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StarFish Medical Analysis: FDA Issues new guidance on Pediatric Medical Device Clearance

By Vincent Crabtree, Mar 27, 2014

Background

On March 24, 2014, the FDA issued a revised guidance document 'Premarket Assessment of Pediatric Medical Devices', ucm089740, which supersedes 'Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices' dated May 14, 2004.

Medical devices developed solely for children are generally rare. Most developers need to get to market quickly, so even though a device may be applicable to pediatric cases, the additional regulatory burden is added to the 'to do later' list. In reality, these things never get done, so there is a lack of appropriate medical devices for children. Because of this, clinicians have to off-label use devices intended for adults with children, which is far from satisfactory.

US Congress recognized this unmet clinical need problem in 2007, which prompted the FDA to instigate the pediatric device consortia grant program. This program has been active since 2009 and awarded $3.5 million in 2013 to seven consortia.

The latest guidance appears part of the agency's continued efforts in this area. It clarifies the agency's regulatory expectations for pediatric medical device submissions, while maintaining the expected high standards for clinical study integrity, and device safety and efficacy, one would expect for use with children.

The document has guidance in five main parts:

- Pediatric Population and use
- Unique Characteristics of Pediatric Patients
- Clinical Data
- Labelling
- Protection for pediatric population in clinical studies

Pediatric Population

The guidance recommends defining pediatric cases according to the following table:

Pediatric Subgroup	Approximate Age Range
Newborn (neonate)	Birth – 1 month
Infant	> 1month – 2 years
Child	> 2 years – 12 years
Adolescent	> 12 years – 21 years (up to 22 Birthday)

The guidance document notes that the upper age range definition varies amongst different experts. Given the scope of medical devices, such as the effects of growth, the range presented is most useful for clinical trials. The document notes 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.

The guidance document references the standard principles for development of medical devices:

- Biocompatibility, including toxicity and carcinogenicity
- Sterility and infection control (as applicable)
- Environmental factors related to location of use, such as electromagnetic fields and radiation
- Design controls and good manufacturing practices (GMP)

In addition, the agency recommends special attention for the following areas:

- Height/weight
- Growth and development
- Disease or condition
- Hormonal influences
- Anatomical and physiological differences from the adult population
- Activity and maturity
- Immune Status

Unique Host Characteristics

The guidance document is quite detailed on the special characteristics of children compared to adults. It recommends that subgroups are employed in the intended use and labelling, rather than pediatric as a whole, where appropriate. In particular, the agency discusses:

- Age – the definition is arbitrary, and other characteristics may better represent the intended pediatric population. Weight, body size, physiological, neurological, and neuromuscular coordination may be more appropriate.
- Size – design modifications may be required as necessary to address difference in on size (e.g., weight, height, body mass, or surface area).

- Growth and Development – as the child is expected to grow, the developer is expected to consider the impact of growth on the device, whether adjustments may be required due to growth , whether the device will require changing/swapping and the associated risks such as interventions, whether the device can be upgraded as technology progresses.
- Body Habitus – the developer is expected to consider the bodily characteristics of the child, and the impact a particular pathology may have. For example, normal and abnormal variations of the target pediatric subgroup, anatomic landmarks anticipated deviations, and the impact of any anomalies, particularly congenital anomalies.
- Developmental Milestones – the document recommends the impact of the device be assessed in terms of impact of the device on the child activity, ambulatory, maturity status and subsequent physical and mental development).
- Pathophysiology – the developer is particularly expected to consider the impact of the disease or condition on the child, such as maturity or immaturity of the organ systems, including the immune system, the impact of materials, chemicals, electromagnetic radiation, electrical stimulation, and other agents, the impact of hormones, and the short-term and long-term effects of device use.
- Behavioral factors – the developer should consider the behavior expected in the targeted pediatric subgroup and anticipate the potential impact of the device, e.g. rebellious teenager.
- Psychosocial factors – as appropriate, the developer should consider the impact of 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 – the developer should consider that each pediatric subgroup will have different needs which should be addressed in the device design for each subgroup. For example, invasiveness, optimal size, required dexterity/strength to operate, resistance to damage/wear and tear, labelling, ease of use, level of required interaction, age/mentally appropriate user interface, age/maturity/mental acuity required 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 pediatric subgroup, the developer should consider the surgical site and anatomical landmarks, required surgical expertise and appropriate techniques, short and long term effects of the required surgery, immune status and update immunizations, if indicated, any special issues for combination products and the need for antibiotic prophylaxis.

Clinical Data

The guidance document discusses clinical studies, but starts by pointing out that, as with medical devices in general, well designed bench testing may be sufficient and clinical study data will not be required for all pediatric medical device submissions. 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.

Fortuitously, the agency is still following the least burdensome approach for regulatory submissions for pediatric devices, and recommend a pre-submission meeting is undertaken to obtain feedback on the study protocol before it commences.

If a clinical study is definitely required, the preferred course of action could be to perform incremental studies in addition to adult clinical study data previously obtained. In these cases, a risk analysis should be performed, which may raise new mitigations to address the risks. That would require subsequent verification, or the product may need to be validated in a pediatric study. Otherwise, the adult condition may be sufficiently different or poorly understood so as to raise concerns on effectiveness or safety, which would require pivotal, rather than incremental studies.

