Pediatric Medical Devices
— Survey of Pediatric Cardiologists and Cardiovascular Surgeons in Japan —

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**Background:** In Japan, the choice of pediatric medical devices is limited because of 2 “device lag” problems: Japan lags behind the USA and Europe in device development, and development of pediatric devices lags behind that of adult devices. We aimed to identify the problems with and impediments to pediatric medical device development as recognized by pediatric physicians in Japan.

**Methods and Results:** A voluntary survey of pediatric medical devices for all council members of the Japanese Society of Pediatric Cardiology and Cardiac Surgery was conducted in 2019. The response rate was 47.1% (154/327). The respondents were 115 pediatric cardiologists (74.7%) and 39 cardiovascular surgeons (25.3%). Approximately 90% believed that difficulties in development existed. Approximately 70% were dissatisfied with the pediatric medical devices currently available in Japan, which was a result of the unavailability of medical devices approved overseas, few types and sizes, and off-label use. Factors that hindered the development of pediatric medical devices included anatomical issues specific to children with congenital heart disease, as well as system issues such as lack of corporate profitability, development cost, and amount of time for development.

**Conclusions:** Pediatric cardiologists and cardiovascular surgeons regard “device lag” and “off-label use” in Japan as important hindrances to the delivery of better medical care for pediatric patients with congenital heart disease.

**Key Words:** Device development; Device lag; Off-label use; Pediatric medical devices; Regulation
Methods

This observational study was based on responses to a questionnaire. Pediatric cardiologists and cardiovascular surgeons in Japan participated in a voluntary survey about pediatric medical devices. The survey was conducted through the Questant system (Macromill, Inc., Tokyo, Japan) in 2019 from October 4 to November 18. An anonymous and optional questionnaire was sent by e-mail to all council members of the Japanese Society of Pediatric Cardiology.

Table 1. Baseline Characteristics and Clinical Experience of Pediatric Physicians (n=154)

| Clinical specialty                                      | Pediatric cardiologists (n=115) | Pediatric cardiovascular surgeons (n=39) |
|---------------------------------------------------------|---------------------------------|----------------------------------------|
| Professional qualification for pediatric cardiology     | 109 (95%)                       | 0                                      |
| Professional qualification for pediatric cardiovascular surgery | 0                               | 38 (97%)                              |
| ASD or PDA closure plug certified operator              | 32 (28%)                        | 0                                      |
| CVIT certified operator                                 | 0                               | 0                                      |
| Catheterizations or operations as the first surgeon within previous 5 years |                                |                                        |
| 0 per year                                              | 2 (2%)                          | 3 (8%)                                 |
| 1–20 per year                                           | 42 (37%)                        | 1 (3%)                                 |
| 21–50 per year                                          | 27 (23%)                        | 3 (8%)                                 |
| 51–99 per year                                          | 24 (21%)                        | 8 (21%)                                |
| 100–199 per year                                        | 11 (10%)                        | 10 (26%)                               |
| ≥200 per year                                           | 9 (8%)                          | 14 (36%)                               |
| Years of clinical practice                              |                                 |                                        |
| 1 to <5 years                                           | 0                               | 1 (3%)                                 |
| 5 to <10 years                                          | 4 (3%)                          | 1 (3%)                                 |
| 10 to <20 years                                         | 33 (29%)                        | 9 (23%)                                |
| ≥20 years                                               | 78 (68%)                        | 28 (72%)                               |
| Age of patients being treated with medical devices      |                                 |                                        |
| Fetus                                                    | 6 (5%)                          | 0                                      |
| Newborn to less than 1 year                             | 83 (72%)                        | 37 (95%)                               |
| 1–6 years                                               | 98 (85%)                        | 37 (95%)                               |
| 7–12 years                                              | 77 (67%)                        | 17 (44%)                               |
| 13–18 years                                             | 26 (23%)                        | 2 (5%)                                 |
| ≥19 years                                               | 28 (24%)                        | 13 (33%)                               |
| Clinical setting for care                               |                                 |                                        |
| University hospital                                     | 46 (40%)                        | 19 (49%)                               |
| General hospital other than university hospital and pediatric hospital | 41 (36%)                      | 4 (10%)                                |
| Pediatric hospital                                      | 16 (14%)                        | 13 (33%)                               |
| Specialty hospital other than university hospital and pediatric hospital | 9 (8%)                         | 3 (8%)                                 |
| Clinic                                                  | 3 (3%)                          | 0                                      |
| Pediatric medical devices currently mainly used          |                                 |                                        |
| Device closure                                          | 47 (41%)                        | 0                                      |
| Balloon                                                 | 78 (68%)                        | 0                                      |
| Vascular occlusion device                               | 76 (66%)                        | 0                                      |
| Intravascular stent                                     | 41 (36%)                        | 3 (8%)                                 |
| Arrhythmia-related devices                              | 18 (16%)                        | 8 (21%)                                |
| Surgical materials                                      | 3 (3%)                          | 38 (97%)                               |
| Ventricular assist device                               | 6 (5%)                          | 8 (21%)                                |
| Physicians with experience in development or clinical trials | 28 (24%)                      | 10 (26%)                               |

ASD, atrial septal defect; CVIT, cardiovascular intervention and therapeutics; PDA, patent ductus arteriosus.
and Cardiac Surgery, which is most closely associated with pediatric therapeutic medical devices in Japan. We sent reminders twice during the survey period.

