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Discussions on Evaluation of Medical Devices in Pediatric Use

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The Subcommittee on Evaluation of Medical Devices in Pediatric Use of the Pharmaceuticals and Medical Devices Agency (PMDA) Science Board discussed how to assess the pediatric use of medical devices, in view of the current pediatric use of medical devices reviewed and approved for use in adults. The subcommittee also discussed points to consider at stages from development to regulatory review through approval.

1. Introduction

In the 9th Science Board meeting held on August 7, 2014, the following opinion was raised: “How medical devices reviewed and approved for use in adults are actually used in clinical practice should be examined to determine whether pediatric use of such devices have caused any problems. By doing so, points to consider upon the review of medical devices should be discussed.” This led to the recognition that further discussions focusing on the pediatric use of medical devices were necessary, and thus the expert advisors were invited to this subcommittee in cooperation with the Japan Pediatric Society.

Medical devices used in pediatric patients are classified into three categories: “Approved with adult data only,” “Approved with a combination of data from adults and pediatric patients,” and “Approved with pediatric data only.” Many of the approved medical devices

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are supplied in a number of sizes due to variations in patients' body size. The devices in different sizes are approved based on the basic device performance; whether they are used by pediatric patients is not confirmed in the regulatory review. Nevertheless, these devices are actually used for pediatric patients in clinical practice, causing a concern because of limited clinical evidence in pediatric use.

Recently, the Food and Drug Administration (FDA) of the United States has been focusing on "Unmet Medical Needs" in the orphan diseases and pediatric patients, and policies to protect pediatric patients in clinical trials for medical devices have been established and reinforced. In response to this, two sets of guidance (Premarket Assessment of Pediatric Medical Devices; Providing Information about Pediatric Uses of Medical Devices) for regulatory procedures including pre-marketing reviews were announced in 2014. The guidance states that assessment and information on pediatric use are required for the regulatory review of medical devices.

2. Current status and problems in the use of medical devices in three pediatric areas

Key issues related to the assessment of medical devices for pediatric use were discussed, in view of the current status and problems concerning three areas described below.

2.1. Cardiovascular area

Various types of medical devices are needed for cardiovascular diseases in pediatric patients due to the disease characteristics. The current status of regulatory approval of pediatric devices markedly differ between Japan and other countries. There are many "medical devices already approved overseas or evaluated in overseas clinical trials but not in Japan." For example, pediatric ventricular assist devices (VADs) have long been available for clinical use in the US and Europe but are still undergoing clinical trials in Japan. In addition, a clinical trial of an implantable VAD has already begun in Europe and is expected to dramatically improve patient activities once the VAD is marketed. Unfortunately, Japan has not been participating in the global clinical trial and yet to start a clinical trial. Meanwhile, in Japan, a pediatric VAD was approved in June 2015 and began to receive health insurance coverage in August 2015.

Some medical devices approved in Japan are not actually used in clinical practice because most children's hospitals do not satisfy the facility eligibility criteria for using the devices. In

Japan, many pediatric patients with refractory diseases are treated at children's hospitals. Facility eligibility criteria for using medical devices should therefore be carefully defined to allow children's hospitals to use the devices appropriately.

2.2. Surgical area

Pediatric surgical diseases require delicate surgical technique because of small body size of pediatric patients. Surgical interventions for a pediatric patient should be considered and selected in view of immature organ functions, age-related physical changes, and the patient's life for the next several decades as well as small body and organ size. Moreover, surgical procedures in pediatric patients often have to be performed in small surgical fields due to small tissue and organ size, and pediatric patients have vulnerable organs. Delicate surgical technique is there required.

The following are examples of problems associated with pediatric use of surgical medical devices: Vessel sealing devices (surgical instrument for cutting and cauterizing blood and lymph vessels) designed for adults are also used in pediatric patients; models with less heat diffusion to surrounding areas are therefore required for pediatric patients. Also, automatic anastomotic devices and jejunal tubes designed for adults are used in pediatric patients; models of smaller size or diameter are needed but are currently unavailable.

