

Draft: Food and Drug Administration Pediatric Device Development Plan

TITLE III, FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007 (FDAAA) PEDIATRIC MEDICAL DEVICE SAFETY & IMPROVEMENT ACT OF 2007 Sec. 304. Encouraging pediatric medical device research

On September 27, 2007, this legislation went into effect requiring, among other things, that the Secretary of Health and Human Services, acting through the National Institutes of Health, the Food and Drug Administration and the Agency for Healthcare Research and Quality (NIH-FDA-AHRQ) develop a plan for expanding pediatric medical device research and development. The following summarize FDA's current activities to further pediatric device research, some of the gaps in pediatric research, and possible proposals for items to include in a research agenda:

Draft guidance. FDA is currently working on a draft guidance for industry and FDA staff, "Pediatric Device Use Information and Tracking Pediatric Device Approvals." This guidance will describe how Premarket Approval Applications (PMA), Product Development Protocols (PDP), Humanitarian Device Exemptions (HDEs), and PMA, PDP, and HDE panel-track supplements and Annual Reports can meet the new statutory requirements of section 302 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which involves tracking pediatric device approvals. Pediatric data obtained through PDP/PMA submissions will help further the understanding of medical device use in the pediatric population while identifying areas of pediatric device research and development that need to be addressed. This pediatric data will provide information that will help formulate the research agenda of the Agency and help address unmet pediatric medical device needs as mandated in section 304.

Review and analysis of information submitted to the FDA. Information submitted to FDA on both known and potential use of medical devices in pediatric patients should provide further insight into future directions where to direct pediatric device research. The FDA has made a concerted effort to encourage device submissions which target the pediatric population. The Federal Food, Drug, and Cosmetic Act (the Act) and the Center for Devices and Radiological Health (CDRH) define pediatric patients as patients who are 21 years of age or younger at the time of the diagnosis or treatment (520(m)(6)(E)(i) of the Act). The pediatric population comprises the following subpopulations: neonate, infant, child and adolescent.

The following are examples of pediatric devices: fetal bladder stents, pediatric sized heart valves, newborn hearing screener and neonatal screening tests for disorders such as phenylketonuria and hypothyroidism.

Based on premarket applications and postmarket reports it has received, the Agency is aware that there are many unmet needs for the pediatric population, resulting in use of adult devices, not approved for pediatric use, being retooled to try to address these needs. One of the major areas of need is in the neonatal age range (the first 28 days of life). As a result of

amazing achievements in neonatology, leading to better survival rates of premature, low-birth weight and very low birth weight babies, there is a growing need for appropriately sized devices in almost every area of intervention. These include, but are not limited to, catheters, intubation tubes, feeding tubes, infusion pumps, cardiovascular devices, surgical instruments, diagnostic devices, radiologic and imaging devices. These areas represent those with the most pressing needs. The challenges are the same for the various subpopulations of pediatric patients, where the differences in size, anatomy and physiology make it difficult to find appropriate devices – one size does not fit all.

While size is an important parameter, it is not the only factor. Devices for children must take into consideration the differences in growth and development within each subpopulation and among each subgroup of the pediatric population. The needs of a neonate will be far different, in many cases, from those of an adolescent. The needs of a normal, healthy neonate will be different from a premature, small for gestational age or low birth weight baby. The Agency has observed that there is a need for manufacturers to recognize the unique host characteristics within each of the subpopulations, and, where possible, address these through clinical studies.

Pediatric clinical data are needed to ensure that the device is properly designed for the intended population; that safety and effectiveness are demonstrated rather than presumed; that accurate risk assessments have been done; and that instructions for use are clear. FDA's premarket guidance for industry and FDA staff, entitled "Premarket Assessment of Pediatric Medical Devices" (www.fda.gov/cdrh/mdufma/guidance/1220.html), elaborates on these and other important considerations.

Other areas in need of increased attention in pediatric device labeling include the following:

- (1) Unique human factors that are specifically related to the use of a device in the pediatric population need to be considered. The Agency encourages usability studies to address human factors, such as ease of use, fit, and impact of the device on the child and vice versa.
- (2) Risk mitigation entails addressing each targeted subpopulation or age range for which the device is indicated and is crucial in the pediatric population.
- (3) The growing use of antimicrobials on devices has raised concerns in the general population, and is of greater concern for the pediatric population. Antimicrobials are being added to devices by impregnation, bonding, or coatings and may include antibiotics, metals, or other chemical agents. Potential adverse effects include, among others, antimicrobial resistance, superinfection, endocrine disruption, hypersensitivity, allergic, and idiosyncratic reactions.
- (4) During emergency preparedness exercises for pandemic avian influenza and SARS, the need for pediatric respirators became apparent. Respirators could serve as major tools to reduce exposure and spread of disease. However, there are no approved or cleared appropriately sized or pediatric-specific masks/respirators. This is an urgent area of need.
- (5) During the review of many Investigational Device Evaluations (IDEs), sponsors may submit mathematical models and algorithms to support their studies. In many cases, the pediatric population is not represented sufficiently. CDRH has been encouraging more robust evaluation of the various subsets of the pediatric population in these models and

algorithm development. This may be an area for further development and may be applicable to other device types.

