Delays in the introduction to the Japanese market of drug-eluting stents (DES) developed overseas (i.e., “device lag”) decreased sharply between 2004 and 2012. The reduction accompanied a shift in clinical development from a succession pattern (initial product development and approval overseas followed by eventual entrance into the Japanese market) to parallel development (employing multiregional clinical trials (MRCTs)). Although resource-intensive in the short-term, MRCTs are proving to be an effective tool in simultaneous global product development. Creative study designs and the absence of significant ethnic differences in Japanese subjects regarding DES safety and efficacy and the pharmacokinetic behavior of their coating drugs propel this process. More general factors such as medical need and industry incentivization also encourage this shift. Physicians’ preference for DES over other percutaneous coronary interventions, the expanding global DES market, and streamlined development and approval prospects each motivate industry to continue investing in DES product development. The efforts of various stakeholders were also integral to overcoming practical obstacles, and contributions by ‘Harmonization by Doing’ and a premarket collaboration initiative between the USA and Japan were particularly effective. Today, USA/Japan regulatory cooperation is routine, and Japan is now integrated into global medical device development. MRCTs including Japanese subjects, sites, and investigators are now commonplace.

**Key Words:** Device lag; Harmonization by Doing; Medical devices; Multiregional clinical trials
All of the DES are commercially manufactured and marketed by multinational MD companies headquartered in the USA.

**Figure 1.** USA-Japan device lags for the DES cited in Table 1. The labeling of the products (A–E) corresponds to their arrangement in Table 1. There was a marked increase in total lag (red line) and application lag (blue line) between the Cypher stent (Product A) and the TAXUS Express2 stent (Product B). But after TAXUS Express2, a declining trend can be observed in the total and application lags affecting each subsequent product. The review lag (black line) was constant except for Zilver PTX (Product E), which was reviewed far more quickly by the PMDA than by the FDA. DES, drug-eluting stent; FDA, US Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency (Japan).

**Integration of American and Japanese DES Clinical Development Programs and Subsequent Decreases in Device Lag**

Between 2004 and 2012 the MHLW/PMDA approved 5 original DES (first-generation DES) that did not have similar precedent products after thorough review by PMDA as well as deliberation by the Pharmaceutical Affairs and Food Sanitation Council, MHLW’s advisory board. Table 1 shows these products’ brand names, drug coatings, dates of market authorization application and approval in Japan and the USA, dates of CE mark acquisition for European markets, and the types of clinical trials providing the principal evidence for approvals. All data are currently available on the public websites of the PMDA and FDA.3,4

**Table 1.** Information on New DES Approved in Japan Between 2002 and 2012

<table>
<thead>
<tr>
<th>Product</th>
<th>Patent name</th>
<th>Drug coating</th>
<th>Application</th>
<th>Approval</th>
<th>Application</th>
<th>Approval</th>
<th>CE mark acquisition</th>
<th>Clinical studies that gave principal evidence for Japanese approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>XIENCE V/ Promus Everolimus</td>
<td>2008/5/29</td>
<td>2010/1/8</td>
<td>2007/6/1</td>
<td>2008/7/2</td>
<td>2006/1</td>
<td>US study + Japanese study</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>ZILVER PTX Paclitaxel</td>
<td>2010/7/30</td>
<td>2012/1/24</td>
<td>2010/6/4</td>
<td>2012/11/14</td>
<td>2009/7</td>
<td>MRCT (US, Japan, and Germany)</td>
<td></td>
</tr>
</tbody>
</table>

DES, drug-eluting stents; MRCT, multiregional clinical trial.

obtaining Japanese approval, taking into consideration Japan-specific requirements. Applications for DES in Japan often required sponsors to conduct yet another clinical study in Japan or simply forego Japanese market access.3 This succession pattern in clinical development results in substantial application lag for MDs introduced to Japan.

The lag in clinical development and review is illustrated in Figure 1.

