Global Cardiovascular Device Innovation: Japan-USA Synergies
– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

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Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

Conclusions: This kind of program is very important to deliver novel medical devices. Involvement of physicians in this type of activity is also very helpful to achieve these goals. (Circ J 2013; 77: 1714–1718)

Key Words: Cardiovascular devices; Harmonization by Doing; Medical device innovation
initiative to demonstrate how cardiovascular device development and evaluation can be efficiently conducted using such a global approach, to the benefit of patients in both countries.

**Device Lag in Japan and the USA Compared to Europe**

Historically, new medical devices have been launched onto the market in Europe, because the regulatory standard in the European Union (EU) is the demonstration of safety and performance, which typically has been accomplished through a small or medium-sized clinical study. Additional preclinical evaluation and larger pivotal clinical trials are then performed to support marketing of these devices in the USA, and sometimes further trials in Japan lead to marketing approval and release in Japan. Despite the fact that the USA and Japan constitute the 2 most lucrative medical device markets in the world, this approach has meant that doctors and patients in Japan and the USA have had, at times, significant delays in access to new medical devices, and certain devices are never marketed in these countries at all. In Japan, this delay has been called “device lag” and the Japanese regulatory authority the Pharmaceuticals and Medical Devices Agency (PMDA), recognizes this phenomenon as an important issue. PMDA has made tremendous efforts to solve this problem since the first Mid-term Plan started in April 2004.6 The current approach followed by industry, to obtain marketing approval in Europe first, and only then in the USA and Japan, not only results in time delays to access, but also to redundancy and added cost in research and development as clinical trials are independently performed in each country. Most importantly, such fragmented efforts can ultimately lead to poorer quality data overall, particularly for information related to rare but catastrophic safety problems.

**Global Regulatory Collaboration**

The recognition that the biology and epidemiology of cardiovascular disease is largely driven by common risk factors independent of ethnic, scientific, clinical and economic factors, has encouraged growing interest in efforts to study new devices through more efficient, high-quality global collaborations. Such efforts respect the independence of individual governmental jurisdictions of national regulatory authorities, while concomitantly encouraging the convergence of basic principles of medical device safety and performance evaluation through the best ethics, science, and methods of human clinical research. The Global Harmonization Task Force (GHTF), through its founding member nations, Japan, Canada, Australia, the EU, and the USA, has focused manufacturers and regulators on the development of consensus guidelines for such principles for more than a decade. Moreover, a new consortium, the International Medical Device Regulators Forum (IMDRF) was set up in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. The IMDRF is a voluntary group of medical device regulators from Australia, Brazil, Canada, China, the EU, Japan and the USA, as well as the World Health Organization, who have come together to build on the strong foundational work of the GHTF, and to accelerate international medical device regulatory harmonization and convergence. Furthermore, a more pragmatic program that includes academic clinicians along with other stakeholders, the Japan-US Harmonization by Doing (HBD) program,8 was initiated in 2003.

**HBD Program**

The HBD program provides a forum for collaboration between Japanese and US regulators, industry, and academic clinicians, where all stakeholders can engage in open discussions toward the identification and resolution of obstacles to conducting global clinical trials and harmonization of regulatory processes. The objective of HBD is to eliminate redundancies, added costs, and time delays inherent in sequential clinical trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective breakthrough cardiovascular technologies to benefit patients worldwide. HBD is uniquely different from other global harmonization initiatives in that the program aims to fulfill its mission through practical experience – that is, by doing – and sharing lessons learned from these experiences. This is achieved through proof-of-concept projects, in which specific challenges are identified and potential solutions are tested. The current membership of HBD includes members of the FDA, Japan’s Ministry of Health,

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**Table. Harmonization by Doing Working Groups**

