Changes Brought About By HBD and Future Direction

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Disclosure Statement of Financial Interest

I, Neal Fearnot, am an employee of Cook Medical. My employment with Cook does not present a conflict of interest in the context of the subject of this presentation.

HBD on Forefront of Global Regulatory Collaboration

Years ago, the medical device regulatory world was focused on one country at a time. There was a device lag between EU, US and Japan delaying patient access to new medical technology. For 15 years, brave academicians, regulators and industry (through GHTF, HBD, IMDRF etc.) have worked to harmonize regulations, for the benefit of patients.

Through its Japan/US collaboration, HBD has been a pioneer in “DOING”.

Significance of HBD's Role

Through its 15 year course, HBD has enabled industry to benefit from:

- Appropriate access - a seat at the table
- Opportunities to "do" – conducting better harmonized regulatory/clinical work in a proof of concept setting
- Results – meaningful steps toward regulatory and clinical predictability

What are our results?

What changes has HBD enabled?

What is HBD's contribution to global regulatory collaboration?

See next page for impressive list of HBD CONTRIBUTIONS…

Agenda - Contributions

HBD's Contributions – what we have done!

- Contributed to elimination of device lag
- Improved the definition/implementation of quality clinical infrastructure for institutions and industry
- Demonstrated the transportability of data (GCP to global standard)
- Demonstrated 3-way regulatory communication among Japan and US regulators and industry
- Demonstrated viability of single protocol US/Japan clinical studies
- Demonstrated viability of coordinated US/Japan regulatory processes
- Led development of an effective post-market tools (INTERMACS)
- Showed compatibility of clinical data inspection process
- Showed many times that the POC process works
- Conducted programs at conferences to share lessons learned
- Dispelled myths about regulator/industry collaboration
- Strengthened academic/regulator/industry relationships and proven that pre-competitive collaboration can benefit all stakeholders and contribute to global collaboration

Agenda – Future

HBD Future Direction – continue DOING!

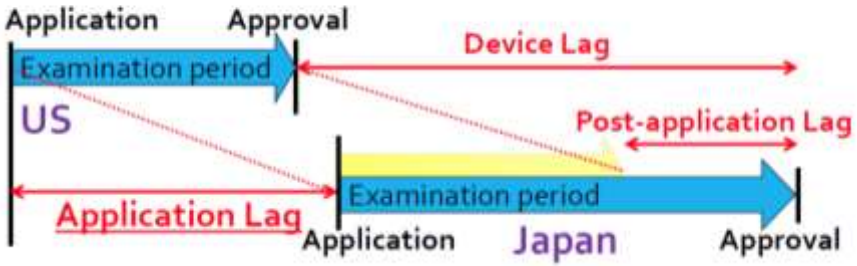
- Continued contribution with current POCs
- Initiate POC for Pediatrics
- Initiate POC for Real World Evidence
- Continue educational programs at conferences
- Continued building of trusted relationships

Elimination of Device Lag

An early concern, largely alleviated, was the period of lag between US approval of a medical device and Japan approval of the same device.

"The PMDA now approves submissions for Novel and Improved devices as quickly as FDA approves PMA original submissions."
Keisuke Suzuki, July 12, 2017

Not entirely correct to compare two different systems, and many factors influence each approval process…
But the clear lag 15 years ago has largely decreased.