HDEs. Through the Humanitarian Device Exemption (HDE) regulatory pathway, patients with conditions that affect 4,000 patients or less may receive access to a medical device showing a probable benefit to health. Examples of devices that have been approved for marketing in this way include the following: Vertical Expandable Prosthetic Titanium Rib (VEPTR), DeBakey VAD Child Left Ventricular Assist System, and the Contegra Pulmonary Valved Conduit.

FDAAA encourages manufacturers to study and apply for approval of pediatric devices by allowing them to make a profit from sales of an HDE device, up to 4,000 sales per year.

OSEL. FDA's Office of Science and Engineering Laboratories (OSEL) has been important in applied research for both the premarket and postmarket activities. During the premarket phase OSEL assesses the adequacy of test protocols and test results. On the postmarket side their experts have been consulted to help identify the root cause of device failures and assess the adequacy of proposed remediation. One example of an important area of research is on pediatric mechanical circulatory support devices. Further pediatric expertise can be developed for newer products used in pediatric subpopulations.

Adverse events. FDA collects data on device-related adverse events and product problems through a nation-wide reporting system. Reports are also gathered through FDA's Medical Product Safety Network (MedSun), a network of about 350 hospitals. Both sources provide reports of events affecting the pediatric population that often stimulate further investigation and interventional efforts. For example, a nationwide investigation of childhood meningitis associated with cochlear implants was initiated based on reports received through these reporting systems. The investigation led to a device recall, public health notifications, and to a change in national vaccination recommendations. MedSun has recently initiated a more targeted effort, with a subset of pediatric hospitals known as KidNet, to better understand device performance in neonatal and pediatric ICUs. Some of these systems with adverse event reports have highlighted the need for better safety measures on incubators, phototherapy systems, and infusion pumps.

Condition of approval studies. FDA may require manufacturers to conduct studies, as a condition of premarket approval, to address certain remaining issues of device safety and/or effectiveness (e.g., long-term device performance). Currently, about 45 of 60 devices with such requirements, ordered since January 2005, include studies involving the pediatric population. Information gathered in these studies help inform a device's performance profile and potential opportunity for further device improvements.

Postmarket studies. FDA also has the authority to require manufacturers to conduct post-market studies of their device (Section 522 of the Act). FDA currently has two such studies underway that involve the pediatric population. FDAAA expanded FDA's

authority to order such studies to include devices that are expected to have significant use in pediatric populations and to issue orders for these studies as a condition of approval or clearance for pediatric devices. Additional use of this authority, to further understand pediatric device performance, is expected in the future.

IOM Report. The Institute of Medicine report, *Safe Medical Devices for Children* (Committee on Postmarket Surveillance of Pediatric Medical Devices, Board on Health Sciences Policy, Marilyn J. Field MJ, Tilson H (eds[LAW3]). Institute of Medicine of the National Academies, Washington, DC, July, 2005) made several recommendations aimed at improving postmarket surveillance in general, and pediatric surveillance in particular. FDA has moved to implement several of these recommendations, including the expansion of Section 522 authority and the establishment of KidNet. As previously noted, these efforts will evaluate device performance in the postmarket period and may offer a window into device improvements as well.

Orphan Product grants. The Office of Orphan Products Development (OOPD) administers a \$14 million dollar grant program which sponsors clinical research to advance therapies for rare diseases or conditions, affecting less than 200,000 people in the United States.

Established in 1983, the OOPD grants program has awarded over \$232,000,000 towards rare disease research. While over four hundred and fifty grants have been awarded, only twenty of these grants have been for device studies.

These twenty device grants have included several promising treatments for pediatric patients. One example of an Orphan Products funded study was the Vertical Expandable Prosthetic Titanium Rib (VEPTR) for children born with thoracic insufficiency. This device study and approval has spurred research interest in pediatric devices for rare conditions. Other pediatric device grants include cultured skin substitutes for closure of burn wounds and magnetic alteration of pectus excavatum.

The Orphan Products Grant program could further contribute to pediatric device research through increased participation of device manufacturers in the Orphan Grant Program. Funding from this program could be used to support the development of devices for the pediatric population. Only clinical studies qualify for consideration. Funded grant applicants may receive up to \$400,000 annually for up to four years.