be undertaken by several different approaches. Women who receive the drug for therapeutic purposes and happen to be pregnant should be noted. Despite attempts made to avoid this situation, it will occur. The utmost advantage should be taken of this situation. Infants exposed in utero in this manner

should be carefully examined at birth and followed with extensive psychologic and physiologic evaluation. This will enable ascertainment of adverse effects other than those noted at delivery. Evaluation at delivery usually detects only gross anatomic malformations.

The second approach to drug evaluation during this period of intra-uterine life involves administration of the drug to the mother, usually as a single dose, when termination of pregnancy is planned. In this instance, drug distribution, localization within the fetus, and metabolism within the fetal-placental unit can be examined. Metabolic products should be defined within the fetal-placental unit to determine whether drug biotransformation differs from that occurring in the adult. The use of radioisotopes may be permissible because of the termination of pregnancy. In cases where there has been repeated administration of a drug to treat a maternal illness, and subsequent therapeutic or elective abortion occurs, careful histopathologic study of the aborted fetus may detect adverse effects on organogenesis.

A third approach involves careful assessment of infants receiving the drug in utero because potential therapeutic benefit for the mother was sufficient to warrant the unknown risk involved in drug administration to the fetus. Such infants should be examined meticulously at birth and followed carefully thereafter until such time as satisfactory evaluation of effects on psychologic and physiologic development can be made. The duration of this follow-up will depend on the availability and sensitivity of testing devices, the nature of the drug and its known pharmacologic, toxic and teratologic effects.

3. Special Problems

In the preceding paragraphs it has been implied that drugs will be administered mainly for therapeutic benefit of the mother. The same considerations which apply to the design and execution of clinical trials during phase II are applicable, including controls, randomization, etc. Pregnancy per se should not preclude women from participating in Phase III studies when potential therapeutic benefit of a new agent may be obtained. Special attention must also be given to the effects which pregnancy itself may exert on drug action during the randomization of phase III clinical trials.

Agents will be developed solely for the benefit of the fetus. Determination of efficacy and safety will be difficult, but objectivity demands careful assessment of such benefit in controlled trials following drug disposition studies in pregnant animals (including primates). The considerations of safety outlined for intra-uterine development are applicable when drugs are administered for the benefit of the fetus. Dosage may have to be altered considerably when the drug is administered directly to the fetus via either amniotomy or intraperitoneally. The diagnosis must be firmly established prior to administration of drugs for the treatment of fetal disease. In addition, potential benefit from the drug will have to be sufficient to warrant the risks of administration directly to the fetus.

B. NEONATAL (BIRTH TO ONE MONTH)

1. General

Newborn infants have been shown repeatedly to be much more sensitive than adults to various pharmacologic agents. This has been most often the result of differences in pharmacokinetic processes. A number of other basic considerations, including receptor sensitivity, may also account for this phenomenon. The few available data show some of the pharmacokinetic

differences peculiar to neonates. They include differences in general metabolism, inequities caused by dissociation of gestational from maturational ages, a larger body surface to body weight ratio, variation of protein concentration and drug-protein binding affinity, the presence of fetal hemoglobin, immature renal tubular function, and changes in pharmacodynamic response. Small infants are most susceptible to changes of ambient temperature, and the subsequent decrease in body temperature may have notable effects on the rates of drug metabolism and excretion. Moreover, the major variations of fat and water content in the newborn and between individual neonates may result in differences in distribution and subsequent kinetics.

2. Safety

a. **General Considerations of Safety:** The alterations in absorption, distribution, metabolism, and excretion in the neonate may lead to accumulation of the drug with resultant toxicity. Modification of dosage may avoid this type of adverse effect. The unique physiologic state of the neonate (particularly during illness) and the wide ranges of such pharmacokinetic determinants as pH, blood gases, electrolytes, protein concentrations, and temperature present additional possibilities which may result in toxic manifestations. The very rapidity of change of such determinants makes it necessary to provide assay methods of minimal sample size.

b. Specific Toxicities

(i) Central Nervous System Effects: Evidence exists for the enhanced penetration into the brain of many drugs. The cardiovascular, respiratory, and thermo-regulatory mechanisms are extremely sensitive to depressive effects in the neonate. In addition, neuronal maturation, cell migration, dendritic arborization, and cell differentiation are occurring at this age and may be affected by drugs and/or their metabolites.

