Draft Guidance for Industry and FDA Staff

Premarket Assessment of Pediatric Medical Devices

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Preface

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Premarket Assessment of Pediatric Medical Devices

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Background

FDA reviews pediatric devices through all of its premarket pathways, including premarket notification (510(k)), premarket approval (PMA), biological license application (BLA), and humanitarian device exemption (HDE). A manufacturer may show substantial equivalence to a previously marketed device, or may seek approval by demonstrating with reasonable assurance that the device is safe and effective for its intended use. Clinical evaluation may be needed to support marketing of a device indicated for pediatric use. If such studies are needed, they should be conducted in accordance with the investigational device exemptions (IDE) regulation (21 CFR 812). FDA has oversight of significant risk studies, whereas the oversight responsibility for non-significant risk studies has been delegated to Institutional Review Boards (IRBs).

On October 26, 2002, the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) was signed into law. Among other things, MDUFMA amends the Federal, Food, Drug, and Cosmetic Act (the Act) by adding new provisions intended to promote the development of safe and effective pediatric devices and to protect this vulnerable patient population during the course of clinical trials involving such products. This guidance, as well as a collateral guidance on procedures for ensuring appropriate pediatric expertise on FDA Advisory Panels, "**Pediatric Expertise for Advisory Panels; Guidance for Industry and FDA Staff**"

(http://www.fda.gov/cdrh/ode/guidance/1208.html), will help the agency achieve the intent of the pediatric provisions of MDUFMA.

MDUFMA also requires FDA to request the Institute of Medicine (IOM) to conduct a study of whether the existing postmarket surveillance provisions of the Act provide "adequate safeguards regarding the use of devices in pediatric populations." Within four years of enactment of MDUFMA, FDA is to submit a report to Congress concerning IOM's findings and any recommendations we have "for administrative or legislative changes to the system of postmarket surveillance" for pediatric devices. Representatives from FDA and IOM have held several discussions to formulate the scope and objectives of the study to be conducted.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

This guidance should be used in conjunction with other device-specific guidances to help ensure that medical devices intended for use in the pediatric population provide reasonable assurance of safety and effectiveness.

II. Objectives

1. To help define pediatric population and pediatric use for medical devices and device clinical trials.

2. To help identify the types of information needed to provide reasonable assurance of the safety and effectiveness of medical devices intended for use in the pediatric population.

3. To help define the protections sponsors should consider for pediatric subjects in device clinical trials.

III. Pediatric Population and Use

A. Definition of Pediatric Population Subgroups

For purposes of this guidance, we are proposing the following ranges of pediatric subpopulations to be used as a guide for manufacturers in developing medical devices:

Table 1 Age Ranges of Pediatric Subgroups

Pediatric Subgroup	Approximate Age Range
Newborn	birth to 1 month of age
Infant	1 month to 2 years of age
Child	2 to 12 years of age
Adolescent	12 to 21 years of age

Although the upper age limit used to define the pediatric population varies among experts, including adolescents up to the age of 21 is consistent with the definition found in several sources.[1,2,3] Given the scope of medical devices and the impact that a device could have on a growing adolescent as well as the effect growth could have on the device, we believe that including the upper age limit identified above may be useful for some devices and device clinical trials. The agency recognizes, however, that the descriptions are somewhat arbitrary and that, in fact, the subject's weight, body size, physiological development, neurological development, and neuromuscular coordination may often be more appropriate indicators than chronological age. In addition, when clinical trials are to be conducted, sponsors should consider the age of consent in the state(s) where the trial will be performed to determine the age range for the oldest subgroup.

Other terminology that describes subgroups in the pediatric population includes:

- low birth weight describes babies less than 2.5 kilograms (Kg)
- very low birth weight describes babies less than 1500 grams (g)

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[1] Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company; 1996.

[2] Rudolph AM, et al. Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill; 2002.

[3] Avery MD, First LR. Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994.

- preadolescent age group typically ranges from 11 to 13 years.

B. Definition of Pediatric Use

For purposes of this guidance, FDA will consider a pediatric use to be any use of a medical device in a pediatric population, as defined above, in which there is a primary pediatric indication. General indications, where considerable pediatric application is anticipated, are also included in this definition.

