Partnership Between Japan and the United States for Early Development of Pediatric Medical Devices
— Harmonization By Doing for Children —

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on behalf of the Harmonization by Doing for Children Working Group

Background: The Harmonization By Doing (HBD) program was established in 2003 as a partnership among stakeholders of academia, industry and regulatory agencies in Japan and the United States, with a primary focus on streamlining processes of global medical device development for cardiovascular medical devices. While HBD has traditionally focused on development of devices intended to treat conditions prevalent in adults, in 2016, HBD established the “HBD-for-Children” program, which focuses on the development of pediatric devices as the development of medical devices for pediatric use lags behind that of medical devices for adults in both countries.

Methods and Results: Activities of the program have included: (1) conducting a survey with industry to better understand the challenges that constrain the development of pediatric medical devices; (2) categorizing pediatric medical devices into five categories based on global availability and exploring concrete solutions for the early application and regulatory approval in both geographies; and (3) facilitating global clinical trials of pediatric medical devices in both countries.

Conclusions: The establishment of the HBD-for-Children program is significant because it represents a global initiative for the introduction of pediatric medical devices for patients in a timely manner. Through the program, academia, industry and regulatory agencies can work together to facilitate innovative pediatric device development from a multi-stakeholder perspective. This activity could also encourage industry partners to pursue the development of pediatric medical devices.

Key Words: Global clinical trial; Global harmonization; Harmonization By Doing for Children; Pediatric medical device
Pediatric Uses of Medical Devices; and 2016 Guidance on Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices. In addition to these pediatric-specific efforts, the FDA also initiated the Breakthrough Device Program and other such pathways to encourage medical device innovation. PMDA, Japan’s Ministry of Health, Labour and Welfare (MHLW) and FDA have also supported the use of registry data in order to improve the system of evaluating the effectiveness and safety of pediatric medical devices, and reduce the cost and efficiency of data gathering in the regulatory process. To further these efforts, the regulatory agencies have engaged with several academic groups, including Japan Pediatric Interventional Cardiology (JPIC), the Congenital Cardiovascular Interventional Study Consortium (CCISC), and the Advanced Cardiac Therapies Improving Outcomes Network (ACTION).

Despite these efforts, the interest in pediatric device development remains low. The current challenges and approaches around the development of pediatric medical devices in Japan and the United States are similar.

**Harmonization By Doing (HBD)**

In 2003, stakeholders from academia, industry and regulatory agencies in Japan and the United States initiated the Science Board, which was commissioned by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, started a discussion related to the development delay of pediatric medical devices, and a summary report was issued in 2015. New unique regulatory pathways, such as “the high-clinical needs medical devices”, “Orphan medical device designation system”, the “strategy of Sakigake”, “Fast-break scheme for innovative medical devices”, and “clinical evaluation report system”, were created to support the development of orphan medical devices in Japan. One of major barriers in the approval process of medical device for orphan disease is a requirement of clinical evaluation. Novel approval pathways such as the clinical evaluation report system and the Fast-Break Scheme were established as an alternative to the application pathway with clinical trial data.

Likewise, in the United States, approximately 447 novel devices have been approved from 2008 to 2017, and 96 were approved with an indication for use in a pediatric population or subpopulation at the initial time of marketing authorization. Three recent Food and Drug Administration (FDA) guidance documents were published to encourage the early development of pediatric medical devices: 2014 Guidance on Premarket Assessment of Pediatric Medical Devices; 2014 Guidance on Providing Information about...
the complexity of a global regulatory strategy for pediatric devices while improving safety through approved pediatric labeling.

**Methods and Results**

**Questionnaire to Industry in Japan and the United States**

In starting the HBD-for-Children program, PMDA and FDA conducted a voluntary questionnaire to members of the medical device industry in Japan and the United States in January 2017 in order to assess the current climate of pediatric medical device development in both countries. This questionnaire captured the current challenges and industry experiences in the development of pediatric medical devices. Medical device companies were asked to identify the most common reasons for not pursuing development of pediatric devices, which included any of the following: challenges associated with navigating the regulatory path, cost, market size, conducting pediatric clinical trials, and overall risk of the vulnerable population (Figure 1). In Japan, PMDA distributed the questionnaire to 21 regular membership associations belonging to the Japan Federation of Medical Devices Associations (JFMDA) (as of February 2017) and received responses from 32 companies. There were 16 companies with experience in developing pediatric medical devices, and the issue most frequently raised was that the market is too small (n=13 companies). In the United States, FDA distributed the questionnaire to 23 medical device companies and received responses from 10 companies. A total of five companies identified that they had experiences in developing pediatric medical devices, and two companies responded that the small market is the main issue. While these results were not surprising, they did highlight the main concerns that the HBD-for-Children working group should seek to consider in developing solutions for pediatric device lag.

