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What is the HBD initiative?

The HBD initiative is a pilot project launched in December 2003 that seeks regulatory convergence between FDA and MHLW-PMDA premarket review of device cardiovascular technology. Instead of taking a theoretical approach to harmonization, HBD will utilize parallel development, application submissions and review of actual medical device projects by FDA and MHLW-PMDA in conjunction with the above-named constituencies. The objective is to eliminate redundancies, added costs, and time delays inherent in sequential trials. The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective "breakthrough" cardiovascular technologies to benefit patients worldwide.

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What are the benefits of HBD?

FDA and MHLW-PMDA share similar scientific concerns and reviewers pose similar safety and effectiveness questions. While there may be divergence in regulatory practices, the two agencies are willing to consider ways of approaching the differences in order to allow the availability of novel treatments and innovative, safe and effective medical devices to patients more quickly. Only through international collaboration can global market reviews be conducted in a timely manner. HBD should provide:

- more robust clinical trials
- improved clinical research infrastructure
- better clinical trial data
- better understanding of how the U.S. and Japanese experience can complement one another
- a new approach to early market availability of new treatment and devices to benefit patients in both countries
- a mechanism to decrease lag time between U.S. and Japanese product approval
- an atmosphere of international collaboration between regulators, regulated industry, clinical researchers, patients and academia
- a continuous progression in global harmonization

HBD concept is also a process that can be broadened in scope beyond premarket activities. It can also be applied to postmarket clinical studies, collection of postmarket data and patient registries.

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What does the HBD Pilot program hope to accomplish?

The undertaking of the pilot project is to provide a model for the full HBD program. As we continue to go forward and work together on all levels, we learn to share, develop and document best practices from a global perspective. The ultimate goal of the HBD initiatives is to reduce the amount of time it takes for a new therapy that has been demonstrated to be reasonably safe and effective using global, harmonized protocols conducted in patients worldwide to be available.

It is envisioned that, over time, HBD could expand to include other medical devices such as orthopedic products and others. As the HBD program matures, similar relationships with other regulatory bodies can also be developed in the future.

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Where has HBD been and where is it today?

The vision of HBD had its beginnings several years ago. Its early roots began as a program in 1993 called "Heart Knows No Borders," led by Mitchell Krucoff, M.D. at DCRI, as part of the DOC-HHS-FDA regulatory harmonization working group in the U.S.-Israel Science & Technology Commission. From December 2003 to March 2004, joint meetings between FDA, MHLW-PMDA, DCRI and industry were held at the FDA to talk about the HBD concept and the HBD collaboration process. This was followed by other similar meetings at MHLW, and the first public announcement in a program at the Japan Circulatory Society in March of 2004. DCRI organized the first in-depth HBD East Think-Tank Meeting that took place in Tokyo in December 2005. Three main outcome goals surfaced from the 2005 Think Tank meeting: (1) Build a more robust clinical research infrastructure, (2) Compare medical device good clinical practices to determine if any significant differences exist that could be obstacles to the HBD process, and (3) Define and clarify the rules for increased and better cooperation among all parties involved.

An outcome of the Think Tank meeting resulted in the formation of the HBD steering committee and four working groups. Current participants in the steering committee and working groups include FDA, MHLW, PMDA, industry trade associations such as Advanced Medical Technology Association (AdvaMed) and the Japanese Federation of Medical Device Associations (JFMDA), and academia (DCRI and the Japanese academic community).