Figure 1 shows the changes in total device lag (time between the dates of approval), application lag (time between the dates of application submission), and review lag (difference in time needed to review application dossiers) between the USA and Japan calculated from the data in Table 1.

Device lag decreased as a result of greater integration of American and Japanese studies, eventually reaching full integration as multiregional clinical trials (MRCTs). The progress of the alignment is discussed next. Although not shown in Figure 1, DES product device lag between Europe and Japan also decreased.

In 2004, the MHLW and the former Pharmaceuticals and Medical Devices Evaluation Center (PMDEC, currently PMDA) approved the first DES for the Japanese market, the Cypher stent, 326 days after the product obtained FDA approval in the USA. The pivotal trial evaluating this stent product (the SIRIUS trial), was a multicenter, double-blind, randomized controlled trial (RCT) conducted in the USA enrolling a total of 1,058 patients, which
showed the stent’s superiority to the control device, a bare metal stent (BMS) without a drug coating. Despite the novelty of the device and the drug coating (sirolimus, which had not been used in any form in Japan), the Cypher stent was approved without a trial to demonstrate its safety and efficacy in the Japanese population. Only a small-scale study to assess the pharmacokinetic characteristics of the drug coating released from the DES was conducted in Japan.5

The PMDEC’s review report for this product discusses the applicability of clinical evidence obtained in the USA to the Japanese population.5 In support of the applicant’s claim for data applicability, PMDEC cited (a) that data from the MD’s clinical trial conducted in China (sino-SIRIUS Trial) proved the stent’s efficacy and safety in the Chinese population, which is considered to be ethnically similar to the Japanese, (b) that few differences were observed in the pharmacokinetic characteristics of the drug coating released from the stent between Japanese subjects and Americans, and (c) that postmarketing study data collected in the USA revealed no differences between patients undergoing antiplatelet therapies with clopidogrel and those receiving ticlopidine with regard to the rate of incidence of stent thrombosis after implantation. The Japanese regulator, however, conditioned its approval on the results of a long-term postmarketing follow-up study in 2,000 Japanese subjects.

In our view, the lack of access to any DES product in Japan during this period caused the Japanese regulatory authorities to come under substantial pressure from cardiologists and society in general to fill this gap in care access. The perceived solution was to increase the speed of market access and, in addition, to fill the gap in data and clinical evidence that were needed to demonstrate the safety and efficacy of the DES in the Japanese population. This was done in part by expediting the review process for the DES under consideration, so that it could be approved soon after its FDA approval date was obtained.

This alignment was not limited only to study protocols, but also to the timing of clinical development programs. For the TAXUS Express2 stent, the gap between the start dates of the USA pivotal study and the smaller-scale Japanese study was 3 years (2002 and 2005), and for the ENDEAVOR stent, the gap between the start dates of the ENDEAVOR II and ENDEAVOR JAPAN trials was 2 years (2003 and 2005). Consequently, both the overall and application lags greatly decreased between the TAXUS Express2 stent (Product B) and the ENDEAVOR coronary stent (Product C) (Figure 1).

The MHLW granted conditional approval subject to positive large-scale postmarketing study data. The increase in both overall and application lag (Figure 1) encountered between the Cypher stent (Product A) and the TAXUS Express2 stent (Product B) is attributable to the additional Japanese clinical trial conducted.

The ENDEAVOR Eluting Driver Coronary Stent was approved in Japan in March 2009, with a delay of 417 days behind the USA. This was the first DES for which a clinical trial to assess efficacy and safety in the Japanese population was conducted. The pivotal study for this product, ENDEAVOR II, was also an RCT, and established the product’s efficacy and safety in 1,200 subjects of mainly European origin. The primary endpoint of the study was the TVF (target vessel failure)-free rate within 9 months after implantation, and the safety-related secondary endpoint was the MACE-free rate within 24 months after implantation.

