PERSPECTIVE:
Physician/Clinical Investigator

Attempting to Solve Japan's 'Device Lag Problem' (and Perhaps Even Improve Its Economy)

BY TAKAO OHKI, MD, PHD

It can often take several years for a medical device that is already approved and in use in the West to gain regulatory approval in Japan, a delay called the "device lag problem."[1] For example, the first endovascular stent graft for treating abdominal aortic aneurysms was approved in Europe in 1997 and in the United States (US) in 1999, but it was not until 2008 that one was approved in Japan. Even after that, it was some time before physicians received government or private insurance reimbursement for its use. This is, of course, problematic in that Japanese patients cannot benefit from the latest medical device innovations. However, it is also disadvantageous to Japan's national economy. Japan became an advanced economic power on the strength of its manufacturing, but the country currently has very little presence in the global medical device market. This article describes the root of the problem, as well as progress toward possible solutions and the potential for a positive impact on the Japanese economy.

THE NATURE OF JAPAN'S DEVICE AND REIMBURSEMENT LAGS

Not all medical devices suffer equally from the device lag problem in Japan. Low-risk products categorized as class I or class II devices do not usually require a clinical trial, as is the case in the US with the 510(k) pathway. These devices can be approved using only nonclinical data such as those from animal tests, durability tests, and biocompatibility tests, making the device lag problem less severe. Some class I/II products—in particular, newer products that do not have a predicate—may gain regulatory approval without clinical data in Japan, yet not insurance reimbursement.

In the US, implantable devices such as stents and stent grafts are reimbursed as part of a lump sum payment or hospital fee for the procedure, but in Japan, each implanted device is reimbursed separately. Therefore, the manufacturer may be able to sell the product because it has gained government approval, but, if the device is not reimbursed, the hospital in which it is used must pay the cost of the device. This is what I call the "reimbursement lag problem."

GLOBAL MARKET FORCES

High-risk implants (class III, IV devices) usually require clinical trial data for approval, which results in device lag. However, the root of the device lag problem is multifactorial, and each causal element interacts with the others. One important reason for device lag in Japan is that the market has historically been both small and difficult from a regulatory point of view. In the US, the Food and Drug Administration (FDA) carefully assesses safety and efficacy of class III devices based on scientific evidence, and thus, device approval requires a large amount of clinical

US-Japan International Trials to Date

Product	Sponsor	Specialty	Global PI	Japanese PI	Type	Status
Zilver PTX (SFA DES)	Cook	Peripheral Vascular	Gary Ansel, Michael Dake	Takao Ohki	Randomized controlled	Approved in Japan 2012, US Nov 2012
PROMUS Element (Coronary DES)	Boston Scientific	Cardiology	Gregg Stone	None	Single arm	Approved in Japan Feb 2012, US Nov 2011
Misago stent (SFA BMS)	Terumo	Peripheral Vascular	Takao Ohki	Takao Ohki	Randomized controlled	Approved in Japan Jan 2013, US pending
Zenith LP (AAA SG)	Cook	Peripheral Vascular	Ronald Fairman	Takao Ohki	Single arm	Finished enrollment
ZTLP (TAA SG)	Cook	Peripheral Vascular	Karl Illig	Takao Ohki	Single arm	Finished enrollment
InCraft (AAA SG)	Cordis JNJ	Peripheral Vascular	Takao Ohki, Michel Makaroun	Takao Ohki	Single arm	Enrolling

Figure 1. Previous and ongoing joint US-Japan clinical trials. Abbreviations: PI, principal investigator; SFA, superficial femoral artery; DES, drug-eluting stent; BMS, bare-metal stent; SG, stent graft; AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm.

trial data. Companies seeking to gain approval must also be savvy and efficient in compiling and presenting their data. However, the US occupies about 40% of the global device market and is large enough to justify (in many cases) the significant costs associated with overcoming the regulatory hurdle. In European countries, the overall market sizes are smaller, and the average selling price can be around 70% of that in the US. But, because there is no strict regulatory organization like the FDA or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in place, it is a justifiable market for device manufacturers.