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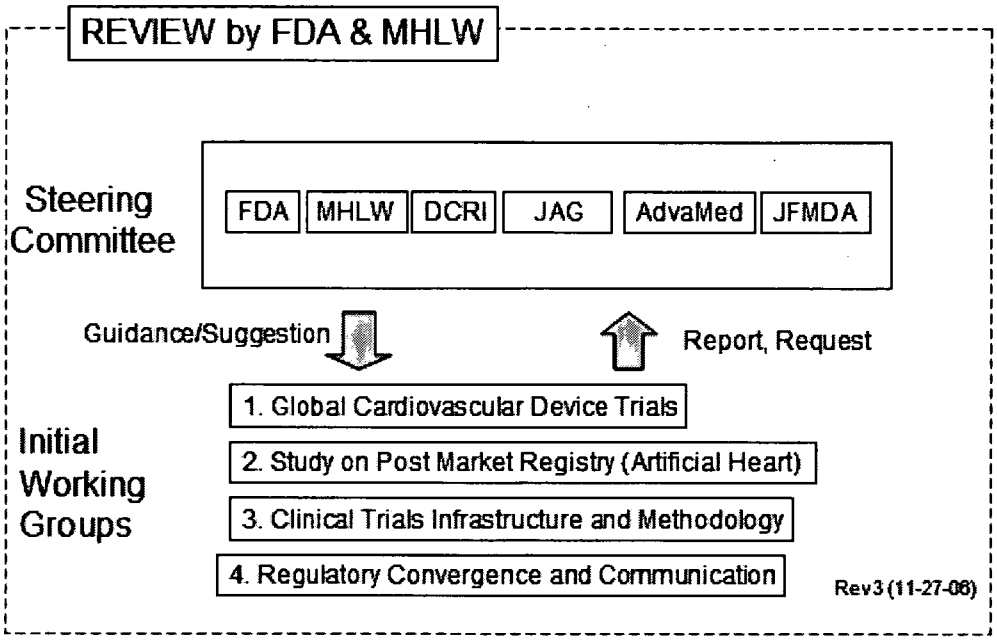
What is the current HBD Structure?

The following block diagram illustrates the structure showing the relationship between the Steering

Committee and the Working Groups.

Proposed Structure of HBD



In general, the steering committee conducts telephone conferences monthly. Typically, the face-to-face meetings are held in conjunction with the Think Tank Meetings.

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What are the Working Groups?

The Steering Committee felt that the key to the success of HBD is to develop practical achievable steps that would improve the process and advance the HBD program. There are four initial working groups. Each Working Group is developing their concept (mission) paper:

- WG1 - Global Cardiovascular Device Trials
- WG2 - Postmarket Registries (e.g., artificial heart)
- WG3 - Clinical Trials Infrastructure and Methodology
- WG4 - Regulatory Convergence and Communication

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Why "Think Tanks" ?

Shared meetings, "think tanks," and other related meetings help develop and facilitate the HBD program. A think tank generally refers to an organization or a group of individuals that researches specific problems, fosters provocative discussions among thought leaders in the field, facilitates interaction, and encourages the discovery of solutions to those problems.

Think tanks play an important role in forming policy. Think tank leaders provide ideas and recommendations pertinent to aspects of future planning and strategy. The main purpose of HBD think tanks is to continue the collaborative discussions that began two years ago. FDA, MHLW-PMDA, DCRI, industry, clinicians, academia and others are discussing and exchanging ideas to develop global clinical research studies for drug eluting stents under common protocols. Additionally, the think tank sessions offer a mechanism to explore real-time clinical trial examples. These examples will allow opportunities for proof-of concept projects, facilitating convergence of the regulatory processes between Japan and the United States.

The first Harmonization By Doing Think Tank East was held in December 2005 in Tokyo, Japan. The first HBD Think Tank West took place in January 2007 in Durham, NC, U.S.A.

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How can you participate in the "Think Tanks" ?

Attendance to HBD Think Tank meetings is open to the public.

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Upcoming Meetings

The Japan-US HBD East 2008 Think Tank Meeting will be held in Tokyo, Japan on July 22-23, 2008.

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Contact Us

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DRAFT

NOT TO BE CONSIDERED AGENCY GUIDANCE

Following the recent Circulatory System Devices Panel meeting on December 7 and 8, 2006, FDA has carefully considered the data presented and recommendations made by the Panel. We have also taken into consideration the need for appropriate balance of pre- and post-market requirements.

We have identified the following questions that all DES clinical programs should address as part of the information needed to provide a reasonable assurance of safety and effectiveness:

1) The rates of critical clinical endpoints related to safety and effectiveness, such as death, myocardial infarction, and need for revascularization should be determined.