Later, ENDEAVOR JAPAN, an open-label study, was conducted to assess the risks and benefits of the product in 99 Japanese subjects under identical inclusion/exclusion criteria and study endpoints as ENDEAVOR II, the only difference being that the observation period for MACE was only 9 months.10-11 ENDEAVOR JAPAN was the first clinical trial designed and conducted in accordance with the international norm (with the exception of being an open-label trial) for demonstrating DES safety and efficacy.

With the larger concern of a total lack of access to DES resolved and with a greater understanding of the risks and benefits of DES, Japanese regulators renewed their focus on the need for domestic clinical data, and no DES product after the Cypher stent received expedited review status.

The TAXUS Express2 stent was approved in Japan in July 2007, 1,121 days behind the product’s US approval. The product’s pivotal study, TAXUS IV-SR, was a prospective, randomized, double-blind, multicenter safety and efficacy trial conducted in the USA with 1,326 subjects who were observed over a 9-month period. The trial established this DES’s superiority over BMS. Later, an open-label trial was conducted to assess this product in Japan with 40 subjects observed for 30 days, with the goal of confirming the product’s safety. The primary endpoint of the study was the MACE (major adverse cardiac event)-free rate. The DES’s efficacy was not assessed in the Japanese patients and the 30-day observation period was shorter than standard. Despite this, the PMDA determined that the device was safe for Japanese patients and that the results of the American study could be extended to the Japanese population. Similar to the Cypher stent, the
early failure cases in the PTA arm (e.g., developing restenosis) were randomized, again creating DES and BMS study arms. The DES demonstrated superior efficacy over the PTA balloon and the BMS, and its safety was determined to be not inferior to the comparators. Approximately 50 subjects from Japan participated in the study. There were no significant differences in the observed efficacy and safety between the Japanese subjects and others. The study was the first MRCT for a DES to include Japan. The outcome of this study constituted the primary body of evidence upon which the MHLW/PMDA based their decision to approve the product.

The application lag for this product was the least of the DES listed in Table 1, and approximately the same as was encountered by the Cypher stent, which was exempted from the Japanese trial data requirement (Figure 1).

Designing the pivotal trial for this product posed various challenges. When this product was being developed, there was a BMS with the same indication available in the USA but not in Japan, which at the time had only approved a percutaneous transluminal angioplasty (PTA) balloon catheter for the same indication. Thus, the standard-of-care differed between the USA and Japan in this case. This realization was the source of the difficulty in designing the coordinated trial between the 2 countries. The applicant, in consultation with the FDA and PMDA, chose the PTA balloon as the principal control product. The pivotal study randomized approximately 500 subjects located in the USA, Germany, and Japan into 2 study arms: a DES treatment group and the PTA balloon catheter control group. Next, early failure cases in the PTA arm (e.g., developing restenosis) were randomized, again creating DES and BMS study arms.

The DES demonstrated superior efficacy over the PTA balloon and the BMS, and its safety was determined to be not inferior to the comparators. Approximately 50 subjects from Japan participated in the study. There were no significant differences in the observed efficacy and safety between the Japanese subjects and others. The study was the first MRCT for a DES to include Japan. The outcome of this study constituted the primary body of evidence upon which the MHLW/PMDA based their decision to approve the product.

The application lag for this product was the least of the DES listed in Table 1, and approximately the same as was encountered by the Cypher stent, which was exempted from the Japanese trial data requirement (Figure 1).

However, the application lag for this product increased in comparison with the ENDEAVOR coronary stent despite the synchronized clinical development, for unknown reasons (Figure 1).

The ZILVER PTX drug-eluting peripheral stent, intended to treat lesions in superficial femoral arteries, was approved in Japan in January 2012, 295 days ahead of the product’s USA approval. To our knowledge, this was the first case of “reverse device lag” for a MD of USA origin.