(ii) Cardiovascular

Cardiogenic effects - Drugs may affect cardiac contractility, rate, and rhythm, thereby causing severe or possibly fatal adverse drug reactions. This has been a particular problem with local anesthetic agents used during delivery. The neonate may also display delayed CNS depression or the induction of seizures and unexpected excitation resulting from the administration of some agents; he may also become addicted or dependent.

Circulatory adjustment occurring during the change from the intra-uterine to the extra-uterine environment may be hampered by the presence of certain drugs. In particular, closure of the ductus arteriosus may be impaired if respiratory depression results in hypoxemia and acidosis.

(iii) Metabolic Derangements: Changes in serum glucose, calcium, pH, sodium, potassium, etc. may be the result of drug-induced alterations in the infant's metabolic processes or may influence drug evaluation. Metabolic data obtained during the care of the sick newborn infant may provide valuable information in assessing safety and efficacy.

(iv) Changes in Bilirubin Kinetics: Prior to administration of any drug to the neonate, it is mandatory to study the drug in its final dosage form and, if possible, its metabolites and protein bilirubin binding. When

appropriate, effects of the drug on conjugation, uptake, excretion, and enterohepatic circulation of bilirubin should be performed.

(v) Dermatotoxicity and Persorption: The topical application of pharmacologic agents to the neonate must be approached with an awareness of two peculiarities of this age group. First, the skin is more susceptible to dermatotoxicity expressed as photosensitivity and various forms of rash, including bullous eruptions. Second, the thin or absent statum corneum allows increased persorption, leading to systemic concentrations which may exert a toxic effect on other organs (e.g., hexachlorophene and brain damage). In addition, systemic reactions (e.g., cyclopentolate with atropine-like toxicity) may result from increased drug absorption through mucous membranes.

(vi) Gastrointestinal: Evaluation of the effects of a drug should include consideration of such adverse effects as the inhibition of gastrointestinal motility, change of flora, vomiting, or a malabsorption-type syndrome caused by direct irritation, as well as effects on absorption of nutrients.

(vii) Hematologic: Methemoglobinemia, thrombocytopenia, and hemolysis (especially in G-6-PD-deficient neonates) may be induced in the neonate necessitating investigation of this potential in the evaluation of new agents.

c. Drugs in Breast Milk: Most, if not all, drugs administered to the mother are excreted in the breast milk. Concentrations of the drug and/or of its metabolites should be determined with due regard for the individual variations of lactation volume itself. The mere presence of the agent in the breast milk does not necessarily indicate any effect on the neonate, deleterious or otherwise, and should not in itself mitigate against approval for use in lactating women. Various factors such as concentration, the total dose delivered, the absorption by the infant, etc. must be considered in evaluating potential effects mediated through breast feeding.

d. Delayed Effects: Consideration of long-term postmarketing studies on cognitive, behavioral and physical growth depends upon the nature of the drug.

3. Efficacy

Survival rates from severe illnesses such as neonatal sepsis, idiopathic respiratory distress syndrome, erythroblastosis fetalis and hemolytic disease of the newborn, and necrotizing enterocolitis may be the only measures of efficacy available.

4. Special Problems

Some major obstacles to be overcome in establishing efficacy and safety in this age group are:

a. The Influence of Maternal Disease: The variations in physiologic states of the neonate, secondary to the pathophysiologic conditions of the mother (e.g., infants of diabetic mothers) may (1) negate the random assignment of infants to controlled, matched study populations, and (2) alter the pharmacologic response of the infant to an administered agent.

b. The Influence of Infant Disease: The wide variability within each disease state and the relatively small population of affected individuals in any single institution, together with the marked influences of the host subject in terms of gestational and maturational ages, etc., present limitations in study design, random assignment, statistical analysis, etc.