IV. General Principles in Medical Device Evaluation

The underlying mission of FDA is to promote and protect public health. In general, FDA assesses safety and effectiveness of devices in the pediatric population using the same regulatory bases, scientific approaches, and processes we use to assess all devices. General device considerations that are also germane to pediatric devices include, but are not limited to, the following preclinical and clinical testing as well as other regulatory controls:

- biocompatibility, including toxicity and carcinogenicity
- sterility and infection control
- environmental factors, such as electromagnetic fields and radiation
- design controls and good manufacturing practices (GMP)

Because the pediatric population represents a particularly vulnerable group, specific measures are needed to protect the safety of pediatric study participants. Adult devices may be inappropriate for use in pediatric patients for a variety of reasons, or may require specific design changes and/or specific labeling to accommodate their use in pediatric patients. We recommend that you consider the following issues when you develop devices or plan a clinical trial for devices intended for pediatric patients:

- height
- weight
- growth and development
- disease or condition
- hormonal influences
- anatomical and physiological differences from the adult population
- activity and maturity level.

V. Preclinical Studies

Since there is a wide spectrum of devices, the necessary preclinical testing will vary depending on the specific device. FDA may request bench or animal data depending on the type of device, the target population, and the extent of existing knowledge about the device. In many cases, FDA has developed device-specific guidance documents that will provide information on the types of pre-clinical testing that should be completed either to support marketing or to support initiation of a clinical trial. We recommend that you contact the reviewing division or visit the CDRH or CBER websites for a complete listing of relevant guidances.

VI. Clinical Studies

As is true for medical devices in general, FDA does not believe that clinical data will be necessary to demonstrate safety and effectiveness for all devices intended for pediatric populations. The agency recognizes that the amount and type of evidence required will depend on a number of factors, including the nature of the device, what is already known about the product in the adult population (if relevant), what is known or can be extrapolated about the device to the pediatric population, and the underlying disease or condition being treated. In some cases, well-designed bench and animal testing will be sufficient to evaluate the device. In others, clinical data may be needed to evaluate the safety and effectiveness of the device.

If clinical data are needed, it may be that the course of the disease and the device's effects are similar in adult and pediatric patients. In such a situation, the pediatric indication may be supported by the adult data with limited additional safety data in the pediatric population. In other cases, the prognosis, severity, or symptoms of the disease in the adult population may be significantly different than in the pediatric population, the device's effects may not be understood well enough, or there may be risks specific to the pediatric population necessitating clinical data in this population.

In some situations, devices that are already approved and indicated for adult populations are modified for pediatric uses. To support the modifications, the manufacturer should conduct a risk analysis of the changes and develop methods to adequately address/mitigate the identified risks. This may require verification testing alone, or validation testing may be needed in the intended pediatric population.

Finally, because weight, body size, and physiological and neurological development all vary among pediatric subpopulations and change as the child grows, clinical data may be needed to assess safety and effectiveness in the various subgroups. In other cases, it may be possible to extrapolate from one group to another, thus limiting or obviating the need for clinical data. When clinical trials in

a pediatric population are necessary to support a marketing application, these trials should follow existing scientific approaches and methods to ensure the safety of subjects.

In summary, therefore, FDA believes clinical data is appropriate when any of the following circumstances apply:

- supporting information from sources, such as pre-clinical bench or animal testing, literature, or adult clinical trials, are inadequate to establish safety and effectiveness for the pediatric indication
- adult data are inadequate to predict pediatric risks and adverse events
- pediatric data are needed for validation of design modifications
- pediatric data are needed to develop an age-appropriate treatment regimen.

When these circumstances exist, clinical data from pediatric subjects help ensure that manufacturers will:

- design the device properly for the intended population
- perform accurate risk assessments
- provide clear instructions for use.

Compared to drugs, devices present additional challenges due to the wide spectrum of them with varying applications. It is difficult to outline a prescriptive approach that would be appropriate for evaluating all devices. For example, some devices are relatively simple in terms of design and use, such as blood pressure cuffs and bilirubinometers. FDA generally requires only pre-clinical testing to support pediatric use of these types of products. Other devices may present additional risks, e.g., intraosseous access devices. The supporting information for this device included performance studies in animals and cadavers, clinical experience in the adult population, and a clinical trial in a pediatric population. The study design addressed issues relating to differences in bone density and depth of penetration requirements in children of various ages and between children and adults. The study also addressed issues related to the growth plate and epiphyseal closure in children.