The survey was designed to elicit information about a number of aspects regarding the need for pediatric therapeutic medical devices that are fundamental in the care of patients with CHD. Personalized survey URLs allowed respondents to engage the survey intermittently at their convenience. The survey consisted of 39 closed-ended questions. Key topics included (1) satisfaction with current pediatric medical devices and the need for new or improved devices; (2) factors impeding the development of pediatric medical devices; and (3) requests by pediatric physicians that concerned the development of pediatric medical device. Professional demographic information and information about experience in development or clinical trials were also collected.

Data were calculated as numbers and percentages or as means±standard deviations. There were no missing data because respondents could not complete the survey without answering all the questions. “Very agreed” and “somewhat agreed” answers were summarized as “agreed.” “Very dissatisfied” and “somewhat dissatisfied” were summarized as “dissatisfied.” The response categories of factors impeding development of pediatric medical devices were ordinal: 0=no impediment, 1=small extent, 2=moderate extent, and 3=large extent. We used Fisher’s exact test to evaluate categorical variables. A P value of less than 0.05 was considered significant in all analyses. JMP 11 (SAS Institute, Cary, NC, USA) was used for data analysis.

### Results

#### Baseline Characteristics

Of the 327 council members of the Japanese Society of Pediatric Cardiology and Cardiac Surgery, 154 (47%) answered the survey. Of these respondents, 115 (75%) were pediatric cardiologists and 39 (25%) were cardiovascular surgeons. Baseline characteristics and their clinical experience involving patients with CHD are listed in Table 1. Most of them had extensive clinical experience with catheterizations or operations and more than 20 years of clinical practice involving patients with CHD. Conversely, only 25% of the respondents had experience in development or clinical trials of medical devices.

#### Table 2. Satisfaction With Current Pediatric Medical Devices and Need for New or Improved Devices According to Experience or Lack of Experience in Development or Clinical Trials (n=154)

| Lack of experience (n=116) | Experience (n=38) | P value |
|---------------------------|------------------|---------|
| **Difficulties in development or clinical trials** |                   |         |
| Intention to be involved if there is an opportunity for development or clinical trials | 51 (44%) | 27 (71%) | <0.01 |
| Agreement that new pediatric medical devices must be developed | 66 (57%) | 30 (79%) | 0.02 |
| Dissatisfaction with pediatric medical devices currently available in Japan | 80 (69%) | 30 (79%) | 0.30 |
| **Reason for dissatisfaction with pediatric medical devices** |                   |         |
| Medical devices approved overseas cannot be used in Japan | 59/80 (74%) | 27/30 (90%) | 0.07 |
| Few types and sizes | 65/80 (81%) | 19/30 (63%) | 0.08 |
| Off-label use | 56/80 (70%) | 25/30 (83%) | 0.22 |
| Expensive | 21/80 (26%) | 7/30 (23%) | 0.81 |
| Poor performance and usability | 12/80 (15%) | 9/30 (30%) | 0.10 |
| **Effect of delays in medical device development on clinical practice** |                   |         |
| Limited options | 92 (79%) | 33 (87%) | 0.35 |
| Limits of adaptation | 69 (59%) | 24 (63%) | 0.71 |
| Poor patient quality of life | 44 (38%) | 19 (50%) | 0.25 |
| Poor treatment outcomes | 45 (39%) | 11 (29%) | 0.33 |
| Prolonged hospitalization | 29 (25%) | 15 (39%) | 0.10 |
| Increased health care costs | 22 (19%) | 14 (37%) | 0.03 |
| No effect | 6 (5%) | 0 | 0.34 |
| **Outcome obtained by promoting the development of medical devices** |                   |         |
| Expanding the range of options | 84 (72%) | 30 (79%) | 0.52 |
| Wider use of minimally invasive treatments | 78 (67%) | 31 (82%) | 0.10 |
| Improvement in patient quality of life | 65 (56%) | 25 (66%) | 0.35 |
| Less need for invasive treatment | 51 (44%) | 25 (66%) | 0.02 |
| Prolongation of survival | 48 (41%) | 18 (47%) | 0.57 |
| Preservation and substitution of organ functions | 41 (35%) | 13 (34%) | 1.00 |
| Temporary improvement in symptoms | 19 (16%) | 11 (29%) | 0.10 |
porate profitability”, “cost of development”, “time for development”, “government regulations”, and “need for clinical trials” were also mentioned. Physicians who had experience in development or clinical trials were more concerned about “government regulations” than were those who had no such experience (P<0.01). Neither clinical specialty nor experience in clinical practice affected these factors (data not shown).