Hashimoto, Yusuke, PMDA's effort to accelerate medical devices to development

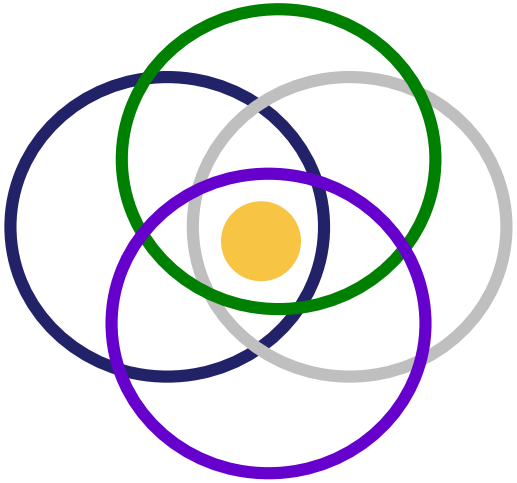
Quality Clinical Infrastructure

Improvements Within Institutions
More GCP-equipped institutions and more GCP training for Principal Investigators
More CRCs dedicated to clinical research and GCP-trained technical support services
Storage and personnel training for device accountability
Standardized study contracts for study duration and with friendly terms
Fair and reasonable budgets based upon patient enrollment
Timely IRB/EC and regulatory review
Standardized informed consent across sites; standardized AE reporting
Monitoring and auditing to global standard
Improvements Within Industry
Use global SOPs and organize the company to prepare Japan and US submissions simultaneously.
Assign top engineers and technical staff with good communication skills; enable communication.
Be sure US side understands information needed to meet Japan’s approval criteria; use cross-referenced templates; test reports to include data needed on both sides.
Prioritize high quality translation; provide version control and regulatory professional proofreading.

Transportability of Data: GCP to Global Standard

ISO 14155:2011

US regulations for device GCP



Japanese regulations for device GCP

ICH E6

- No instances where compliance with one GCP will cause non-compliance with another GCP.
- Differences in GCPs have been studied and can be reconciled by reasonable additional effort.

3-Way Regulatory Communication

HBD Pilot: FDA and PMDA Announce Collaborative Program

U.S. Department of Health & Human Services www.hhs.gov

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Device Advice: Device Regulation and Guidance

International Information (Medical Devices)

- Important New Changes to Canadian Regulatory Quality Systems Requirements
- Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative
- Contacts

Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative

ANNOUNCEMENT (June 23, 2009): U.S. – Japan Pilot Program Regarding Medical Device Collaborative Consultation and Review of Premarketing Applications

Japan MHLW/PMDA and U.S. FDA announced this week the launch of a bilateral pilot program on collaborative consultation and review of new cardiovascular devices. The 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. This collaboration would permit the scientific review staff of both MHLW/PMDA and FDA to discuss the contents of an individual submission in order to gain valuable regulatory information pertaining to device development and clinical trial design.

The Collaborative Scheme is one of several focused topics that will be discussed at the upcoming Japan-US Harmonization By Doing (HBD) West 2009 Meeting, July 16-17 at the FDA White Oak Campus.

- FDA announcement (English)
- MHLW announcement (*tsuchi*) (Japanese)

Single Protocol Japan/US Clinical Trials

Q: How does a sponsor solve the puzzle of a global clinical trial?

A: Intentionally plan and execute a single-protocol clinical trial:

- With valid science meeting requirements of JGCP and US GCP
- With near simultaneous timing in Japan/US of key milestones

With attention to a coordinated regulatory process…

Coordinated Japan/US Regulatory Process

Steps to support coordinated process - 1

Consult early and often with regulators from each country.

Enlist input from key physicians in both countries for guidance on medical science, differences in standard of care, potential impact of ethnic differences and patient preferences.

Develop a global protocol with valid science to address requirements of Japan/US regulations and regulators.

- Ensure non-clinical testing meets requirements in Japan/US
- Ensure study design meets requirements in Japan/US
- Use the same informed consent in US and Japan, for primary endpoint and long-term follow-up with local interpretation.
- Comply with US GCP and JGCP. Information is available; a comparison has been done and gap analysis is available.

Coordinate training: Train and support company staff in both countries.

Provide equivalent training and support for Japan/US sites; Conduct Investigator training in kickoff meeting(s) and site initiation visits with near coincident timing.

Coordinated Japan/US Regulatory Process

Steps to support coordinated process – 2 (cont.)
Pursue IRB approvals in parallel.
Pursue contracts in parallel.
Submit IDE/CTPN in parallel.
Enable regulator to regulator communication.
Initiate patient enrollment in parallel.
Utilize central clinical trial management and infrastructure (AE reporting, centralized monitoring and analysis, centralized core lab and data monitoring committee).
File modules of PMA and corresponding portions of Shonin at same time, enabling coincident review process.
Coordinate responses to questions from both FDA and PMDA.
Strive for near-coincident inspections, panel reviews and marketing approvals.
Plan coincident and complementary post-approval studies.