If clinical data are needed, other sources of data, such as published studies and reports and actual use information, may help reduce the burden. FDA advises sponsors to consider these alternative sources of information when designing their clinical trial. Sponsors should also consider if adequate data may be gathered by including pediatric patients as well as adults in the original studies conducted on the device. Finally, the type and extent of the studies needed, especially in different age groups, is often best decided on a case-by-case basis. FDA encourages you to discuss your clinical trial plan with the reviewing division.

FDA recommends that when developing medical devices for pediatric use, you consider the following:

Risk Assessment and Mitigation

Because the risk posed by the device may vary depending on the particular pediatric subgroup, you should determine the types of risk for each targeted pediatric subgroup by conducting a risk assessment. When assessing risk, the following critical factors should be considered: (1) age and degree of physiological maturity of the child, (2) nature and natural history of the clinical condition to be treated, (3) presence of complicating clinical conditions, (4) safety and effectiveness of the device that may have been demonstrated in older patients, or that is expected on the basis of other clinical or preclinical investigations, and (5) likely duration of device use and its impact on the growth and development of the child.

Using the results of the risk analysis, you should develop methods to address/mitigate the identified risks. In many cases, this may be accomplished through well-designed bench and animal studies. In others, clinical data will be necessary.

Pediatric Subgroups

If clinical data are needed to support a pediatric indication, you should make every effort to gather data such that each targeted pediatric subgroup is adequately addressed. In some cases, the expected benefit and safety information can be determined without separate studies in each subgroup. That is, it may be extrapolated from one age group to another. In other cases, such as with neonates, clinical data gathered specifically in that subgroup will likely be needed. You should be prepared to provide data for each targeted subpopulation or a justification as to why it is either not needed or can be extrapolated.

VII. Unique Host Characteristics

We recommend that you specify relevant subsets of the pediatric population in your intended use and indications rather than pooling them all into a single pediatric population. You should address the factors discussed below with respect to your device design, clinical study design, and labeling for each population. We recommend that you address these factors in devices specific to pediatrics and in general use devices with pediatric indications, where there may be unique issues when used in the pediatric population.

Age

As discussed in Section III, the identification of specific age limits for pediatric subpopulations is somewhat arbitrary. Characteristics such as the subject's weight, body size, physiological and neurological development, and neuromuscular coordination may be more appropriate when deciding upon the appropriate subpopulation for a device. For example, the use of cochlear implants in certain pediatric subgroups may be inadvisable due to the size of the implant or inappropriate due to the stage of the neurological development of the child. Therefore, when designing the clinical trial or the device labeling, age may be used as a preliminary approximator, but other factors should be considered to further define the appropriate population.

Size

We recommend that you determine if design modifications are necessary based on patient size (e.g., weight, height, body mass, or surface area).

Growth and Development

We recommend that you consider the following:

- impact of growth on the device and vice versa
- if the child will outgrow the device
- if adjustments will be necessary
- if further intervention may be needed
- impact of technological advance in the device (e.g., will the device be easily upgraded?)

Body Habitus

We recommend that you consider the following:

- normal as well as abnormal variations in the targeted pediatric group
- normal anatomic landmarks for each subgroup and anticipated deviations based on the targeted population
- impact of anomalies, particularly congenital anomalies.

Developmental Milestones

We recommend that you consider the following:

- impact of the device on the child
- activity level of the child
- ambulatory status of the child
- maturity level of the child

- stage of puberty (for example, in the pre-adolescent and adolescent, breast bud development may influence device placement).

Pathophysiology

We recommend that you determine the impact of the disease/condition on the pediatric patient and take into account the following:

- maturity or immaturity of various organ systems
- impact of materials, chemicals, electromagnetic radiation, electrical stimulation, and other agents
- hormonal influences, for example, effects of puberty in the preadolescent and adolescent population
- short-term and long-term effects of use.