In short, the US market has a high hurdle and a high return. European countries, South America, and some Asian markets have low hurdles and relatively low returns (at least in comparison to the US). Each market can have economic rationality from a device manufacturer's point of view.

Japan, which has a $6.7 billion drug market and a $2 billion device market, is the second largest market in the world, although much smaller than the US (about 13% and 10% of global market, respectively). However, the approval hurdle in Japan is usually equal to or higher than that experienced in the US, meaning that by comparison, the Japanese market has historically had a high hurdle and a low return. These forces combine to lower device manufacturers' prioritization of launching new products in Japan, let alone conducting a stand-alone Japanese clinical trial.

Based on the aforementioned global market characteristics, major US manufacturers (1) initially release new products in European or South American market based on nonclinical data, in some situations evaluating success and failure there; (2) obtain FDA approval by conducting a clinical trial in the US; and (3) submit a Japanese translation of the US FDA Investigational Device Exemption trial data to the PMDA.

In an effort to solve the device lag problem, the Japanese government expanded funding to the PMDA, recruited more reviewers, and placed reimbursement incentives so that the manufacturers will submit more promptly. However, these solutions were palliative, and as long as the "US clinical trial first, followed by a Japanese translation" sequence existed, the device lag problem could not be solved completely; no matter how fast the PMDA reviewed the documents, they were still reviewing them late in the cycle.