Coordinated Post-Market Tools

INTERMACS: Effective post-market tool

- Based on J-Macs
- Prospective NIH funded registry
- Provides Enhanced Surveillance:
  - AEs, Device Malfunctions
  - QOL
  - Survival

Intermacs
SUPPORTING HEARTS THROUGH KNOWLEDGE

- Develops clinical “Best Practices” (reducing complications)
- Provides means for designing & conducting post-approval studies in cost efficient way
- Standardizes information available in postmarket data registries
- Allows manufacturers to obtain data from INTERMACs to fulfill post-market requirements

Feasibility of Shared Inspection of Clinical Data

Comparing methods for evaluating quality and integrity of data submitted for medical device approval in Japan and US

•HBD Working Group conducted a comparative analysis of FDA's Bioresearch Monitoring Inspection Program (BIMO) and PMDA's audit of the sponsor's Quality Management System

•Comparison showed feasibility of shared inspection

POC Process – “Doing” Works!

Medtronic’s Endeavor™ Drug Eluting Coronary Stent, evaluated in the US and Japan (ENDEAVOR trial), was one of the first POC opportunities for HBD.

Abbott’s XIENCE V® Everolimus Eluting Coronary Stent, also evaluated in the US and Japan (SPIRIT III trial), was another early HBD POC.

Cook’s Zilver® PTX® drug eluting peripheral stent was chosen March 2010 to participate in Collaborative Review Pilot Program and to serve as an HBD POC (exploring Japan/US single protocol clinical study).

Terumo’s Misago self-expanding stent was chosen March 2010 to participate in Collaborative Review Pilot Program and to serve as an HBD POC.

Orbus Neich’s Combo dual-therapy stent (endothelial progenitor cell capture on drug-eluting stent) - active, current POC. Becoming first POC for HBD for Children.

First HBD POCs are landmark studies, generating globally transportable clinical data, supporting prompt approval of novel therapy in Japan and the US.

POC Process – “Doing” Works!

Cardiovascular Systems’ Orbital Atherectomy System - active, current POC.

TVA Medical’s Hemodialysis Access System - active, current POC.

LVADS - INTERMACS represented partnered post-market POC.

4C Medical – active, new POC of novel device for treatment of mitral valve regurgitation

Infrastructure Comparison was early and ongoing HBD focus, and yielded suggestions for improvements in both countries.

GCP Comparison Study showed possibility of compliance with multiple GCP’s and, importantly, compliance with one GCP did not deny compliance with another GCP.

STED Comparison examined comparable processes in each country.

BIMO Comparison showed compatible inspection process and supported IMDRF initiative.

Orphan Product Comparison found shared interest in providing products for small populations.

Educational Programs
Sharing Lessons Learned

HBD organizes scientific sessions in conjunction with annual scientific conferences to promote regulatory convergence between FDA and MHLW/PMDA premarket reviews and discuss advances in cardiovascular technology and other topics of shared regulatory interest among stakeholders.

Recently, sessions have been devoted to shared interest in harmonization for the benefit of approval of devices for pediatric use.

Scientific sessions and Town Hall meetings have been sponsored at CVIT, JCS, Kamakura Live, TCT, CRT, and VIVA, in addition to annual Think Tank meetings, alternately sponsored by PMDA/MHLW and FDA.

Dispelling Myths

- Regulatory agencies are locked into inflexible laws that may not fit with new technology.
- Regulators are not willing and able to explore alternate, new regulatory processes.
- Industry is not willing to risk asking, “Is there a better way?” because approval will be delayed.
- Academics focus on theoretical, not “practical” issues.
- If more than one government is involved, the process will be slower because regulators will share and promote concerns.

<u>While legitimate fears, HBD experience has shown these are truly myths.</u>

Strengthen Stakeholder Relationships

HBD is for courageous, concerned industry, academics and regulators

…industry courageous enough to ask questions about better regulatory paths,

…academics courageous enough to consider new approaches to evaluating products, and

…regulators courageous enough to consider alternate, less burdensome pathways providing the same safety and effectiveness.

HBD is for bold stakeholders willing to build pre-competitive trust and good will to improve our service to patients.

Future Direction

Our next contributions

- Continued contribution with current POCs
- POC for Pediatrics
- POC for Real World Evidence?
- Continue educational programs at conferences
- Continue building relationships of trust to support novel regulatory processes

With Appreciation for Leadership

These and many others have provided leadership and vision for HBD…

Thank You

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