Table 2. Number of Medical Devices Approved in Japan With Clinical Data

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<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
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</table>

MRCT, multiregional clinical trial.
trial sites have been a major vehicle for acquiring the requisite domestic clinical evidence for Japanese authorities, as in the case of the PLATINUM WH trial, a MRCT conducted in 2012 with 1,530 subjects (124 Japanese) to evaluated the Promus Element, a successor product to the Promus DES. Trial facilities were located in Japan, the USA, Europe, and in the Asia-Pacific region. The CENTURY II study was an MRCT conducted primarily in Europe and Japan from 2012 to 2013 by a Japanese MD manufacturer for its Ultimaster DES product developed in-house; 722 of the 1,123 subjects enrolled in CENTURY II were Japanese. That trial provided the pivotal body of evidence upon which the product was granted marketing approval in Japan and the CE mark for European markets.

Table 2 presents a breakdown of MDs approved by the MHLW/PMDA with the submission of clinical data over time: 2011 was the first year when MDs were approved based on MRCT data. The MDs approved in 2011 were the ZILVER PTX drug-eluting peripheral stent and 2 other DES categorized as modified MDs. DES were the first products developed in Japan in an internationally coordinated manner, and were also the first to be evaluated through MRCTs. MRCTs are well-suited to studies requiring large numbers of subjects, and as such are especially appropriate for pivotal studies of DES, which can require over 1,000 subjects. Out of the 11 MDs that the MHLW/PMDA has approved based on MRCT data to date, 9 were DES and 2 were resynchronization therapy defibrillators (CRT-D).

Ethnicity-Linked Differences in Clinical Results

The MHLW/PMDA requires Japanese clinical data for DES that contain drugs that have not been used in DES already approved in Japan, and also for DES exhibiting a novel structure/function change or intended use. DES containing drugs for which there is an approval precedent can be approved based on foreign clinical data alone. The major points considered by the PMDA’s reviewers with respect to DES regarding possible ethnic differences in clinical data are as follows:5,8,10,16,18

(1) Differences in the preventive effects of the drug coating against restenosis between ethnic groups, overall effectiveness and safety, and accumulated experience in using the drug contained in the DES coating (e.g., sirolimus coating on Cypher stents had been used as an oral immunosuppressant in the USA since 1999, before the stent’s approval (2003), whereas the drug had not been used in any form in Japan).

(2) Differences in concomitant antiplatelet therapies (until 2006, clopidogrel, a standard-of-care drug used to treat patients at risk for heart disease in the USA and Europe, was not available in Japan. At the time, ticlopidine remained the standard-of-care in Japan, despite overseas data suggesting a higher frequency of blood and liver-related side effects than clopidogrel, which had not yet been approved).

(3) Differences in the size and location of the target vessel between Japanese and other populations (e.g., Caucasian).

(4) Differences in lifestyle (e.g., Japanese sit with their legs folded under them more often than other populations, which increases the risk of damage to DES implanted in the thigh).

No significant differences in efficacy or safety were reported between the Japanese population and other populations with respect to the DES listed in Table 1. In addition, minimal differences in systemic pharmacokinetic characteristics (Cmax, Tmax, area under the curve etc.) of the drug released from the DES were reported between the Japanese and other populations, although serum concentrations of the drug coatings were too low to exert systemic pharmacological effects. For example, the maximum concentration of sirolimus in the serum after implanting 2 Cypher stents peaked at approximately 2ng/mL, while the drug’s trough blood concentration after continuous oral administration (2mg/day) to achieve systemic effects (immune-suppressing) was 8.6ng/mL.

The findings made through global pivotal studies were found to be applicable to the Japanese population. In MRCTs, Japanese clinical data were able to be combined with other populations’ data for analysis. The differences in concomitant antiplatelet therapies did not have a significant effect on the therapies’ overall evaluation.5,8,10,16,18 The realization that ethnicity-linked differences were uncommon accelerated the shift towards simultaneous global development.