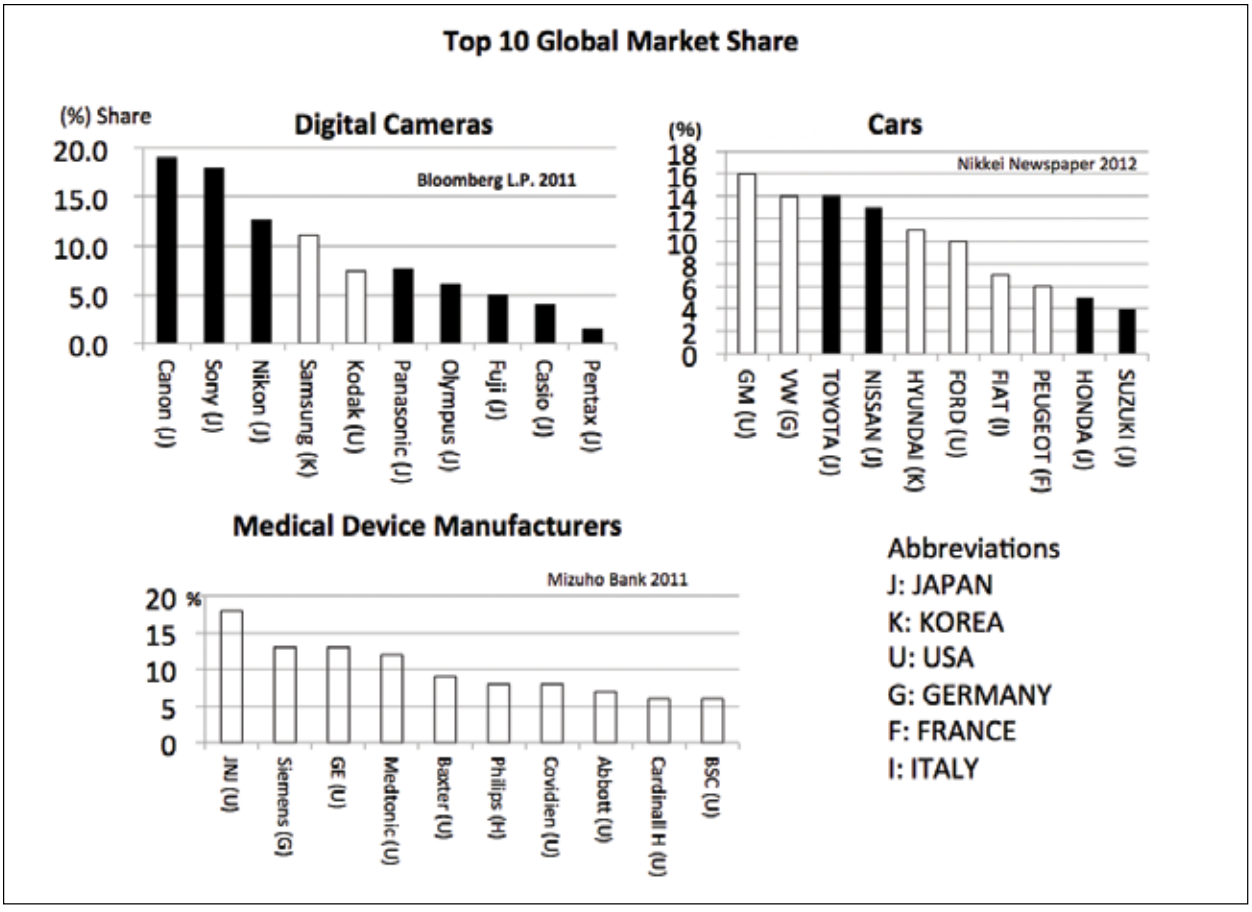

Figure 2. Global top 10 market shares for digital cameras, automobiles, and medical devices. Those made in Japan are shown in black bars. Note the presence of Japanese manufacturers in digital cameras and automobiles but the absence in medical devices.

HARMONIZATION BY DOING: ATTEMPTING TO SOLVE THE PROBLEM

In 2003, an initiative called Harmonization By Doing (HBD) was launched in order to allow creation of trials that would be conducted simultaneously in the US and Japan. Using this model, a company can provide its trial design and protocol to the FDA and PMDA simultaneously before beginning a clinical trial, and once the protocol is accepted, conduct a clinical trial in both countries' populations simultaneously. Data obtained in both countries can be combined and submitted to their respective regulatory bodies. The goal was to enable conduct of a clinical trial under a single protocol, review, and approval process simultaneously in both countries. However, the original HBD concept did not account for the differences in drug legislation and civil law in both countries—obstacles that had to be overcome before getting a trial started. Furthermore, device manufacturers were apprehensive about conducting a large-scale clinical trial in Japan for the following reasons: (1) Few Japanese investigators were experienced in clinical trial participations that are based on Good Clinical Practice standards; (2) the absence of human resources such as a clinical research coordinator in Japanese hospitals; (3) enrollment of patients was anticipated to be slow; and (4) fear that Japanese investigators might not comply with protocol. In short, manufacturers feared a "poor data are worse than no data" scenario.

Before my return to Japan in 2006, I worked as a vascular surgeon in the US for 12 years. I had experience in designing and writing clinical trial protocols, negotiating with the FDA, and conducting clinical trials as an investigator and a principal investigator. For these reasons, I managed to gain a level of trust from US manufacturers and the FDA. In addition, when I was still practicing in New York in 2005, I happened to be a member of the Cook Medical (Bloomington, IN) Zilver PTX US clinical trial steering committee. These facts probably helped minimize the aforementioned concerns that US manufacturers had regarding conducting a clinical trial in Japan and led to the invitation of Japan into what would become the first joint US-Japan trial. I felt that the future of joint clinical trials between Japan and the US and

any chance at the resolution of the device lag problem were dependent on whether or not the Zilver PTX trial would succeed.

IMPACT OF THE FIRST JOINT CLINICAL TRIALS IN JAPAN AND THE US

In 2007, a randomized trial studying the Zilver PTX peripheral drug-eluting stent was launched simultaneously in Japan and the US. Patients were randomly assigned to receive either the drug-eluting stent or its traditional bare-metal counterpart. We carefully selected four leading medical institutions for the enrollments taking place in Japan, including Jikei University, Kokura Memorial Hospital, Nara Medical University, and Kyoto University. Based on the shared understanding that properly conducting this trial would be a watershed event for the device lag issue, the four sites prepared with full-scale effort. Patient enrollment and compliance with the study protocols at the institutions were excellent, with complete data collected at each. We completed the enrollment of patients in astonishing speed. The Zilver PTX drug-eluting stent demonstrated the expected clinical benefits,[2] and Cook submitted the application documents for approval to the FDA and the PMDA simultaneously. At that point, the ball was in the regulatory bodies' court.