Requests by Pediatric Physicians That Concerned Pediatric Medical Device Development

Respondents’ requests to academic societies that are concerned with pediatric medical device development referred to “bridging with industry and regulatory authority” and “information provision”. Requests to industries referred to “willingness to develop pediatric medical devices” and “cost burden on the trial implementation and approval”. Requests to regulatory authorities referred to “addition of insurance points for pediatric medical devices” and “deregulation” (Figure 2). Requests did not differ significantly among respondents with different clinical specialties, experience in clinical practice, or experience in development or clinical trials (data not shown).

Factors Impeding Development of Pediatric Medical Devices

The 13 impediments posed in the survey as options for lack of pediatric medical device development are listed in Table 4. The most consequential impediments to pediatric medical device development were “disease rarity/complexity” and “various sizes to match growth”, which were specific to pediatric patients with CHD. In addition, “lack of corre-
### Table 3. Satisfaction With Current Pediatric Medical Devices and Need for New or Improved Devices According to Clinical Specialty (n=154)

| Reason for dissatisfaction with pediatric medical devices | Pediatric cardiologists (n=115) | Pediatric cardiovascular surgeons (n=39) | P value |
|----------------------------------------------------------|--------------------------------|----------------------------------------|---------|
| Difficulties in development or clinical trials           | 101 (88%)                     | 34 (87%)                               | 1.00    |
| Intention to be involved if there is an opportunity for development or clinical trials | 55 (48%)                     | 23 (59%)                               | 0.27    |
| Agreement that new pediatric medical devices must be developed | 69 (60%)                     | 27 (69%)                               | 0.34    |
| Dissatisfaction with pediatric medical devices currently available in Japan | 85 (74%)                     | 25 (64%)                               | 0.31    |

### Table 4. Impediments and Exploratory Factors in Pediatric Medical Device Development (n=154)

| Exploratory factor | Mean±SD | None (0 pts) | Small (1 pts) | Moderate (2 pts) | Large (3 pts) |
|--------------------|---------|--------------|---------------|------------------|---------------|
| Disease rarity/complexity | 2.6±0.6 | 0            | 4             | 30               | 66            |
| Lack of corporate profitability | 2.6±0.6 | 1            | 5             | 31               | 63            |
| Various sizes to match growth | 2.4±0.6 | 1            | 6             | 49               | 44            |
| Cost for development | 2.4±0.7 | 0            | 10            | 37               | 53            |
| Time for development | 2.4±0.6 | 1            | 7             | 45               | 47            |
| Government regulations | 2.2±0.7 | 1            | 13            | 53               | 33            |
| Need for clinical trials | 2.2±0.7 | 0            | 15            | 47               | 38            |
| Technical issues | 1.8±0.7 | 3            | 31            | 49               | 17            |
| Lack of a central hospital for patients | 1.7±0.8 | 4            | 35            | 46               | 15            |
| Difficulties in determining therapeutic effects and superiority | 1.7±0.7 | 3            | 37            | 50               | 10            |
| Frequent upgrades | 1.6±0.6 | 2            | 42            | 49               | 7             |
| Reliability of medical device performance during clinical trials | 1.6±0.6 | 1            | 40            | 55               | 4             |
| Reliability of existing treatments | 1.5±0.6 | 2            | 50            | 46               | 2             |

Data for each exploratory factor are shown as percentage. The response categories of impediments were ordinal: 0=no impediment, 1=small extent, 2=moderate extent and 3=large extent. SD, standard deviation.
Figure 2. Requests by pediatric physicians that concerned pediatric medical device development. Percentages of requests from pediatric physicians addressed to academic societies (A), industries (B), and regulatory authorities (C) are presented. FDA, US Food and Drug Administration.
Discussion

The results of this survey demonstrated the problems, impediments, and requests concerning the development of pediatric medical device recognized by pediatric physicians in Japan. The respondents were pediatric cardiologists and cardiovascular surgeons with extensive knowledge and clinical experience of catheterizations or operations, but relatively little experience in the development or clinical trials of medical devices. Although the respondents recognized that device innovation is necessary to optimize care for pediatric patients with CHD, most of them believed that implementing development or clinical trials would be difficult. Those who had experience in development or clinical trials tended to have newly developed pediatric medical devices and intended to be involved in available device development or clinical trials. Therefore, the involvement of physicians is important for promoting the development of pediatric medical devices.