In addition, a noticeable disparity exists in the timing of clinical trials and regulatory approval between Japan and other countries for some surgical medical devices, as with medical devices for cardiovascular diseases. For instance, fetoscopy used for the treatment of congenital diaphragmatic hernia is already available overseas but still at the clinical research stage in Japan. Manufacturing and marketing medical devices for pediatric surgical diseases may not be profitable because of limited number of patients who require such devices. This hinders medical device companies from developing pediatric surgical devices. Another problem is that sufficient number of patients may not be recruited for clinical trials of pediatric surgical devices.

2.3. Neonatal area

Medical devices are widely used in the treatment of neonatal diseases because neonates, especially those with low birth weight, have immature organ functions and low reserves.

Japan's birth rate is slowly decreasing, but the percentage of low birth weight infants is increasing, owing to advances in medical technologies. Approximately 10% of all neonates

have a low birth weight of ≤2500 g, with approximately 100,000 low birth weight infants born every year, according to the vital statistics conducted by the Ministry of Health, Labour and Welfare. Furthermore, the percentages of very low (≤1500 g) and extremely low (≤1000 g) birth weight infants are increasing. As stated above, many low birth weight infants have immature organ functions, with at least 70% of all neonatal deaths occurring in low birth weight infants. On the other hand, it is no longer uncommon that neonates weighing ≤500 g at birth are subsequently discharged from hospital to home.

A wide variety of medical devices are used to treat neonatal diseases: artificial ventilators, phototherapy devices, artificial heart-lung machine, hemodialysis devices, therapeutic hypothermia devices, nitric oxide inhalation devices etc. Recent advances in medicine have enhanced the understanding of neonatal diseases, leading to advances in individual medical devices. This certainly has contributed to the improvement in neonatal care.

Still, some problems and issues remain in cases where various medical devices are used in combination. For instance, some medical devices have not been confirmed to operate normally when used in combination with other devices. Unexpected events that cannot be predicted from the individual performance of each device may occur. In addition, the management of catheters, cardiopulmonary bypass, and blood purification circuits, which can be used in very/extremely low birth weight infants, is not adequate.

Some neonates or infants discharged from hospital after surviving a neonatal disease may need home care. As with hospitalized neonates or infants, those receiving home care need various medical devices. Accordingly, standardization of home care medical devices is another issue that should be addressed.

2.4. Other issues

In Japan, clinical trials and regulatory approval of some medical devices are delayed because foreign medical device companies are reluctant to obtain approval of their products in Japan, and because Japanese medical device companies are not actively seeking approval for pediatric use of their products even though they have been developed in Japan. The reasons the companies are reluctant to seek regulatory approval are as follows: the market size for pediatric devices is small because of limited number of patients; pediatric devices need to be manufactured in many different models with smaller production scale compared to devices for adults; and companies have a biased

assumption that benefits do not outweigh the cost and efforts of obtaining regulatory approval in Japan. This can lead to another concern: some Japanese medical device companies, from the early stages of development, may have no intention of making their products available for pediatric use.

3. Points to consider when evaluating medical devices in pediatric use

Discussions on the three areas of pediatric diseases revealed a common problem affecting all pediatric medical devices: Companies are discouraged from developing medical devices not by scientific obstacles, but by social obstacles, i.e., high cost and low profit due to the small population of rare pediatric diseases. Accordingly, the points to discuss and consider when evaluating medical devices in pediatric use should be clearly disclosed, so that medical device companies know how to proceed to the stages of development, review, and approval of their products. By doing so, discussion by this subcommittee shall encourage companies to develop pediatric medical devices.

This subcommittee discussed “Points to discuss and consider when evaluating medical devices for pediatric use in Japan” in view of the FDA’s guidance. The details are described below.