In 2012, with great efforts by the PMDA staff, the Zilver PTX drug-eluting stent was granted device approval in Japan. The Japanese approval would prove to be months before the device's FDA approval, which came in November 2012. Therefore, our first attempts to improve the device lag issues in Japan in this case resulted in an unexpected "reverse device lag."

WHAT'S NEXT?

The success in this pioneering trial experience has had a positive effect on administrative authorities from both nations, as well as other interested device manufacturers. The feasibility of simultaneous trials in Japan and the US was demonstrated successfully for the first time, which alleviated the concern regarding trial implementation in Japan. On the heels of this successful endeavor, many other trials have been scheduled between Japan and the US, most of which are in the vascular field (Figure 1); no joint trials for other medical specialties have been conducted yet. Terumo Medical Corporation has conducted the second US-Japan trial, evaluating the effectiveness of the Misago SFA stent. The Japanese arm not only completed enrollment 1 year sooner than the US, but the Misago stent has already been approved in Japan (January 2013), whereas in the US it is still under review by the FDA. If the Misago stent wins approval in the US, it will be the first "Made in Japan" implant to be marketed in the US. Success in additional vascular trials may promote conducting simultaneous clinical trials in Japan and the US in other fields such as orthopedic surgery, cardiology, neurosurgery, and urology.

However, Japan is still faced with the reality of not being a leader in the production of medical devices, or even much of a global player. Although there is great potential, Japanese manufacturers have previously not been involved in the development of any advanced medical devices, with most major innovations in this field largely being patented by American device manufacturers. Nearly all of the implantable devices used in Japan, including vascular stents, stent grafts for aortic aneurysms, prosthetic joints, and pacemakers, are manufactured in the United States. It is unfortunate that an industrial country like Japan does not have a single "Made in Japan" class III product being sold in the US, especially when Japan's success in other technological fields is considered (Figure 2). I moved to the US in 1995 and became a professor of surgery in my tenth year in the country. One substantial foothold in gaining this position was working toward refinements and miniaturization of surgeon-made stent grafts.[3] Miniaturization is traditionally a hallmark skill of Japanese industry, but this has not yet been applied to the field of surgically implanted devices.

The manufacturing quality in Japan is superb, but the country cannot compete with other developing countries in terms of costs such as personnel expenses. Also, economic growth due to population increase is not expected in Japan, with a declining birth rate and an aging population. Therefore, a shift or augmentation is needed in Japanese manufacturing—from the traditional low-technology, large-volume model (eg, automobiles, personal computers) to high-technology items with small-volume production (eg, medical devices), with the latter having high profit potential.

Future improvement of the clinical trial environment in Japan will not only resolve the device lag issue, but also enable high-level Japanese manufacturing technology to be utilized in the profitable field of medical equipment. Imagine if Sony made a pacemaker or Panasonic made a stent graft. This could also help us to counteract our currently shrinking economy in Japan.[4] ■

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1. Ohki T. Medical device approval delay in Japan. Yomiuri Newspaper, April 7, 2006.
2. Dake MD, Ansel GM, Ohki T, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv. 2011;4:495-504.
3. Ohki T, Veith FJ. Endovascular grafts and other image-guided catheter-based adjuncts to improve the treatment of ruptured aortoiliac aneurysms. Ann Surg. 2000;232:466-479.
4. Ohki T. Infrastructure to conduct new device clinical trials may be the solution for the shrinking Japanese economy (editorial). J Japan Surg Society. 2011;112:155.