REGULATORY FOCUS

Summary Technical Documentation (STED): Harmonizing a Predictable Regulatory Submission

By the Harmonization-by-Doing Working Group 4

Introduction

Practical experience harmonizing global submissions today is somewhat limited. However, harmonizing regulatory approval processes may benefit from industry participation and further activities to promote a standardized format for medical device submissions. The Japan–US "Harmonization-By-Doing" (HBD) Pilot Program was launched in December 2003 to develop harmonized clinical trials and clinical trial requirements between Japan and the US along with a focus on regulatory convergence. This is one example of the practical application of an international regulatory harmonization initiative.

Hopes were high in 1992 when the Global Harmonization Task Force (GHTF), a voluntary partnership between government and industry representatives from the US, Australia, Canada, the EU and Japan joined together to promote international harmonization in the regulation of medical devices. Each of these five founding members actively regulates medical devices using its own unique legal, regulatory and administrative framework. Among other work products, GHTF prepared and disseminated harmonized guidance documents on basic regulatory practices and documentary evidence of a medical device's safety and performance through demonstrated conformity to the relevant harmonized essential principles. The GHTF guidance document *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)* (GHTF/SG1/N11: 2008) was developed by Study Group 1 (SG1) and published in final form on 21 February 2008. Like all GHTF guidance, it is recommended but non-binding guidance for regulators, conformity assessment bodies and industry. The guidance allows a manufacturer to prepare and submit essentially the same documentation to more than one Regulatory Authority or Conformity Assessment Body and covers devices in all regulatory classes. Countries such as Japan, Australia and Canada have adopted this harmonized approach as an acceptable format and content for their regulatory

dossiers. The GHTF STED also forms the basis for the Common Submission Dossier Template (CSDT) of the Asian Harmonization Working Party (AHWP) and the Association of Southeast Asian Nations (ASEAN) Medical Devices Product Working Group.

Japan started trial use of the STED in 2002, based on discussion in GHTF SG1 and formally launched the STED requirement with entry into force of the revised *Japanese Pharmaceutical Affairs Law* (*JPAL*) in April 2005. In Japan, the STED format differs among the application categories of "brand-new medical device," "improved medical device" and "generic (me-too) medical device." Originally, Japan Ministry of Health Labour and Welfare (MHLW) notice *Yakushokukihatsu No. 0216003* of February 16, 2005 described the STED format for medical device approval applications. Subsequent notifications for specific application categories were published:

- Medical devices which need approval review: *Yakushokukihatsu* No. 0216003 of 16 February 2005
- Medical devices which need registered certification bodies' review (designated Class II medical devices): *Yakushokukihatsu* No.0331008 of 31 March 2005
- Generic (me-too) medical devices with approval standards: *Yakushokukihatsu* No. 0401003 of 1 April 2005
- Generic (me-too) medical devices without approval standards: *Yakushokukihatsu* No. 0327004 of 27 March 2009
- Improved medical devices without clinical trial data: *Yakushokukihatsu* No. 0131-1 of 31 January 2011

In the US, the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) implemented a voluntary pilot premarket review program in June 2003. The objective of the program was to assess the feasibility of the STED format and content for certain premarket notifications (510(k)) and premarket approval (PMA) applications. The *Guidance for Industry and FDA Staff: A Pilot Program to Evaluate a Proposed Globally Harmonized Alternative for Premarket Procedures* was issued in the *Federal Register* on 26 June 2003 (68 *FR* 38068), and revised on 23 July 2004 (69 FR 44040). It was superseded by revised guidance issued 10 November 2005. Under the 2003 guidance, the term of the pilot program was to be until FDA received an adequate number of submissions to evaluate the STED Pilot Program. Its scope included US Traditional and Abbreviated 510(k)s for Class II devices as well as Class III PMAs. However, this pilot program excluded special 510(k)s, Product Development Protocols, Humanitarian Device Exemptions and certain types of PMA supplements.