5. Ethics

The neonate presents a number of unique ethical problems. Among these are:

a. The possibility of unusual toxicity and the extreme difficulty in identification of such a problem. The late appearance, the inability of the subject to exhibit common early signs of toxicity, and the inability to verbalize symptomatic complaints all contribute to the dilemma.

b. The higher risk potential inherent in this population dictates the most substantial evidence of benefit to be derived from the use of a new drug.

C. INFANT/TODDLER (1 MONTHS TO 2 YEARS)

1. General

This period is characterized by notable increments in physical growth and rapid maturation of all organ systems with associated functional change. Noteworthy in these regards are the central nervous system and the immune system. Of direct relevance to the effect of a drug on infants in the early months of this age group are alterations in protein binding and drug metabolism.

2. Safety

a. Immediate Drug Toxicity

(i) Difficulty in detecting toxicity by clinical assessment: Toxicity may or may not be apparent in infants, especially in the early months of this age group. This may be particularly true for central nervous system toxicity. Therefore, blood levels of pharmacologic agents should be monitored and cautiously interpreted because therapeutic blood levels for older children and adults may not be safe for infants.

(ii) Gastrointestinal tract: Acute and chronic gastroenteritis is frequently encountered in this age group. Certain drugs are more likely to cause diarrhea in infants than in older children. Gastroenteritis will affect drug absorption and may complicate interpretation of efficacy and toxicity. Dehydration with resultant hypovolemia, a frequent consequence of gastroenteritis in infants, may affect drug distribution and serum concentrations.

(iii) Central nervous system: Drugs may affect myelinization and brain differentiation, which are actively occurring in children of this age group. Such effects may not be limited to drugs which localize in the central nervous system or which exhibit a predominant effect on the brain.

b. Delayed Reactions

(i) General: Toxicity is difficult to assess in this age group by clinical observations alone. Furthermore, it may not be possible to distinguish adverse effects following any single dose in a repeated series of drug administrations because of delayed reactions. Although this

problem also applies to older age groups, it is particularly pertinent to infants because of their relatively immature organ systems and their limited ability to communicate.

(ii) Hypersensitivity: In this stage of initial exposure to foreign protein (e.g., foods and inhaled particulate protein), drugs may predispose to hypersensitivity through such diverse mechanisms as inhibition of secretory antibody production or induction of partial blockade of beta adrenergic receptors.

(iii) Physical growth: Physical growth may be affected by various classes of drugs such as adrenocorticosteroids and tetracycline antibiotics. Consideration of long-term postmarketing studies on cognitive, behavioral and physical growth depends upon the nature of the drug.

3. Efficacy

Although easier than for the neonatal age group, evaluation of efficacy is far more difficult than in adults. Infants cannot cooperate in a number of commonly used tests of pharmacologic action; therefore, indirect parameters (e.g., length of illness, length of hospital stay, frequency of complications and subsequent disability), and certain laboratory tests will, of necessity, be used to determine efficacy.

4. Special Problems

a. Deficiency States: The presence of iron-deficiency anemia and diminished concentrations of certain serum proteins is more likely to occur in this age group than in any other age group. Such deficiencies may alter drug kinetics.

b. Breast-feeding: The possibility of interaction from chemicals, hormones, and drugs in breast milk should be considered when suckling infants participate in drug evaluation.

5. Ethics

Before evaluating new drugs in infants, substantial evidence of benefit or superiority over accepted agents should be demonstrated in older children and adults because infants may have a higher risk potential. Included among these increased risks are those pertaining to physical growth and neurological and intellectual development.

6. Other - Research Needs

Certain research needs can be identified as relevant to the study of new drugs for this age group. (a) Relatively noninvasive techniques for determining blood levels (e.g., salivary drug concentration) should be sought; (b) noninvasive techniques for establishing efficacy of a drug should be developed; (c) much additional information is needed on the effect of drugs on the development of the immune response (both humoral and cellular components).