3.1. Judgment on pediatric use

The FDA defines “Pediatric patients” as persons aged up to but not including the 22nd birthday, consisting of neonates (from birth through the first 28 days of life), infants (29 days of age to less than two years of age), children (two years of age to less than 12 years of age), and adolescents (12 years of age to less than 22 years of age). However, body weight, physical size, physiological development, neuropsychological maturity, etc. may be more appropriate criteria in some cases rather than patients’ age. Thus, whether a medical device can be used in pediatric patients should be judged not based simply on patients’ age but on appropriate criteria defined according to the characteristics of individual devices or diseases. This approach should apply not only to pediatric diseases but also to adult diseases in which medical devices are assumed to be used by pediatric patients as well.

3.2. Providing information on medical devices for pediatric use

The FDA requests that information such as annual incidence and prevalence of the target disease be provided upon the regulatory application for new medical devices. However, in Japan, accurate epidemiological data are not available for most pediatric diseases.

Meanwhile, Healthcare Subsidy Program for Specific Pediatric Chronic Diseases and patient registries would provide useful alternative data sufficient to evaluate the pediatric use of medical devices, although the data may not include accurate incidence or prevalence of a disease. To accelerate the development of medical devices, it is desirable to establish a system that allows such data to be used effectively.

3.3. Evaluation of efficacy and safety in pediatric patients

The safety and efficacy of pediatric medical devices should be evaluated, in principle, in the same manner as for other medical devices. Because of the vulnerability of the pediatric population, special consideration and protective measures are required.

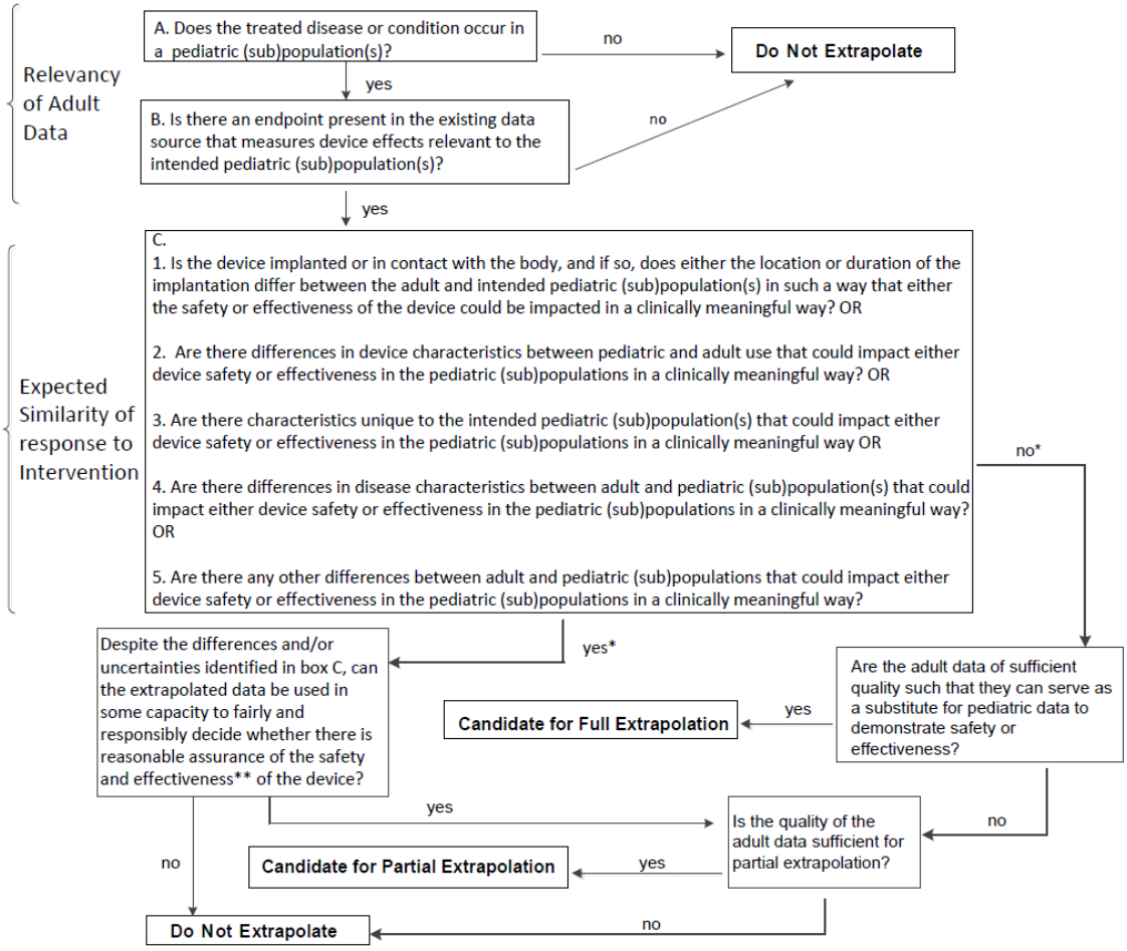
In non-clinical studies, data on biocompatibility (toxicity and carcinogenicity) and sterility should be thoroughly evaluated based on the characteristics of individual devices. The necessity of clinical trials must be determined based on detailed data on the target disease, feasibility of extrapolating the existing data, risks associated specifically with the development of new pediatric devices or with the modification of existing adult devices, and other information.