The agency also pints out that, due to differences in pediatric subgroups, data may be required from all subgroups, depending on device type. This is particularly required, for example, for devices which may be affected as the child grows.

Labelling

As with all medical devices, the purpose of labelling is to indicate the correct usage, risks and hazards of a particular device. The agency wants the labelling to provide supporting information to permit clinicians and caregivers the ability to properly evaluate the risks when using the device, such as:

- Indications for use, contraindication, warnings and precautions – particular attention should be paid relating to the pediatric subgroups as defined earlier. E.g. device description and indication for use should reference any sizing issues or recommendations. The indications for use should define the target pediatric profile. Again, where other metrics, such as weight etc are more appropriate, these should be employed, rather than age, and the submitter should be prepared to justify the indications with appropriate data if queried.
- Adverse events – the labelling should contain a description of all known device related adverse events.
- Clinical Studies – any clinical study data should be summarized in the labelling in a clear, objective and meaningful manner that permits the reader to easily recognize substantive differences in performance between children and adults and between various pediatric subgroups, preferably with qualitative or quantitative analyses, recognizing that, due to small sample sizes, statistical significance may be difficult to demonstrate.
- Instructions For Use (IFU) – The document notes that understanding how to use a medical device correctly can be as important as the design, manufacturing, and testing

of the device. An IFU for a prescription device should be written to provide instructions for safe and effective use, such as addressing anatomic, developmental, educational, and other age-related factors, and prevent avoidable device-related adverse events. Instructions for the pediatric patient or caregiver should be age-appropriate and employ visual and auditory tools.

The document also requests that there should be sufficient information submitted to ensure the labelling is satisfactory for all pediatric subgroups targeted in your intended use. If the intended use covers a subgroup which was not tested and there may be questions on safety and/or effectiveness, the labelling should indicate the device has not been tested, and whether there is insufficient information to establish safety and effectiveness in that particular subgroup.

Protections for Pediatric Populations in Clinical Trials

A large proportion of the document relates to clinical governance due to the vulnerable nature of pediatric patients. When designing clinical studies, two main questions must be considered:

- Is there an identifiable prospect of direct benefit to the individual child participant? Can that benefit be achieved through alternative means?
- Is there an identifiable prospect of risk to the individual child participant? If so, 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?

As with other medical devices, the study should be conducted under GCP, and the IRB must protect the rights and welfare of those involved by considering the study in accordance with the following criteria:

- Clinical study with minimal risk to participants
- Clinical study with greater than minimal risk but presenting the prospect of direct benefit to participants
- Clinical study with greater than minimal risk, and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the disorder/condition
- Clinical study not otherwise approvable that presents the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

In particular, the document discusses consent and assent. Written Informed Consent is required from the legal guardian or parent of the child, and where able, assent from the child is also required. Materials must be made available to facilitate the child's understanding of their participation in the study, and the materials should reflect the age range, mental acuity and maturity of the child. The method of documenting assent must also be considered, for example, a third party witnessing the assent of a younger child, or a form for a teenager who can sign their name.

Summary

The guidance document notes the FDA believes clinical data is appropriate when information from other sources, such as pre-clinical bench or animal testing, literature, or adult clinical trials, are inadequate to establish safety and effectiveness for a pediatric indication, e.g.

- 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 the above circumstances exist, clinical data from pediatric subjects help ensure that manufacturers:

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

The FDA recommends a risk based approach is taken since the risk posed by the device may vary depending on the particular pediatric subgroup, with special consideration for

- age and physiological maturity of the child
- nature and natural history of the clinical condition to be treated
- presence of complicating clinical conditions
- 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
- likely duration of device use and its impact on the growth and development of the child.

The risk analysis is then used to address or mitigate the identified risks – in some cases, well designed animal and bench studies will be sufficient; in others, pediatric clinical data will be required.

If pediatric clinical data is required, data should be captured for each pediatric subgroup. In some cases, extrapolation may be possible, but there should be sound justification available for the validity of any extrapolation. In other cases, such as neonates, clinical data will likely be required.

Medical devices cover a broad spectrum of devices, from external IVD to implantable structural, implantable functional and implantable electro-medical. The document notes it is difficult to be prescriptive across such a broad range: pragmatically, the FDA recommends pediatric clinical studies are conducted only when absolutely necessary. For example, IVDs would usually be evaluated with bench top studies. Other devices may be evaluated in animal and/or cadaver studies.

Finally, the document recommends a pre-submission meeting is held with the FDA to understand the scope of any clinical testing required.

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About the author: Vincent Crabtree is a StarFish Medical Project Manager and Regulatory Advisor, with an emphasis on Project Leadership ensuring projects conform to consensus standards such as ISO14971, IEC60601-1 and managing clients setting-up Quality Management Systems that comply with ISO13485 and FDA Quality System Regulations. He is passionate about commercializing innovative technology, and brings an entrepreneurial perspective.

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