D. CHILDHOOD (2 YEARS TO ONSET OF ADOLESCENCE - 12 YEARS)

1. General

This age group is characterized by slower growth and the highest incidence of infectious diseases. Increasing motor and social independence results in exposure to environmental hazards which lead to various accidents such as

poisoning, burns, drowning, and physical trauma. Cognitive processes involved in school performance and school attendance - vital to intellectual and psychosocial development - are being rapidly acquired. At the end of this age period, rapid bone growth and epiphyseal maturation occur secondary to changes in endocrine activity. Accordingly, pharmacokinetics may differ from the infant and adolescent age groups, depending on the characteristics of the drug and the child's age within the broad age range of this period.

2. Safety

a. General: Safety considerations in general differ little from those in Section I. A specific need at this age, when accidental poisoning is common, is information dealing with acute toxicity and treatment of drug poisoning.

b. Specific Toxicities

(i) Immediate drug toxicity: A disease for which a drug is given may enhance its toxic potential. Thus, interaction with disease states which would apply particularly to drugs used at this age should be studied, e.g., antibiotics, bronchodilators, antihistamines, and anti-convulsants. An example would be the altered toxicity of ampicillin when employed in infectious mononucleosis or increased toxicity of isoproterenol (ventricular tachycardia) when the patient has hypoxemia and acidosis.

Hypersensitivity manifested by anaphylactoid and anaphylactic reactions are more likely to occur at this age and in adolescents than in younger children because of longer periods for sensitization and greater exposure to antibiotics and similar substances to which antibodies may be induced.

(ii) **Delayed Reactions**

Hypersensitivity manifested by serum sickness or drug fever--This may be seen with a variety of agents ranging from antibiotics to anticonvulsants and is common in this age group and in adolescents.

Drugs interfering with school performance and other childhood activities--These may include, but are not limited to, side effects which interfere with attention span (e.g., drowsiness) or reduce perception (e.g., tinnitus and decreased hearing).

Drug-nutritional interactions--The prolonged use of a drug in a child may affect his nutritional requirements. Recent observations on the rachitic effect of long-term administration of diphenylhydantoin illustrate this concern.

(iii) **Late Onset Reactions**

Chronic administration of a variety of agents may affect linear growth and/or weight gain.

Selective growth changes include advancement or retardation of puberty or of menarche.

3. Efficacy

Evaluation of efficacy based on objective criteria is possible in the school-aged child who is able to cooperate. Objective measurements should be stressed in

study design. School performance and school attendance provide additional parameters which may be extremely useful in determining efficacy. Even though the rate of physical growth has slowed in this age group, changes in growth rate may provide additional evidence of efficacy, especially in those diseases which depress linear growth or interfere with normal weight gain. Assessment of osseous development (e.g., bone age) is one parameter of growth that may be useful where indicated. The efficacy of agents in preventing or altering morbidity from infectious diseases may be best studied in this age group when the incidence of viral and bacterial infections is high.

4. Special Problems

Accidental poisoning and overdosage are of prime consideration at this age. The manifestations of acute poisoning with the drug and its metabolites can be studied in juvenile animals. Information concerning specific antidotes and therapy of overdosage (e.g., peritoneal dialysis) should be included in the protocol and ultimately in the package insert.

5. Ethics

Special ethical consideration in this age group involves school absenteeism for studies as well as the psychological effects of such studies on the child. These should be discussed with parents before informed consent is obtained. Older children may be able to participate in the consent process.

E. ADOLESCENT (ONSET OF ADOLESCENCE TO ADULT LIFE - 12 TO 18 YEARS)

1. General

Adolescence may be defined as the transition period in which the child undergoes changes in physical, sexual, and psychosocial development transforming her/him into an adult. During this time period, the child's body is rapidly changing in form, undergoing final rapid growth to mature stature and the development of secondary sexual characteristics. Coupled to the dramatic changes in body form, the adolescent develops a new perception of her (him)self as an individual in relation to her/his niche in the family and in the general fabric of society.

