First Approval of Improved Medical Device Conditional on Use-Result Survey in Japan
— Regulatory Review of Polymer-Free Drug-Coated BioFreedom Coronary Stent —

Akihide Konishi, MD, PhD; Mami Ho, MD, PhD; Yuko Shirai, BSc; Haruki Shirato, PhD

A prospective randomized clinical trial showed that the BioFreedom stent (Biosensors International), which is a polymer-free and carrier-free drug-coated stent, was significantly superior to a bare-metal stent (BMS) in patients at high bleeding risk who were receiving a 1-month course of dual antiplatelet therapy (DAPT). However, the stent thrombosis rate (2.01% for BioFreedom vs. 2.20% for BMS) was 4–6-fold higher than that of approved drug-eluting stents based on real-world data in Japan. Furthermore, the frequency of stent thrombosis at more than 1 month with the BioFreedom stent was slightly higher than that at less than 1 month. This result suggested that it would not be acceptable to stop DAPT universally at 1 month. Thus, the target patients for the BioFreedom stent are unspecified patients at high bleeding risk needing to continue DAPT for as long as necessary in Japan. Therefore, based on the pre- and post-marketing balance of medical devices regulations, regulatory approval was given for unspecified patients conditionally upon real-world data collection of 2,000 patients with a Use-Results Survey, instead of conducting additional pre-marketing clinical trial(s). The Use-Results Survey System is part of a strategy to expedite patients’ access to innovative medical devices and to accelerate the development of medical devices.

Key Words: BioFreedom coronary stent; Medical device regulation; Polymer-free drug-coated stent; Use-results survey

Classification of Approval Applications in Japan

In Japan, medical devices are regulated in harmonization with the Global Harmonization Task Force (GHTF) classifications, depending on the risk level. For Class I devices, review is not required and only pre-market notification is necessary. For Class II and some Class III devices, for which certification standards exist, third-party certification by a Notified Certification Body is required. Class II and III devices that do not meet the certification standard, or for which standards do not exist, and all Class IV devices are subject to approval review by the Pharmaceuticals and Medical Devices Agency (PMDA) (Figure 1).

There are 3 categories of PMDA approval application: brand-new medical devices, improved medical devices and generic medical devices. Brand-new medical devices are defined as medical devices that have clearly different structure, usage, indications, performance, etc., as compared with existing approved medical devices or certified medical devices. Generic medical devices are defined as medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. Improved medical devices are defined as medical devices that do not fall under “new medical devices” or “generic medical devices”. Medical devices are reviewed accordingly by the PMDA.

Current Use-Results Survey System in Japan

All new medical devices were required to be re-examined after a certain period of time after introduction into the market according to the Re-Examination System under the old Pharmaceutical Affairs Law. However, the old law did not enable the PMDA to mandate post-marketing surveillance to manufacturers of improved medical devices. Further, the re-examination period was specified uniformly within the brand-new medical device classification (i.e., 7 years for all orphan devices, 4 years for all devices with new structure, and 3 years for other new medical devices). As this system seemed insufficiently flexible, the re-examination system under the old law was replaced with the current Use-Results Survey System under the Pharmaceuticals and Medical Devices Act (PMD Act) on November 25, 2014.

Under the Use-Results Survey System, the PMDA can mandate evaluation of the results of actual usage for whatever period is necessary to obtain confirmatory evidence of the effectiveness and safety of devices that require such evaluations. In this case, the subjects are not only brand-
Figure 1. Global Harmonization Task Force Classification in Japan. For Class I devices, only premarket notification is necessary. For Class II and some Class III devices, for which certification standards exist, third-party certification by a Notified Certification Body is required. Classes II and III devices that do not meet the certification standard, or for which standards do not exist, and all Class IV devices are subject to approval of the Minister of Health, Labour and Welfare.

Figure 2. Flow chart of Use-Results Survey System. Regulatory review starts after submission of an application. When the review is complete, the advisory council is consulted before the final decision for approval. The Use-Results Survey starts after marketing approval is given, and the survey should be conducted under Good Post-marketing Surveillance Practice, which is a Japanese system to ensure the quality and reliability of the survey. Use results of the device will be reported on an annual basis. The application for review of overall use results should be submitted within 3 months after the end of the survey period.
ST rate can actually be reduced by using the BioFreedom stent in unspecified patients receiving DAPT for as long as necessary, we considered that further evaluation was needed. Detailed discussions took place among academia, the applicant and the Ministry of Health, Labour and Welfare on whether to do an additional clinical trial or to give approval. Finally, considering the pre- and post-marketing balance of medical devices regulations over a product’s life cycle, regulatory approval was given for unspecified patients at high risk for bleeding conditionally upon real-world data collection from 2,000 patients by means of a Use-Results Survey, instead of conducting an additional pre-marketing clinical trial.