HBD and the US-Japan Pilot Project in Pre-Market Collaboration

The alignment of clinical development between Japan and the USA progressed fairly rapidly; every new DES trial design exhibited greater commonalities over previous DES trials. However, the transition encountered multiple difficulties. The convergence of clinical trial protocols and practices presented difficult challenges. For example, there were concerns regarding differences in how Good Clinical Practice (GCP) regulations were implemented, which could prevent data obtained in 1 country from being accepted by the other. Another challenge was the perceived high cost of conducting clinical trials in Japanese medical institutions. There were also concerns about the competence of the clinical trial investigators in Japanese institutions.

These hurdles discouraged Japanese investigators from applying to work in international collaborative studies, and often repelled risk-averse MD manufacturers from including Japan in their initial development locations.

To allay these concerns and demonstrate the feasibility of USA-Japan simultaneous clinical development, the ‘Harmonization by Doing’ (HBD) initiative was begun in 2003 by American and Japanese cardiovascular specialists, the MHLW/PMDA, and FDA staff members involved in the reviewing and licensing of MDs in this field. Their goal was to actualize clinical trials conducted simultaneously in the USA and Japan to deliver innovative MDs to physicians and patients in both countries more quickly. HBD later gained American and Japanese MD industry participants, and has worked for the past 14 years to eliminate redundancies, added costs, and delays inherent to the succession pattern of development. HBD also works to promote regulatory convergence pertaining primarily to the premarket review of cardiovascular MD technologies.22

Among HBD’s activities was a line-by-line comparison of the device-related GCP implemented in the USA and Japan, which discovered no substantive differences.23,24 HBD also surveyed the relative costs of conducting clinical trials at sites in the USA and Japan and directly compared
them in HBD-related clinical trials. Japanese sites were found to be more expensive per subject, but this was not regarded as significant. There were also no observable differences between the USA and Japan in the level of training of supporting staff and investigators.

HBD’s members discussed designs for simultaneous USA/Japan cardiovascular MD studies internally and with other experts. Clinicians participating in HBD cooperated with MD manufacturers to advance bilateral clinical trials, assuming central roles such as principal investigator. The ENDEAVOR and XIENCE V are DES developed with the involvement of HBD. As a result, USA-Japan study protocol alignment has advanced regardless of whether the products are manufactured and developed by different companies.

HBD spun off the USA-Japan Pilot Project In Pre-Market Collaboration (hereinafter, the “Collaborative Project”) in 2009. In this project, the Center for Devices and Radiological Health of the FDA and the Medical Device Review Divisions of the PMDA jointly advised the sponsors of cardiovascular MD clinical trials that were simultaneously carried out in the USA and Japan using the same or similar protocols. The reviewers of both agencies discussed the same protocols and clinical data before their respective approval decisions. The ZILVER PTX was one of several products developed and approved under the Collaborative Project.

HBD and the Collaborative Project demonstrated that MRCTs including Japan were feasible, and that they could reduce device lag. Once this model was accepted as viable, Japanese trial sites’ contributions began to increase. Although the proportion of Japanese subjects generally did not exceed 10% in the DES MRCTs mentioned before, in more recent studies such as the US/Japan Coronary Atherectomy System Study (COAST) conducted in 2014 with the involvement by HBD, the Japanese sites enrolled over 25% of the total subjects (26/100 subjects were Japanese). The PMDA reviewers recognized, however, the sizable burden faced by DES manufacturers, such as managing simultaneous interactions and negotiations with multiple regulators during global product development. Although conducting an MRCT is much more efficient than running independent trials in multiple countries, it is always resource-intensive, mainly because of sponsors’ obligation to comply with various countries’ regulations and medical practices. In general, engaging in MRCTs is limited to companies with vast resources. Although it is important to note that international cooperative studies and regulator collaboration can save resources in the long term, they can be lengthy and expensive in the shorter term. Such resource requirements can become a barrier that excludes smaller companies and regulators from participation in a globalized system.