Changes in physiology may produce alteration in the absorption, distribution, metabolism, and excretion of drugs as well as in receptor respose. The development of puberty and the known effects of sex hormones on drug metabolism warrant consideration in drug evaluation in the adolescent.

2. Safety

a. General Considerations of Safety

The major concerns relating to drugs given to an adolescent involve:

(i) the potential for abuse;

(ii) the possibility that the agent may alter the final stages of physical and endocrine development completing the growth cycle to maturity.

In addition, in this age group, medication may not be taken as prescribed. The adolescent frequently omits doses of medication, takes it at erratic intervals, and may take more than prescribed. Safety considerations should be addressed not only to the therapeutic dosage, but also to the consequences of suboptimal dosage and overdosage.

b. Effect of the Age Group on Safety Considerations

(i) Immediate Adverse Effects

Drug misuse includes that of accidental or intentional overdosage or underdosage and that of inappropriate use. The adolescent may fail to take the medication as frequently as prescribed, or he may employ it in larger doses than prescribed or for inappropriate reasons. The effects of such practices on the disease process and adverse effects will have to be anticipated.

Hypersensitivity reactions include anaphylaxis, serum sickness, and contact dermatitis. Although not unique for the age group, these reactions may occur as a result of self-medication or inappropriate routes of administration of medication.

(ii) Delayed Reaction

Dependency and habituation are among the major delayed reactions.

(iii) Late Adverse Effects

Psychosocial and behavioral alterations may occur as a late, even unexpected, action of a drug and should be considered in drug evaluation. These may occur either as a direct effect or as an exaggeration of an underlying problem.

Other--Growth changes, advancement or delay of puberty and of menarche, and effect on fertility may consitute other delayed drug reactions in this age group. Consideration of long-term post-marketing studies of possible drug effects in these areas depends upon the nature of the drug.

Pregnancy test on female participants--Because of the presence of unknown or hidden early pregnancy, adolescent girls should have pregnancy tests before entering any drug trials.

3. Efficacy

The same objective measurements used in adult patients to define efficacy should be used.

4. Special Problems

a. General: The plasticity of evolving form and functions in the adolescent produces unique therapeutic problems for this age group which can be grouped into three major categories.

(i) Drugs used to alter physical growth and sexual development. Drugs given to regulate growth or secondary sexual manifestations are unique to the adolescent. Many pharmacologic agents are employed in an attempt to make the subject "normal" or "superior" regarding growth, muscular development, or sexual development. Pressures to use drugs are generated by the adolescent's peer group. An adolescent who is too tall or too short, too obese or too thin, or not athletic enough is made the object of derision by his or her peers. Synthetic androgens are often used under these circumstances. Their effects on hepatic function (and metabolism of other drugs) and hepatic carcinogenesis should be taken into consideration.

The problems of potentially tall girls and of irregular menses may both be treated with synthetic sex hormones. The long-term effects of these practices must be studied with regard to fertility and carcinogenesis. The latter is highlighted by the development of uterine carcinoma in patients with Turner's syndrome after stilbestrol treatment.

Conditions affecting both males and females are obesity and sexual precocity. Growth and fertility could be affected by agents used in their treatment. For example, medroxyprogesterone - used in treatment of sexual precocity - has been shown to suppress the pituitary-adrenal axis, cause Cushingoid features, and produce "sticky-chromosomes" in the male gonad. These examples of adverse effects warrant consideration when new drugs of this class are evaluated.

(ii) Drugs used to regulate mood and behavior. The adolescent is prone to psychosocial disturbances; the ambivalence created by his/her striving for self-identity and his/her dependent needs coupled with rapid changes in physiology and body form create a milieu of stress. Bizarre and unusual behavior may result when family interrelationships are strained or if school and peer interactions break down. Depression, anxiety, and acting out are common psychological symptoms which the physician is requested to control with drugs. There the problem of evaluating efficacy may be confounded by concurrent psychotherapy; this must be considered when adolescents are enrolled in a psychoactive drug study.

Effects on school performance, social behavior, and operation of vehicles should be kept in mind.