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<th>Working group</th>
<th>Current mission</th>
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<td>1. Global Cardiovascular Device Trials</td>
<td>Improve the interactions and exchange of ideas between Japan MHLW/PMDA, US FDA, academia, and industry, and to provide a forum to identify, discuss, and develop solutions to barriers to single-protocol clinical trials to be conducted in both the USA and Japan, in order to facilitate the timely and more cost-effective global introduction of new, safe, and effective device technologies.</td>
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<td>2. Study on Post-market Registry</td>
<td>Facilitate multilevel discussion and collaboration between Japanese and US institutions regarding post-market global monitoring of MCSDs, including the incorporation of Japanese data with that of the USA in the INTERMACS registry and to use these data to guide future use of this technology. While the current WG2 mission is currently concentrated on MCSDs, WG2 activities should be expanded to include global post-market data collection for other cardiovascular devices, and the application of this information to guide the continued use of these device technologies, as well as to guide the evaluation of future devices.</td>
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<td>3. Clinical Trial Infrastructure and Methodology</td>
<td>Facilitate the development of a robust and effective clinical trial infrastructure in the USA and Japan to support the conduct of global clinical trials to allow the timely introduction of new safe and effective medical devices into the USA and Japan.</td>
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<td>4. Regulatory Convergence and Communication</td>
<td>Facilitate the timely global introduction of new medical technologies by identifying and addressing specific regulatory barriers through proof-of-concept projects, specifically, to improve administrative practices within the context of existing regulations with the goal of convergence between Japanese and US practices and improved communication between stakeholders.</td>
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FDA, Food and Drug Administration; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCSD, mechanical circulatory support device; MHLW, Ministry of Health, Labor and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency.
Labour and Welfare (MHLW)/PMDA, US industry (represented by the Advanced Medical Technology Association [AdvaMed] and other cardiovascular device manufacturers who are not members of AdvaMed), Japanese industry (represented by the Japan Federation of Medical Devices Associations [JFMDA]), US cardiovascular academia (represented by Duke Clinical Research Institute [DCRI]), and the Japanese academic community from cardiovascular fields. The HBD program is overseen by a steering committee, which includes members from each stakeholder group, and includes 4 working groups (WGs). Table outlines the 4 WGs and their current mission. Through the activities of each of the WG, as well as the HBD steering committee, the complex array of challenges faced when designing and executing global clinical trials can be overcome in a more manageable stepwise manner. Furthermore, potential harmonization of regulatory practices and communication between US and Japanese regulatory authorities can shorten the device approval time lag through the streamlining of processes and the gaining of a common understanding of the scientific challenges, without adversely affecting current review practices or time lines. HBD’s premise is that if all stakeholders share a portion of their experiences on different aspects of global trials, as well as lessons learned through the regulatory review processes required to conduct such global trials and achieve market approval for new devices where possible, all parties involved would benefit through a reduction in duplicative efforts by solving common problems. This sharing of information, however, must be carried out in a manner that protects the confidential and trade secret information of industry sponsors that are involved, and with the agreement of all stakeholders involved.

**HBD History**

From December 2003 to March 2004, joint meetings between FDA, MHLW-PMDA, DCRI and industry were held at FDA in Rockville, Maryland, USA to talk about the HBD concept and the HBD collaboration process. This was followed by other similar meetings at MHLW in Tokyo, Japan, and the first public announcement in a program at the annual scientific meeting of the Japan Circulation Society in March of 2004. The first in-depth HBD East Think-Tank Meeting took place in Tokyo in December 2005. Three main outcome goals were agreed on at the 2005 Think Tank meeting: (1) build a more robust clinical research infrastructure; (2) compare medical device good clinical practice (GCP) to determine if any significant differences exist that could be obstacles to the HBD process; and (3) define and clarify the rules for increased and better cooperation among all parties involved. The second HBD Think-Tank Meeting was successfully held in January 2007 in Durham, North Carolina, USA as HBD West 2007. Representatives from more than 25 academic institutions, industry organizations and companies as well as government regulators from the USA and Japan attended and engaged in discussion during this 2-day meeting. During the HBD West 2007 meeting, the HBD structure (Figure) and the initial 4 HBD WG missions were introduced. The third HBD Think-Tank Meeting, HBD East 2008, was convened in July of 2008 in Tokyo, Japan. This meeting provided a forum for discussion on convergence of regulatory requirements and practices through concrete experience “by doing” in the USA and Japan. To continue the discussions and review the past HBD activities, the HBD West 2009 Think-Tank Meeting was held in Silver Spring, Maryland, USA in July of 2009. Unfortunately, the HBD East 2011 Thank-Tank Meeting planned on 16 and 17 March in Tokyo was cancelled due to the earthquake in East Japan that occurred on 11 March 2011. There were several HBD sessions, however, held by each WG to share progress and accomplishment during the AdvaMed Medtech Conferences 2011 on 26 September in Washington, DC, USA, as well as the Transcatheter Cardiovascular Therapeutics (TCT) 2011 meeting on 4–7 November 2011 in San Francisco, California, USA Another global educational program titled “Japan-USA Synergies in Global Medical Device Innovation: Harmonization by Doing” was held at the TCT 2012 meeting. Most recently, an HBD-related open-to-the-public meeting was held during the Kamakura Live 2012 in Kamakura, Japan.