### On Regulatory Harmonization

The activities of HBD and the Collaborative Project indicate that internationally harmonized guidelines alone do not necessarily lead to harmonized practices in regulated activities such as clinical trials. Bridging the gap between recommendations and actual practice across countries often requires substantial effort. In this respect, HBD’s contributions have been considerable. Comparison with the development of drug MRCTs will also yield insight. Drugs also used to undergo country-by-country development. When a drug developed abroad was introduced to the Japanese market, the Japanese authority would request a bridging study (a smaller study involving Japanese subjects) to obtain data demonstrating the applicability of the overseas clinical data to the Japanese population. With the subsequent rise in MRCTs, the MHLW/ PMDA began recommending that sponsors seeking Japanese approval include Japan in their MRCTs to mitigate drug lag. The percentage of MRCTs in Japan’s clinical trials has been increasing and lag has exhibited a declining trend. As such, the historical evolution of clinical development programs for drug products and DES has followed similar paths.

### Changes in Physician Practices and Economic Influences

By 2006, DES were reportedly utilized in approximately 90% of cases involving percutaneous coronary interventions in the USA, largely because of the significantly lower rates of restenosis. Although safety concerns arising around 2007 regarding DES use in cases of late-stage and very-late-stage thrombosis led to somewhat reduced use, DES remain the most frequently chosen option in revascularization procedures. A survey of Japanese medical institutions found that in 2004 more patients were implanted with BMSs than with DES (68,000 vs. 41,000), but by 2012 the number of DES implanted increased to 4-fold the number of BMS (173,000 vs. 43,000). The value of the global DES market grew in tandem with their increasing use by physicians. Between 2005 and 2011, the estimated global DES market size grew from approximately 5.5 billion to 7.2 billion USD. DES are considerably more expensive than BMS. For example, when Cypher, the first DES in Japan, obtained marketing authorization, the Japanese national health insurance system set the reimbursement prices for coronary DES and BMS at 421,000 JPY (~$4,210 USD) and 318,000 JPY (~$3,180 USD), respectively, in 2004. This is believed to have provided great incentive to MD manufacturers worldwide to develop and market new DES products.

The prevalence of DES in relevant medical practices and industry incentives both accelerated the global development of these products. The estimated Japanese market size for coronary stents (BMS and DES) makes up approximately 20% of the global total, second only to the US market. HBD and the Collaborative Project helped to leverage these factors and overcome the various practical obstacles to integrating Japan into the global development and marketing of DES.

### Impact of DES Cases on Current MD Development and Review Processes in Japan

The case of DES products and their globalized development and review is a good example of how a controversial idea can gradually gain acceptance and return great benefits over the long term. The following summarize several prominent changes arising from the case of DES products.

1. **Today, Japan is recognized as an important base for MD development.** MRCTs now routinely include Japanese subjects, investigators, and trial sites.
2. **Interagency communication between the FDA and PMDA on matters such as product reviews has become...**
routine. The Collaborative Project was terminated because its activities had been integrated in the 2 agencies' usual practice. Applicants who submit the results of USA-Japan studies conducted according to a single protocol may still inform the PMDA and FDA to facilitate cooperative and more streamlined review.36

(3) HBD has been shifting its harmonization targets from trial designs that have already been fairly well established (e.g., studies assessing coronary DES products) to those related to emerging technologies such as the study endpoints for MDs to treat severe limb ischemia.37

Conclusions

Japanese clinical development programs for DES products rapidly globalized between 2004 and 2012, particularly in terms of trial protocols and timing. Creative study designs, analyses of the pharmacological characteristics of the drugs contained in DES, and possible ethnicity-linked differences in patients' reactions to products supported this shift. The case of DES products is a clear example of how various factors, such as industry incentives, medical need, and the efforts by different organizations towards international collaboration and harmonization, catalyzed the broad adoption of simultaneous global MD development, which has previously been seen as impracticable.

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Conflict of Interest Disclosure

The authors have 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 PMDA or MHLW.

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