(iii) Drugs used for cosmetic purposes. Awakening interest in the opposite sex is characteristic of the adolescent. The adolescents' self-image in this context is related to their physical attractiveness. Minor skin blemishes may result in an inordinate expenditure of effort, time, and money to correct anything which may be considered a defect. At the same time, physiological changes make them susceptible to acne, seborrhea, and hirsutism. They seek and use a variety of medications, both on prescription and over-the-counter, to contend with these problems. Antibiotics, hormones, and vitamins may be prescribed for systemic use or topical application. Other medications (such as keratolytics, drying agents, and ointment powders to cover blemishes) are limited to external use.

For topically applied drugs, the problem of skin sensitization is superimposed on those of potential abuse and overdosage common to other classes of drugs.

5. Ethics

a. Informed consent should be obtained from the subject as a responsible individual, as well as from her/his parents.

b. The effects of drugs, even in the young adolescent, must include the possibility that females are pregnant and males may be fertile.

c. The possibility that the drug may have an effect on ova or spermatozoa must be considered.

6. Other - Compliance

Patients may fail to take the medication under study according to their protocol. This is particularly true of adolescent patients who are not yet mature enough to realize the need to take even the most important medications (i.e., insulin in juvenile-onset diabetes). Therefore, to evaluate drugs in this age group, methods to evaluate compliance will have to be devised and used.

III. SUMMARY OF REQUIRED STUDIES

The following summary is intended to list those studies which are felt to be required in all (or almost all) drugs to be approved for use in pregnant women, infants, and children. There will be exceptions. The recommendations are divided into two groups: animal studies and studies in pregnant women, infants, and children.

A. STUDIES IN ANIMALS

1. Chronic toxicity studies. This is the usual long-term multidose administration to two species, usually the rat and beagle dog. These studies should include effects on growth and skeletal maturation (bone age).

2. Appropriate methods for determining bioavailability using nonradiation-emitting techniques are to be developed. Initially "hot" methods for animal studies may serve as a prototype for the development of appropriate "cold" methods, but efforts should be directed to developing a sensitive "cold" method. The method(s) should be sensitive enough to measure with small sample size levels in serum expected to be in the therapeutic range. The method(s) should also differentiate the drug from its major metabolites. If the latter are pharmacologically active, additional techniques for these measurements are needed.

3. The pKa and lipid: water ratio of the chemical moiety used in the product should be determined.

4. Studies of absorption, distribution, metabolism, and excretion. These should account for a major percent of the administered dose and lead to formulation of a pattern of metabolism and disposition during both acute and chronic administration. Major metabolites should be identified. Unusual disposition -particularly in growing bone, teeth, or endocrine organs - which might be associated with adverse effects in the pediatric population should be sought.

5. The standard "3-phase" reproduction study.

B. STUDIES IN PREGNANT WOMEN, INFANTS, AND CHILDREN

The following factors are to be determined in each age group for which the drug will be approved. The usual sequence of testing should first involve teen-agers then successively younger children. Exceptions will occur when diseases are peculiar to one age group. The neonate must be approached with great care, since even studies in young children may not yield a reliable estimate of toxicity for the neonate. For studies of the fetus, infants treated as an inadvertent recipient by administration to the mother of a drug for a serious medical problem may be the first studies involving the fetus. Throughout the recommended studies that follow, there apparently are no important sex differences before puberty; thus, data obtained from both males and females may be pooled. This is a reasonable but still untested postulate, however.

1. Blood levels found with the range of doses adopted from studies in adults. If such studies have determined the therapeutic range, the dose required in infants and children to achieve this range must be an early priority.