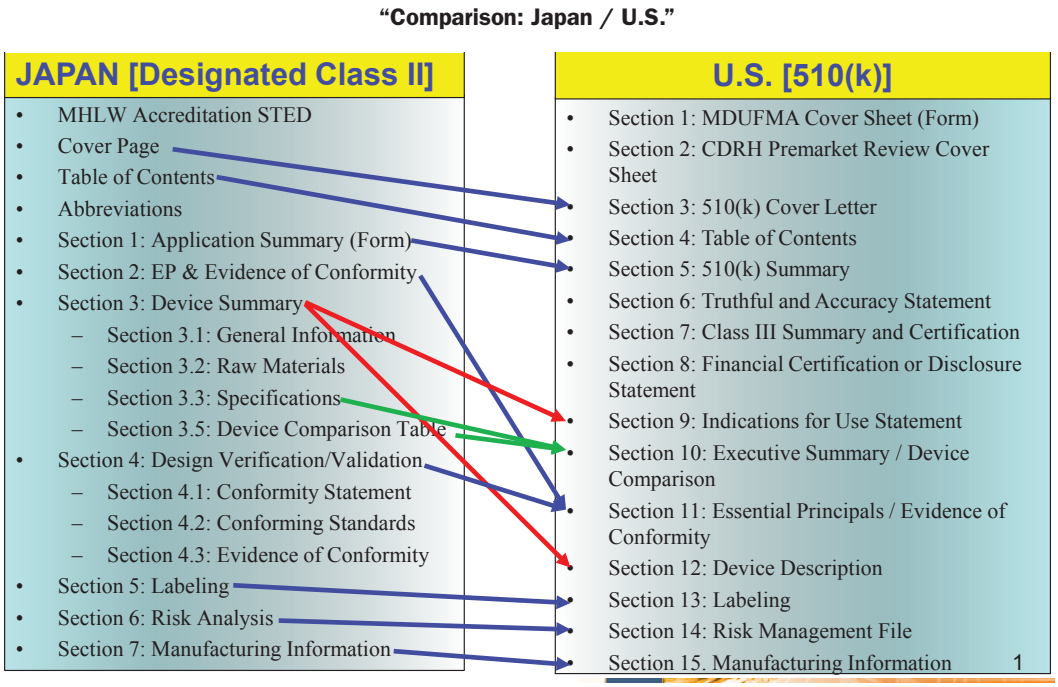
Japan–US Harmonization-By-Doing (HBD) Program

Medical device regulators in the US and Japan have a longstanding bilateral relationship and both are committed to improving regulatory practices and cooperation. Among the goals is seeking regulatory convergence in premarket review of "breakthrough" medical devices in cardiovascular technologies. As a result, the Japan–US "Harmonization-By-Doing" Pilot Program was launched as a cooperative effort to develop harmonized clinical trials and clinical trial requirements between Japan and the US. Moreover, the program specifically targets solutions to overcome regulatory barriers to facilitate patients' early access to innovative devices already available elsewhere. In July 2006, four working groups under the umbrella of a steering committee were formed. They comprised representatives from the US FDA, Japan's Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW and its related regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA), Duke Clinical Research Institute (DCRI), the Japanese academic community, and the Japanese and US medical device industries. Each working group is balanced with two co-chairs, one from the US and the other from Japan. The four working groups are: WG1—Global Cardiovascular Device Trials, WG2—Postmarket Registries, WG3—Clinical Trials Infrastructure and Methodology, and WG4—Regulatory Convergence and Communication.

HBD WG4 STED Program Initiatives

HBD WG4's focus is regulatory and clinical convergence. The working group seeks to reduce barriers that contribute to device lag and impede early market availability of new

Figure 1: STED Section Mapping



treatments and devices that could benefit patients in both countries. One such opportunity is harmonization of the application dossier format and contents along the lines described in the GHTF STED guidance document.

Japan already requires mandatory submissions based on GHTF STED. The US has a voluntary pilot premarket review program to use STED as an alternative to the submission procedures described in FDA guidance documents. Despite soliciting participation and encouraging the medical device industry to use it, there have been few submissions to the FDA in the STED format. Members of HBD WG4 identified this as an important topic to further investigate. A deeper analysis of the similarities and differences may lead to a better understanding of the process and help determine whether the use of the STED format results in effective assessments and improved review times.

Initially, WG4 conducted a "retrospective" STED study of a single device submission that was submitted to both the US FDA and Japan MHLW/PMDA. The results were presented at the HBD Think Tank East meeting in 2008. It evaluated potential differences between the Japan and US STED formats for Japan Designated Class II vs. US 510(k) Medical Devices. The conclusion was that the STED format provides a basis and framework that could be used for MHLW/PMDA and FDA submissions. However, while the framework was the same, i.e., the section titles were similar and consistent between the two (**Figure 1**), there were differences in the specific submission contents within sections of the STED (**Figure 2**). Differences outlined in **Figure 2** were identified in the Japan and US submissions, i.e., requirements for raw materials, evidence of conformity, drawings/photos/specifications, manufacturing process/quality control and the Essential Principles Checklist.