Behavioral factors

We recommend that you consider the behavior expected in the targeted pediatric subgroup and anticipate the potential impact of the device. For example, an adolescent with a learning disorder may not be able to interface very well with certain devices and may require additional help or an alternative therapy.

Psychosocial factors

We recommend that you consider the psychosocial factors of the pediatric subgroups. For some pediatric devices or device trials, the family structure and environment, including how supportive the various family members are and who the primary caregiver will be, are important factors to consider.

Human Factors

Each pediatric subgroup will have different needs; therefore, you should consider these in the design and use of the device. We recommend that you consider the following for each targeted subgroup:

- invasive or non-invasive nature of the device
- level of interaction required for the proper functioning and use of the device
- optimal size of the device
- ease of use
- manual dexterity and strength required
- resistance to damage from wear and tear
- portability

- clarity of the labeling
- age-appropriate usability of the user interface
- age and maturity level needed to safely and effectively operate the device, particularly in adolescents and especially with regard to placement, compliance, and use of the device.

Surgical Factors for Implantable Devices

For each targeted pediatric subgroup, we recommend that you assess:

- the surgical site and anatomical landmarks
- surgical technique and level of expertise needed
- short-term and long-term effects
- immune status and update immunizations if indicated
- special issues pertaining to combination products, such as the possibility of drug/device interactions
- the need for antibiotic prophylaxis.

VIII. Labeling

Labeling requirements for medical devices are defined in the premarket regulations.[4] In general, the goal of medical device labeling is to provide the user with the following information:

- What the device is
- What the device does
- When the device should and should not be used
- How the device should be used to achieve maximum benefit and minimal risk.

To this end, we recommend that labeling for devices intended for use in pediatric subgroups incorporate the elements discussed below.

A. Basic Elements of Labeling

The following list identifies some of the basic elements of labeling and discusses ways to address these elements for pediatric populations.

[4] For premarket notification submissions, see 21 CFR 807.87(e). For PMAs and HDEs, see 21 CFR 814.20(b)(10) and 21 CFR 814.104(b)(4)(ii).

Device Description

Many devices and device accessories come in different models, sizes, shapes, and materials, as well as different modes of operation and different levels of sophistication requiring varying degrees of user interface. The labeling should describe various options recommended for use in pediatric subgroups and, when feasible, present these options in tabular form by age, weight, or other appropriate criteria.

Indications for Use

If your device is intended for use in a pediatric population, you should clearly define the indication(s), as well as the target population in the labeling. The indication may be general (e.g., cut, coagulate, ablate), or specific (e.g., treatment of vesicoureteral reflux). The target population may be broad (e.g., children and adults of all ages) or narrow (e.g., infants between the ages of 6-9 months). You should be prepared to justify and, when necessary, support the indication and targeted population(s) with appropriate data.

Contraindications, Warnings, and Precautions

Contraindications, warnings, and precautions, respectively, alert the potential user to situations where the device should absolutely not be used; data suggest that there is increased risk associated with use of the device; or data are lacking to define risk/benefit for a particular aspect of use or in a particular subgroup. Given the vulnerability of the pediatric population and specific host concerns described above, it is especially important that the contraindications, warnings, and precautions in labeling provide clear descriptions and well-defined actions and consequences. Contraindications, warnings, and precautions for devices intended for pediatric use should clearly address risks associated with age, size, and maturity and alert the user to specific hazards associated with the use of the device in children.

Adverse Events

Another key element of labeling is a discussion of device-related adverse events that have been reported from clinical investigations or literature pertaining to the use of medical devices. Device-related adverse events could be captured in many different ways: by severity, frequency, indication, gender, etc. If your device is intended for use in children, you should make a concerted effort to obtain and report the frequency of device-related adverse events according to the various pediatric subgroups in which the device will be used. This information will assist health care providers in assessing age-specific risk profiles and may be useful in mitigating the risks.

Clinical Studies

As discussed above, gathering clinical information directly on the targeted pediatric subgroup will often be necessary. The importance of summarizing that information in labeling warrants special attention. Your labeling should present information in a way that is clear, objective, and meaningful. You should report study results in a format that allows the user to recognize easily substantive differences in performance between children and adults and between various pediatric subgroups. Labeling should present these data using whatever qualitative or quantitative analyses are most appropriate, recognizing that subgroups may be too small to show statistical significance using standard tests.