2. Studies of absorption, distribution, metabolism, and excretion. The goals of such studies should include localization in tissues, rapidity of excretion, and time of peak onset.

    a. Absorption. The percent of a single and/or multiple dose that is absorbed should be determined.

    b. Distribution. Binding to plasma proteins at therapeutic blood levels should be determined. Studies of displacement of bilirubin from serum albumin are critical if the drug is to be used in neonates or late in pregnancy. If such displacement is found, additional studies with drugs which may be concurrently administered and the effect of pH, free fatty acids, etc., on the drug albumin-bilirubin complex are mandatory.

    c. Metabolism. Determination of the major biotransformation products, including a search for unique or unusual metabolites, may be coupled with studies of blood levels (No. 1). If significant age-related changes are found in metabolism, then a comparative profile of quantitative changes occurring with age may be necessary.

    d. Excretion. The fate of the drug, expressed either as percentage of the multiple daily dose or as single dose with an appropriate time scale as determined from the decline in serum levels or other monitor of excretion, should be ascertaind. Such studies should account for a major protion of the administered dose in most instances.

3. Bioavailability. If the dose form to be used in children is significantly different than that for adults, it must be considered as a new drug, and absorption and excretion studies should first be performed in adults. In any event, the dose form or forms used for pediatric patients must be used for studies of absorption in children. This stipulation will cover the potential problem of toxicity or influences of the vehicle or other components of the formulation.

4. Because of the multiple unique aspects of the neonate, a neonatologist should be part of the team which evaluates the influence of a new agent to which a fetus or a neonate has been exposed. Study must be made of possible interferences by the drug with metabolic reactions unique or of particular importance to neonates, such as the handling of bilirubin, glucose homeostaasis, acid-base balance, oxygen-carrying capacity, development of pulmonary surfactant, etc.

5. Depending upon the drug, consideration should be given to establishing a program for long-term follow-up of the offspring of women receiving the drug during pregnancy. Such studies need to evaluate both possible intra-uterine death and malformations. Since many malformations are not detected at birth, a program of follow-up should insure evaluation at least at 1 year of age. Malformations should include functional as well as anatomic abnormalities. Even longer follow-up is desirable, particularly for drugs which might be anticipated to have an adverse effect on neurologic development. However, the difficulties of such long-term studies are recognized and some compromise must be made. Depending upon the drug, similar but perhaps less intensive and extensive follow-up may be needed for children receiving the new drug during postnatal and later developmental stages.

6. For drugs which may be used chronically, the effects on weight gain, statural growth and skeletal maturation (including, perhaps, in some cases, serial bone age films), and sexual maturation should be assessed. The effects of chronic administration on behavior and learning are important areas, yet ones in which no exact requirements for studies can be delineated. The determination of effects on behavior and learning may be part of the evaluation of efficacy of psychoactive compounds; thus, indirectly, some data on safety will be obtained. However, in addition to specific benefical effects which will be observed, other areas demanding consideration are:

    a. classroom attentiveness and performance,
    b. grades, comments of teachers, etc.
    c. unusual or bizarre behavior,
    d. somnolence, depression, withdrawal,
    e. reports of trained observers, parents, teachers,
    f. formal testing procedures.

    In general, the longer the drug is to be administered the more important long-term follow-up becomes.

7. Studies of hematologic, hepatic, and renal damage from acute and chronic administration are needed because these organs are most readily affected by drugs, even if no toxicity has been demonstrated in adults. Such studies must be done with acute and chronic dosing.

8. Depending on the drug, specialized studies such as ECG, EEG, hearing, vision, etc. may be required. Certain clues can be taken from studies in adults and from the pharmacologic and chemical nature of the drug in determining the number and extent of such studies.

9. Before investigations are begun, provision must be made available for management and treatment of accidental or intentional overdosage and for severe toxic reactions to the drug.

10. Data must be obtained on the influence of the drug on fetal growth and differentiation for drugs which will be approved for pregnant women. Apgar scores, performance in the nursery, etc., are necessary parts of such studies. When appropriate, studies of addiction of the neonate and presence of withdrawal signs or symptoms must be performed or be in progress.

11. Concentrations of the drug and/or its metabolites in breast milk and effects on the nursing infant should be determined for drugs to be used in lactating women.

All recommendations made throughout these guidelines - and particularly in this summary section - must be viewed from the standpoint of flexibility, and appropriate modifications should be made for the individual drug, its indications for use, and the age of the patient for which it is intended.

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