**Figure.** Structure of Harmonization by Doing. The Steering Committee is composed of representatives from the industry, academia, and government agencies in both the USA and Japan. AdvaMed, Advanced Medical Technology Association; DCRI, Duke Clinical Research Institute; FDA, US Food and Drug Administration; JAG, Japanese Academic Group; JFMDA, Japan Federation of Medical Devices Associations; MHLW, Ministry of Health, Labor and Welfare.
WG Key Activities

WG1: HBD-Related Clinical Studies – Endeavor Japan and SPIRIT Japan Trials
As described here, the ultimate goal of the HBD initiatives is to lead to more expeditious development and marketing in both countries for those new therapies that have been demonstrated to be reasonably safe and effective. One important step toward accomplishing this objective is the carrying out of global clinical trials enrolling patients worldwide using harmonized study protocols. In line with this HBD concept, the Endeavor Japan trial was initiated in the spring of 2005 for Medtronic’s Endeavor Zotarolimus-Eluting Coronary Stent. This Japanese study for a new DES utilized the identical study protocol that was used in the global Endeavor-II trial,18 which was an important supporting study for US marketing approval. Following the Endeavor Japan study, a second study, the SPIRIT Japan study, to evaluate the Abbott Vascular XIENCE V Everolimus-Eluting Coronary Stent, was conducted in the USA and Japan simultaneously under a global DES development strategy.

There were several discussion points in executing these clinical trials. One was whether these trials should be separated from a larger global trial of each. It was a dilemma. Future clinical trials might not happen if these trials failed, but if the trials were separated, Japan might lose opportunities to catch up with the advanced countries. Finally, as a learning step, the separated study design with an identical study was chosen.

Experience from these studies then demonstrated that the Japanese cardiology community was in fact ready to participate fully in global DES trials. Ten Japanese sites joined a global DES trial, the PLATINUM trial, and contributed very effectively.19

WG2: INTERMACS and J-MACS
Referring to the INTERMACS program,12 the J-MACS program13 was launched in 2010 for post-marketing follow-up for the 2 left ventricular assist device approved in Japan in 2010, EVAHEARTT14 and DuraHeart.15 HBD WG2 fully supports this program.

WG3: Infrastructure for Clinical Studies in Japan
Through the clinical studies described here (the WGs 1- and 2-related studies), infrastructure for clinical studies in Japan was further developed. This might lead to more clinical studies from Japan such as the 2 post-market studies in cardiology, the TAXUS Japan Postmarket surveillance study,16 and, the MIRACLE-ICD outcome measured in Japanese indication (MOMII) study.17

WG4: Collaborative Consultation and Review of Pre-Marketing Applications Pilot Program and Research Papers
Led by WG4, a direct consequence of HBD is the Medical Device Collaborative Consultation and Review of Pre-marketing Applications pilot program.8,19 This unique program involves the active engagement of the industry sponsor with both US FDA and MHLW/PMDA. A goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit.

WG4 compared GCP between Japan and the USA. The outcome was published as a key accomplishment of WG4.20 The research concluded that there were several administrative differences but no essential differences between the 2 sets of GCP.

HBD Future and Conclusions
The next HBD East Think-Tank Meeting, HBD East 2013 is currently planned for 9 and 10 July in Tokyo, Japan. As a dynamic program, HBD has recognized that it must be able to adapt as necessary to address new therapies and new scientific challenges. In addition to innovations in DES technology, such as the use of biodegradable materials, this meeting will address transcatheter aortic and mitral valve interventions. Moreover, it is envisioned that, over time and with appropriate support from its participating stakeholders, HBD could expand to include other medical devices such as orthopedic products. Finally, as the HBD program matures, other regulatory bodies in other countries could be involved.

Development of innovative medical devices is often a driver for evolution in medicine. Physicians, industry, and regulators all have an important role to play in ensuring that new medical devices provide safe and effective therapy. Physicians are primary contributors to medical device development through their participation in clinical trials. In clinical research activities for medical device development, collaboration among clinicians, the device industry, and regulators is an essential to making innovative therapy available to patients. Unlike GHTF, HBD provides physicians with an open platform on which to collaborate with industry and regulators. Contributions from each stakeholder group will be needed to ensure the future success of HBD, but with a focus on clinical and scientific challenges and new product innovation, HBD will continue to streamline the advance of new medical devices.

Disclaimer
This article represents the personal views of the authors and does not represent official FDA correspondence or guidance or official MHLW/PMDA correspondence or guidance. The HBD program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the USA and Japan.

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Disclosures
Conflict of Interest: Gary Thompson is a full-time employee of Abbott Vascular. He receives travel expenses and salary, which are unrelated to research and exceed an annual total of 50,000 yen from the company.

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