For some devices, facility eligibility criteria may be defined before the evaluation of pediatric use. In Japan, many severe, refractory, or rare pediatric diseases are treated not only in university hospitals but also in children's hospitals; this should be considered when defining facility eligibility criteria.

3.4. Considerations on the evaluation and extrapolation of adult data to pediatric patients

The following decision tree may be used as a reference to determine whether existing adult data can be a candidate for extrapolation to pediatric populations. However, consultation with the PMDA is recommended and the diversity of medical devices and available evidence should be considered, in order to determine whether individual data can be extrapolated.

(Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices - Guidance for Industry and Food and Drug Administration Staff [Document issued on: May 6, 2015])



3.5. Considerations regarding the evaluation of efficacy and safety in Japanese populations using overseas clinical data

Ethnic differences are assumed to be smaller in medical devices than in drugs. Therefore overseas clinical data can be utilized as reference information for the evaluation of efficacy and safety in Japanese populations.

In such case, the following table (excerpted from “Handling of the Data of Clinical Studies for Medical Devices Conducted in Foreign Countries”, Pharmaceutical Affairs Bureau Notification No. 479 dated March 31, 1997) would be helpful when using data from foreign clinical studies.

In particular, when overseas data on a pediatric device are used, the following should be clearly presented: the definition of the pediatric population in overseas clinical trials, the body size of subjects enrolled in the trials, and differences in medical practice (e.g.,

concomitant medications, treatment policies, and guidelines) between Japan and overseas.

Table: Requirements for extrapolation of overseas clinical data

	Requirements
1	Methods of clinical study and clinical evaluation should meet the Japanese criteria or guidelines, or are applicable to medical practice in Japan.
2	Studies were conducted by experienced and qualified investigators in a proper manner at reliable medical institutions such as public research organizations or university hospitals.
3	Studies were conducted in accordance with appropriate procedures and methods (in compliance with the Helsinki Declaration issued by the World Medical Association and GCP for medical devices in Japan, or equivalent or higher level of criteria overseas).
4	Raw data such as individual case reports/statistical analysis records are readily accessible upon investigation.

4. Conclusion

This subcommittee raised the points to discuss and consider regarding the pediatric use of medical devices through discussions on issues surrounding the pediatric use of medical devices in clinical practice. Since pediatric diseases are rare, it is often difficult to promptly collect Japanese pediatric data sufficient to evaluate medical devices. For refractory pediatric diseases for which existing medical devices are not applicable, pediatric use of medical devices should be assessed based on the acceptability of extrapolating existing data as well as on the discussions presented above.

As in the US, it is recommended that submission data for a novel or orphan device filed in Japan include, wherever possible, the number of pediatric patients with the disease, applicability of the device for pediatric use, needs for the device, and other information (partially described in 3.2). This will facilitate the development of medical devices for pediatric use.