Appropriate Least Burdensome Approach to Approving Medical Devices in Japan

The current PMD Act provides more flexibility than the old law. This is exemplified by the approval of the Cook Spectrum M/R Impregnated Central Venous Catheter (Cook Japan), which is a central venous catheter impregnated with minocycline and rifampin to reduce catheter-related bloodstream infections (CRBSI), as a brand-new medical device without a Use-Results Survey in 2015.5,14 There was sufficient evidence to evaluate its effectiveness in reducing CRBSI, including multiple results of randomized clinical trials and meta-analyses.15 Further, there is no substantial difference in the medical environment between Japan and the USA or Europe. Therefore, under the current law, this device was approved without requiring a Use-Results Survey, although re-examination would definitely have been required as a brand-new medical device under the new law, which became effective after bringing a new Act in 2015.

On the other hand, there is a limitation in the Use-Results Survey System, which mainly evaluates the safety of the medical devices because it is impossible to conduct an active control trial under GPSP. Nevertheless, we think the current law will be effective in expediting patient access to medical devices and accelerating the development of medical devices while reducing the premarket regulatory burden of clinical development and enhancing post-marketing commitments. In particular, the Use-Results Survey System is expected to provide greater benefits to patients who require access to medical devices, and to companies via improved transparency and predictability, as well as reducing the social and medical costs incurred for medical innovation.

Acknowledgments

We thank Takashi Ouchi (Office of Medical Devices III, PMDA) for his cooperation in the regulatory review of the BioFreedom stent, and Yoshiaki Mitsutake (Office of Medical Devices III, PMDA) for editorial assistance.

Disclosures

All the authors have approved the manuscript and agree with submission. There are no conflicts of interest to declare.

References

1. Ide K. Medical device regulations and utilization of international standards in Japan. Tokyo: Pharmaceuticals and Medical Devices Agency http://www.mhlw.go.jp/file/04-Houdou-happyou-11123000-0yakushokuhinkyouku-Shinsakanrikia-regulation_medicaldevices.pdf (accessed January 12, 2018).
2. Pharmaceuticals and Medical Devices Agency. Differences among brand-new medical devices, improved medical devices
and generic medical devices (in Japanese). Available at: https://www.pmda.go.jp/files/000155726.pdf (accessed January 12, 2018).

3. Pharmaceuticals and Medical Devices Agency. Use-results survey system under the old pharmaceutical affairs law (in Japanese). Available at: https://www.pmda.go.jp/files/000160083.pdf (accessed January 12, 2018).

4. Pharmaceuticals and Medical Devices Agency. Use-results survey system under the pharmaceuticals and medical devices act (in Japanese). Available at: https://www.pmda.go.jp/files/000197726.pdf (accessed January 12, 2018).

5. Pharmaceuticals and Medical Devices Agency. Fundamental point of view about use-results survey system (in Japanese). Available at: https://www.pmda.go.jp/files/000155726.pdf (accessed January 12, 2018).

6. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrière D, Naber C, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med 2015; 373: 2038–2047.

7. Garot P, Morice MC, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A, et al. 2-Year outcomes of high bleeding risk patients after polymer-free drug-coated stents. J Am Coll Cardiol 2017; 69: 162–171.

8. Ikari Y, Kotani J, Kozuma K, Kyo E, Nakamura M, Yokoi H. Assessment of sirolimus-eluting coronary stent implantation with aspirin plus low-dose ticlopidine administration: One year results from CYPHER Stent Japan Post-Marketing Surveillance Registry (J-PMS). Circ J 2009; 73: 1038–1044.

9. Aoki J, Kozuma K, Awata M, Nanasato M, Shiode N, Tanabe K, et al. Three-year clinical outcome of everolimus-eluting stents from the post-marketing surveillance study of cobalt-chromium everolimus-eluting stent (Xience V/PROMUS) in Japan. Circ J 2006; 80: 906–912.

10. BioFreedom Stent (Package insert; in Japanese). https://www.cordisjapan.jp/content/dam/cordis/web/documents/ifu/cordis-jp-biofreedom-ifu.pdf (accessed March 9, 2018).

11. Costa RA, Abizaid A, Mehran R, Schofer J, Schuler GC, Hauptmann KE, et al. Polymer-free biolimus A9-coated stents in the treatment of de novo coronary lesions 4- and 12-month angiographic follow-up and final 5-year clinical outcomes of the prospective, multicenter BioFreedom FIM Clinical Trial. JACC Cardiovasc Interv 2016; 9: 52–64.

12. Lee SWL, Chan KKW, Lam SCC. The first establishment of early healing profile & 9-month outcomes of a new “polymer-free” Biolimus-A9 drug-coated-stent by longitudinal sequential OCT assessments: The EGO-BioFreedom Study. Euro PCR 2015, Paris.

13. Konishi A, Isobe S, Sato D. New regulatory framework for medical devices in Japan: Current regulatory considerations regarding clinical studies. J Vasc Interv Radiol 2018; 29: 657–660.

14. Pharmaceuticals and Medical Devices Agency. Cook spectrum M/R impregnated central venous catheter review report 2015 (in Japanese). Available at: http://www.pmda.go.jp/medical_devices/2015/M20151009001/250288000_22700BZX00263000_A100_1.pdf (accessed January 12, 2018).

15. Darouiche RO, Raad II, Heard SO, Thornby JI, Wenker OC, Gabrielli A, et al. A comparison of two antimicrobial-impregnated central venous catheters. N Engl J Med 1999; 340: 1–8.