As stated, this study was "retrospective" and based on a single device submission. Therefore, to allow additional evaluation, HBD WG4 published voluntary guidelines on 3 May 2010 for industry to participate in a STED "prospective" Proof of Concept (POC) Initiative. This prospective study was intended to evaluate the differences in format and content between submissions for US Class II and Class III devices per the FDA STED Pilot Program requirements and the Japan Class II, III and IV device submissions in accordance with the *JPAL* STED requirements.

The POC model was intended to use blinded submissions submitted to regulatory authorities or registered certification bodies through normal channels without earmarking them as HBD POC STED Studies. The guidelines provided general methods for study data analysis and comparison of the submission process, format and content. It was hoped the study would help WG4 to better understand differences that may exist between the two

Figure 2: STED - Observed Differences

"Designated Class II / 510(k)"

Key Points	Japan STED [Designated Class II]	U.S. STED [510(k)]
Software Validation	Regulation does not Specifically Require Software "Validation" but Software "Functions" are Included in Device Summary	Documentation required for product containing software & level of detail depends on level of concerns as defined in the FDA software guidance
Raw Material	Details required depending on risk level: refer to administrative correspondence according to ISO	Not included unless body contact or changes from predicate device
Evidence of Conformity	Declaration of conformity - CB certificate is acceptable & conformity data for performance specification 3.3 required	Declaration of conformity (to standards) for abbreviated 510(k) & summary reports for traditional 510(k) – typically no raw data required
Drawings / Photos / Specifications	Details required and also included in labeling	Included in labeling
Manufacturing Process / Quality Control	Summary required, and verified during QMS audit	510(k): Verified during QMS audit
EP Checklist	Follows GHTF requirements – (Ministerial Notification)	Follows GHTF requirements – (FDA recognized standards) - does not specify the clauses

STED formats and content specifications so the working group could define best practices and processes. Except for very few inquiries, FDA and MHLW/PMDA received no submissions from the medical device industry. A year prior to the launch of the STED POC, FDA initiated a thorough review of the 510(k) clearance process. The review included input from a number of internal working groups, public meetings and the Institute of Medicine (IOM). The assessment was completed approximately two years later in 2011, overlapping with the STED POC initiative and potentially having an impact on the lack of submissions from the medical device industry.

In late 2008, Japan implemented an Action Program to Accelerate Review of Medical Devices to improve review times and reduce the device lag. It focused on increasing the number of PMDA reviewers, increasing review fees, outsourcing designated Class II device reviews to registered certification bodies, a three-track review process and semiannual evaluation of review performances based on objective measures. Since then, there has been a noticeable improvement in some categories of review performance. As previously noted, MHLW published notifications regarding STED formats for regulatory dossiers for approval (*shonin*) as part of the action program. These notifications allow applicants to simplify the dossiers depending on the novelty of the device. These improvements in the regulatory review process, along with clarification of STED requirements, have allowed for a more predictable and efficient regulatory submission process in Japan.

Summary

In conclusion, practical experience in harmonization today is limited in regard to format, content and predictability between the US and Japan regulatory dossiers for medical devices. However, these regulatory approval processes may benefit from further harmonization activities. The HBD STED initiative is one example of the practical application of international regulatory harmonization guidance developed by GHTF over 20 years. A new regulator-led medical device harmonization platform, the International Medical Device Regulators Forum (IMDRF), was formed in 2011 to build on the foundational work of GHTF, which was discontinued in 2012. The purpose of IMDRF is "to accelerate international medical device regulatory harmonization and convergence" and it is expected to continue to develop and promote implementation of harmonized regulatory requirements and practices. Among other work items is one to define a common Table of Contents for medical device premarket regulatory submissions. HBD WG4 hopes some of the experience gained in this pilot project will contribute to future IMDRF work in this field.

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Disclaimer
This article represents the analysis and personal views of the authors and does not represent official US FDA correspondence or guidance or official Japanese Ministry of Health, Labour and Welfare (MHLW) correspondence or guidance. The Harmonization-By-Doing program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the US and Japan.

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