Instructions for use

Understanding how to use a medical device correctly can be as important as the design, manufacturing, and testing of the device. Instructions may be provided for the health care practitioner, as is the case with prescription products, or the patient, as is the case with over-the-counter products, or both. You should address the recognition of anatomic, developmental, educational, and other age-related factors in this section of the labeling to help ensure proper use of the device and prevent avoidable device-related adverse events. FDA recommends that labeling, provided specifically for the pediatric patient, be age-appropriate with respect to written language and other visual and auditory tools.

B. Pediatric Information

You should submit appropriate information and summarize it adequately to ensure that labeling is satisfactory for **all** pediatric subgroups or **specific pediatric subgroups** (e.g., all pediatric subgroups except neonates) targeted in your intended use.

If you did not include a particular subgroup, or did not include sufficient numbers in that subgroup in your clinical trials, **and** there is reason to expect that there may be differences in safety and effectiveness among subgroups, your labeling should indicate that the device was not tested in the particular subgroup or that there is insufficient information to establish safety and effectiveness for that subgroup.

We recommend that you describe the specific age ranges rather than using "pediatric" in a broad sense. Please see **Table 1 Age Ranges of Pediatric Subgroups**.

C. Special Considerations

We recommend that you ensure the instructions for use are clear, take into consideration different pediatric subgroups, and address any special issues, where necessary. For example, newborn screening products should have labeling specific for the intended use in the neonatal population. Labeling should also address any special considerations appropriate to your device. For example, including a precaution to consider future breast bud development in female pediatric subjects when selecting a site on the chest for placement of a port or catheter may be appropriate. Another example may be including a precaution that provides advice on the appropriate activity level for the child, especially with respect to participation in certain sports.

IX. Protections for Pediatric Populations in Clinical Trials

The pediatric population represents a vulnerable subgroup of research subjects. Therefore, it is important that special measures be taken to protect the rights, safety, and welfare of the pediatric study participant. Every effort should be made to ensure that adequate protections are provided to these subjects during the conduct of clinical trials. The roles and responsibilities of the Clinical Investigator, Sponsor, and the Institutional Review Board are crucial in protecting the rights and welfare of the pediatric subject.

Clinical trials enrolling children must conform to 21 CFR Part 50 - Subpart D Additional Safeguards for Children in Clinical Investigations. Section 50.3(o) defines children as persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. For the purposes of this guidance, the terms pediatric population and children are synonymous.

FDA regulations governing IRBs identify children as subjects who may be vulnerable and subject to coercion. In such cases, IRBs must determine that additional safeguards are in place to protect their rights and welfare (21 CFR Part 56.111(b)). FDA's guidance document entitled, **Guidance for Institutional Review Boards and Clinical Investigators,** http://www.fda.gov/oc/ohrt/irbs/default.htm addresses issues regarding informed consent and the assent of children. The basic requirements of 21 CFR §50.20 regarding informed consent apply to the pediatric population. See also the guidance entitled, **E11 Clinical Investigation of Medicinal Products in the Pediatric Population,** http://www.fda.gov/cber/gdlns/ichclinped.pdf.

We recommend that you consult 21 CFR Part 50 - Subpart D (discussed below) and other referenced resources dealing with informed consent, assent, permission, financial remuneration, direct benefit, and minimal risk.

A. Definitions

The following terms are defined in FDA's and the Department of Health and Human Services' human subject protection regulations and guidance:

Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not be construed as assent. 21 CFR 50.3(n).

Children means persons who have not attained the legal age for consent to treatments or procedures involved in the clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. 21 CFR 50.3(o).

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage, or procreation.[5]

Family member means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship. 21 CFR 50.3(m).

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of 21 CFR Part 50, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research. 21 CFR 50.3(s).

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. 21 CFR 50.3(l).

[5] IRB Guidebook: Chapter VI Special Classes of Subjects, http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm#g4

Mature Minor: Persons who have not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. [6]

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 21 CFR 50.3(k).

Parent means a child's biological or adoptive parent. 21 CFR 50.3(p).

Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of 21 CFR Part 50 and must include the elements of informed consent described in Sec. 50.25. 21 CFR 50.3(r).

B. Study Design Considerations

As discussed above, FDA recommends that you identify the subgroup in which you wish to evaluate your device, unless the device is intended for the entire pediatric population. When deciding whether a clinical trial is needed for a particular pediatric population, the following points are important to consider:

- Does the research have an identifiable prospect of direct benefit to the individual child participant? Can that benefit be achieved through alternative means?

- Does the research have an identifiable prospect of risk to the individual child participant? What safeguards are proposed to minimize these risks? When procedures involving greater than minimal risk to children are anticipated, are convincing scientific and ethical justifications given?

It is important when designing the study that every attempt is made to anticipate and reduce possible study hazards. Investigators should be knowledgeable of all relevant pre-clinical data and be properly trained and experienced in the pediatric population and medical procedures used for this population.

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[6] IRB Guidebook: Chapter VI Special Classes of Subjects, http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm#g4

We recommend that you ensure appropriate pediatric expertise is reasonably available during the entire trial. We also recommend all clinical sites have staff and equipment appropriate for pediatric care. Your clinical sites should also have pediatric-specific emergency measures, such as properly sized oxygen, suction, and resuscitation devices as well as medications to treat severe anaphylaxis and adverse reactions (see also http://www.ems-c.org.)

Because many procedures used during clinical trials are often new to the child, every effort should be made to ensure the participants' experiences in the study are positive and to minimize discomfort and distress. Additionally, before studies are undertaken, an evaluation should be made to determine if the needed information can be obtained from less vulnerable populations. When studies are conducted in the pediatric population, every attempt should be made to include individuals representing the demographics of the region and the disease being studied. Studies in handicapped or institutionalized pediatric subjects should be limited to diseases or conditions found principally in these populations.

To be of benefit to those participating in a clinical study, the study must be properly designed and conducted to ensure that quality data is obtained. Following Good Clinical Practice (GCP) is crucial to obtaining quality and reliable data from the study.

C. The Role of the Institutional Review Board (IRB)

The principal role of the IRB is to protect the rights and welfare of human research subjects; this is especially true when studies involve children as subjects. To safeguard the child's interests and to protect children from harm, special ethical and regulatory considerations are in place for reviewing research involving children. The regulations at 21 CFR 50 Subpart D, "Additional Protections for Children Involved as Subjects of Research," describe these considerations.

IRBs reviewing research involving children as subjects must consider the benefits, risks and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child subject or to society as a whole. The IRB should weigh the circumstance of the subject under study, the magnitude of risks that may accrue for the research procedures, and the potential benefits the research may provide to the subjects.

The regulations require IRBs to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study. The four categories are:

- Clinical investigations not involving greater than minimal risk (21 CFR 50.51)

- Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. (21 CFR 50.52)

- Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. (21 CFR 50.53)

- Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (21 CFR 50.54)

In all cases, IRBs must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians. (21 CFR 50.55)

D. Consent and Assent

We recommend that you ensure that the informed consent document is clearly written and that the risks and benefits are thoroughly explained. FDA recognizes that consent depends on a number of factors, including:

- age
- maturity level
- legal status of the subject (emancipated or mature minor)
- applicable law of the jurisdiction in which the research is conducted and which in turn determines legal age of consent
- comprehension level of the pediatric research participant, parents, guardians, and legally authorized representative.

We also recommend that you consider:

- prognosis and life expectancy of patients with certain diseases or disorders
- mental capacity, intellectual quotient, and level of functioning
- differing ages and maturity level
- direct benefits and risks of the pediatric participant's research involvement (research versus therapeutic treatment)
- ethical issues
- proper monitoring (data and safety monitoring).

When children or minors are involved in research, the regulations require the *assent* of the child or minor and the *permission* of the parent(s) in place of the consent of the subjects. 21 CFR 50.55. While children may be legally incapable of giving informed consent, they may possess the ability to assent to or dissent from participation. The regulations do not require that assent be sought from children starting at a specific age, but that their assent should be sought when the children are capable of providing their assent. Therefore, children should be asked whether or not they wish to participate in the research particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

Researchers may seek assent of children of various ages. Older children may be well acquainted with signing documents through prior experience with testing, licensing, and other procedures normally encountered in their lives. Signing a form to give their assent for research would not be perceived as unusual and would be reasonable. Younger children, however, may never have had the experience of signing a document. For these children, requiring a signature may not be appropriate, and some other technique to verify assent could be used. For example, a third party may verify, by signature, that the assent of the child was obtained.