**Assessment of Global Accessibility of Pediatric Cardiovascular Medical Devices**

In addition to understanding the challenges faced by industry for pediatric device development, the HBD-for-Children working group also sought to assess the regulatory status of pediatric medical devices currently in use at clinical sites across the globe. Focusing primarily on those devices that have the greatest clinical need, the working group identified five categories describing the current global accessibility to pediatric medical devices (Table 1). The group has used this assessment to discuss strategies for both early development of devices, as well as closing the access gap for devices already available in select geographies.

The following five categories are described. Category 1 is defined as medical devices that have not been introduced to Japan despite having been approved in the United States. The needs in Japan were discussed for each medical device, and was classified in category 1 with consideration...
Starting a Global Clinical Trial of a Pediatric Medical Device

An important goal of the HBD-for-Children initiatives is to facilitate more expeditious development and marketing of pediatric devices in both countries for those therapies that have been demonstrated to have a reasonable assurance of safety and effectiveness. One important step toward accomplishing this objective is the conduct of global clinical trials enrolling patients worldwide using harmonized study protocols. In line with this goal, the HBD-for-Children working group pursued a POC project with the Medtronic Harmony™ Transcatheter Pulmonary Valve (TPV) System as a proof of concept (POC) and supports the process of its global development, including conducting a global clinical trial. The Harmony™ TPV system consists of a self-expanding transcatheter pulmonary valve and a delivery system for a minimally invasive approach. The Harmony™ TPV system is used for restoring pulmonary valve function in patients with pulmonary regurgitation. [Caution: Investigational device, limited by law to investigational USE.]

Discussion

The results of the questionnaire in Japan and the United
and prioritize the early development of each pediatric medical device. By sharing the current situation of each pediatric medical device in the working group, the process for the early development can be clarified.

Finally, the Harmony TPV System POC project marks an important step in the HBD-for-Children program because it represents the potential for global harmonization when there is good communication among academia, industry, MHLW, PMDA and FDA. Each stakeholder played an important role in initiation of the project. Industry was able to obtain current clinical information from physicians in Japan and the United States through the HBD-for-Children program, and industry, PMDA and FDA were able to begin an exchange of information at the early stage of the device development.
The experiences of the HBD-for-Children program showed that “doing” can lead to the promotion of medical device development. The medical devices are characterized by their variety; therefore, it is important to deal with a specific product when discussing each topic concretely. The working group continues to discuss pathways for decreasing the burden of developing safe and effective pediatric medical devices. In addition to conducting global clinical trials to accelerate the effective multinational development of pediatric medical devices, the working group is looking to expand in breadth and depth. Future efforts of the working group include consideration of real-world data in the clinical evaluation and development of pediatric medical devices through collaboration with pediatric registries in Japan and the United States. In addition, the HBD-for-Children program anticipates expansion beyond pediatric structural interventional devices. Future device areas may include pediatric mechanical circulatory support and cardiac electrophysiology devices.

The HBD-for-Children working group began as a global collaboration program by stakeholders from academia, industries and regulatory authorities to further pediatric device development. Over the last 2 years, the activities of the group have shown the potential for improvement in the global development of pediatric devices. The clinical needs and the current situation of “off-label” use in both countries were clarified into five categories in the HBD-for-Children program. The specific information is intended to help industry to develop global strategies with the understanding of the clinical needs in both counties. Moreover, in the process, the HBD-for-Children program fostered discussion among academia, industry, and regulatory agencies about potential concerns and ways to address burdensome aspects supporting expedient approval of pediatric medical devices. The first global clinical trial of a pediatric medical device within the HBD-for-Children framework was initiated. Furthermore, open communication between the MHLW, PMDA, FDA and industry was very helpful at the early stages of development.

Conclusions

Through our experience with the HBD-for-Children program, we consider that the global collaboration by academia, industries and regulatory authorities is necessary for the early development of pediatric medical devices. With these early successes and a focus on clinical and scientific challenges, the HBD-for-Children program will continue to explore ways of advancing new medical devices for pediatric patients across the globe.

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Conflicts of Interest

S.T. has no conflicts of interest to declare. The views expressed in this article are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency (PMDA) or Japan’s Ministry of Health, Labour and Welfare (MHLW). T.J.F. is a consultant for Abbott, Gore, NuMed, Medtronic, Edwards, Siemens, B Braun Medical and AcuNav. F.I. is a consultant for Abbott, Inc. N.F. is an employee of Cook Medical Inc. D.D. is an employee of Medtronic, Inc. R.H. is an employee of Medtronic Japan Co., Ltd. L.A.M.B. is an employee of Abbott Medical Japan Co., Ltd. and Abbott Vascular Japan Co., Ltd. C.E.R. received a research grant from Medtronic, Inc., Abbott, Inc. and Philips, Inc., and holds a patent on Gore, Inc. The other authors have no conflicts of interest to declare.

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