Approximately 70% of pediatric cardiologists and cardiovascular surgeons were satisfied with the pediatric medical devices currently available in Japan. A national survey of physicians who treated rare diseases in the USA revealed that more than 60% of pediatric physicians were dissatisfied with the available pediatric medical devices, and 90% confirmed the need for innovative devices. Medical devices must be tailored for the care of pediatric patients, and physicians were concerned that delays in medical device development would limit treatment options. Off-label use was also a concern, especially among pediatric cardiologists. Actually, in Japan, the majority of pediatric medical devices are used off-label in clinical settings. The FDA recommends that pediatric physicians consider off-label or physician-directed use of medical and surgical devices in children as necessary and appropriate when no device that has been approved or cleared for the specific pediatric indication is available. Such use may be common and appropriate practice for medical and surgical conditions, in addition to CHD.

Factors that hindered the development of pediatric medical devices include anatomical issues specific to pediatric patients with CHD, as well as system issues such as lack of corporate profitability, cost of development, time required for development, and government regulations. Respondents who had experience in development or clinical trials tended to be more concerned about time for development and government regulations than did those who had no experience. Our findings are generally consistent with those of prior studies of rare disease. Previous surveys of physicians who treat rare diseases in the USA showed that “costs of development” and “lack of profitability to industry” were the 2 impediments to device development that were most commonly perceived. A major public health need is the innovation of medical devices to care for pediatric patients with CHD. Too small a market is the most significant cause of delayed development of pediatric medical devices, according to the results of a previous survey conducted in the medical device industry in Japan and the USA. Because the market in the pediatric field is smaller than that in the adult field, it is difficult for pediatric industries to keep a balance between marketing cost and revenue. Promotion of global clinical trials and utilization of real-world data may be needed to develop these devices.

With regard to pediatric medical devices for patients with CHD, pediatric cardiologists and cardiovascular surgeons emphasized the effectiveness and safety of these devices in comparison with standard treatment. Randomized controlled trials are considered the most robust method of proving effectiveness and safety. However, the cost burden on trial implementation is critical. Because clinical trials must be conducted efficiently, single-arm studies may be more appropriate for evaluating device performance in patients with rare diseases, if the technology is very well established and if historical data about comparable treatments, lesion types, and patient demographics are sufficiently informative. Therefore, it is important to select the study design according to the risk-benefit balance based on the characteristics of the new devices and the diseases. Speeding up development is required for both approval of and expanded indications for new pediatric devices. To obtain cooperation from industries, it is necessary to simplify the approval process and reduce costs. For that purpose, we believe that the framework of the HBD-for-Children program will enable these discussions among academia conducting studies, industries, and regulatory agencies.

Study Limitations

First, the response rate to this survey was relatively low. The anonymous voluntary nature of participation may have affected the response rate. Lack of the information on the council members who did not respond the survey may be a source of potential bias. Second, we did not solicit patient or industry input; therefore, we plan to advance the investigation to identify the issues recognized by industry. Third, the proportion of the respondents who had experience in the development of new indications was low in comparison with that in the earlier survey of physicians treating rare diseases. Their background could have been a source of bias towards dissatisfaction and wanting to develop new devices. Finally, because this study was not designed for hypothesis testing, it is difficult to draw clear conclusions that are based on biostatistics. However, despite these limitations, this survey enabled us to comprehensively assess pediatric cardiologists and cardiovascular surgeons’ perspectives about the problem of availability of pediatric medical devices in Japan. Addressing the device lag will require concerted efforts by a broad range of stakeholders to develop new and enhanced solutions that will improve the development of medical devices for children living with CHD.

In conclusion, we reconfirmed that device lag and off-label use in Japan are widely recognized by both pediatric cardiologists and cardiovascular surgeons as important impediments to the delivery of better medical care for pediatric patients with CHD. In the future, using the framework of the HBD-for-Children program through discussions with academia conducting studies, industries, and regulatory agencies, we hope to propose solutions to these problems.

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**Author Contributions**

T.M., A.K., S.T., M.H., and T.K. designed the study; T.M. and T.K. collected and analyzed the data; T.M. and T.K. wrote the manuscript; A.K., M.H., S.Y., H.Y., R.I., S.-H.K., and K.S. revised the manuscript. All authors read and approved the final manuscript.

**IRB Information**

The Ethics Committee at the National Center for Child Health and Development granted an exemption from requiring ethics approval.

**Disclosure**

The authors declare no conflicts of interest. 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 or Japan’s Ministry of Health, Labour and Welfare.

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**Supplementary Files**

Please find supplementary file(s);

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