The informed consent document does not have to contain a space for assent by children, however, many investigators and IRBs consider it standard practice to obtain the agreement of older children who can understand the circumstances before enrolling them in research. The basic requirement of 21 CFR 50.20 applies, i.e., the legally effective informed consent of the subject or the subject's legally authorized representative must be obtained before enrollment. Parents, legal guardians and/or others may have the ability to give permission to enroll children in research, depending on applicable state and local law of the jurisdiction in which the research is conducted. (Note: permission to enroll in research is not the same as permission to provide medical treatment). IRBs generally require investigators to obtain the permission of one or both of the parents or guardian (as appropriate) and the assent of children who possess the intellectual and emotional ability to comprehend the concepts involved. Some IRBs require two documents, a fully detailed explanation for parents and older children to read and sign, and a shorter, simpler one for younger children.

For some research activities, IRBs may require that either an IRB member or an advocate for the child be present during the assent and permission procedures to verify the child understands and to support the child’s preferences. The IRB may also require that the parent(s) or a close family member be present during the research, especially if a young child will be exposed to significant discomfort or inconvenience, or if the child will be required to spend time in an unfamiliar place (i.e., study site).

In all cases where assent is required, the proposed research should be explained to the child in language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomfort and inconveniences the child may expect to experience if he or she agrees to participate. The subject should also be made aware of his or her rights to decline to participate or to withdraw from the study at any time. Additionally, the safety of the subject is always an overriding factor in the continuation of a subject in any study. If a subject wishes to withdraw from a study and, in the opinion of the investigator and the IRB, the safety and welfare of the pediatric subject would be jeopardized by his/her removal from the study, continued parental or legal guardian consent should be sufficient to allow participation in the study.

A useful reference on informed consent for children participating in research can be found in the guidance entitled, "A Pediatric Research- Assent Decision Matrix" (http://ohrp.osophs.dhhs.gov/panels/407-01pnl/riskcat.htm). This matrix is based on the relationship between benefit and risk ratio and the age of the subject. The matrix is arranged in descending order of ratio of benefits to risk as defined in Subpart D, and the age potential for assent by child subjects.

X. Other Resources

FDA Regulations

Protection of Human Subjects 21 CFR Part 50 (see especially Subpart D Additional Safeguards for Children in Clinical Investigations)

Institutional Review Boards 21 CFR Part 56

Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products; Interim Rule 66 FR 20589, April 24, 2001.

Guidance

Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers
http://www.fda.gov/cdrh/ohip/guidance/1128.html

Medical Device Use –Safety: Incorporating Human Factors Engineering into Risk Management
http://www.fda.gov/cdrh/humfac/1497.html

Recognition and Use of Consensus Standards; Final Guidance for Industry and FDA, 06/20/2001 http://www.fda.gov/cdrh/ost/guidance/321.html and CDRH standards database FDA Recognized Consensus Standards.

International Conference on Harmonisation (ICH) Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population http://www.fda.gov/cber/gdlns/ichclinped.pdf

Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update http://www.fda.gov/oc/ohrt/irbs/default.htm

Additional References

IRB Guidebook: Chapter VI Special Classes of Subjects, http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm.

Age Limits of Pediatrics (RE8116). *Pediatrics 1988;81(5):736* American Academy of Pediatrics, http://www.aap.org/policy/02031.html

A Pediatric Research "Assent" Decision Matrix, http://ohrp.osophs.dhhs.gov/panels/407-01pnl/riskcat.htm.

International Organization for Standardization (ISO) 10993-6: 1994 – Biological Testing of Medical Devices.

CDRH Standards Program webpage http://www.fda.gov/cdrh/stdsprog.html

American National Standards Institute (ANSI) - Association for the Advancement of Medical Instrumentation (AAMI) Electrosurgical Devices (ANSI/AAMI) HF18-1993, 4.1 and 4.2.