2) The rate of death and myocardial infarction should be determined. Not only are these critical safety endpoints, but adequate precision around the rates of death and MI is needed to understand the impact of stent thrombosis on the overall safety and effectiveness profile of a DES.

3) The rate of stent thrombosis over time should be addressed. For example, the rate of stent thrombosis up to and after 1 year should be determined, including whether the rate increases, decreases, or plateaus over time. This question should be addressed for both on-label patients and patients treated outside of the label.

4) The following aspects of adjunctive antiplatelet therapy (APT) should be addressed:
   a. describe the profile of patient compliance with recommended antiplatelet therapy
   b. how often dual APT is being extended beyond the recommended duration
   c. describe the frequency and duration of APT interruption
   d. identify what, if any bridging strategies during interruption were used
   e. capture any and all invasive or surgical procedures that were deferred because of the need for continued APT
   f. define the rate of significant bleeding complications associated with APT.

FDA is open to different approaches and trial designs to address these critical questions. One such approach is described below:

Premarket

- RCT, with active control (approved DES)
- Primary endpoint: composite of cardiac death, target vessel MI, ischemia-driven TLR (we recommend use of the ARC definitions for these components) at 12 months of follow-up
- Primary hypothesis: non-inferiority compared to the active control
  - Delta should be relatively small to ensure that the upper 95% confidence interval on the rate of cardiac death and MI is small and clinically acceptable.
- Secondary endpoint: rate of cardiac death and target vessel MI
- Secondary hypothesis: non-inferiority compared to the active control

    - It is acknowledged that this hypothesis will be underpowered at the time of PMA submission. *See postmarket below.*
- Follow-up to 5 years, with a significant proportion of patients with follow-up to 24 months at the time of PMA submission.
- Patient characteristics:
    - Enrollment of patients with 1 and 2 vessel disease is strongly encouraged
    - A minimum number of patients with diabetes mellitus should be enrolled
        - If a claim specific to safety and effectiveness in diabetic patients is desired, a specific hypothesis should be prespecified and an appropriate sample size enrolled.
        - If no claim is desired, a prespecified minimum number of patients in this subset should be enrolled; the statistical plan should include plans to report descriptive statistics on these patients
    - Patients with renal insufficiency represent an important sub-population. We encourage additional assessment of renal function with measures such as creatine and GFR.
- If angiography is collected on pivotal trial patients, the timepoint for data collection should be beyond 12 months. Alternatively, angiography data can be collected on a separate cohort of patients outside of the pivotal trial.
- For trials with CYPHER or TAXUS as the control DES, we recommend that the prescribed antiplatelet therapy follow the AHA/ACC/SCAI guidelines; that is, patients receive aspirin and a minimum of 3 (CYPHER) or 6 months (TAXUS) of clopidogrel with therapy extended to 12 months in patients at a low risk of bleeding.
- Patient compliance with the recommended antiplatelet therapy and significant bleeding events (a definition should be proposed as part of the protocol) should be captured on the case report forms.
- For DES incorporating an NME, a total of 2000 patients should receive the new DES. The total of 2000 patients may be collected across multiple clinical studies within a clinical program.

Postmarket

- An additional cohort of on-label patients should be enrolled to allow for pooling with the premarket pivotal trial. The sample size of this cohort should be sufficiently large to provide adequate power to evaluate the hypothesis comparing the rates of cardiac death and target vessel MI between the new DES and control. This cohort may be in a single-arm or randomized study and pooling may be approached from either a frequentist or Bayesian perspective.

- A cohort of all-comers patients receiving the new DES should be enrolled in a postapproval study.
    - A sufficient number of patients should be enrolled to confirm that the upper bound of the 95% confidence interval around the observed rate of stent thrombosis between 12 and 24 months, 24 and 36 months, 36 and 48 months, etc. is $\leq 1\%$ for on-label population. The total study sample size should be determined by considering the expected ratio of on-label to off-label use.

- Patients should be consented for 5 years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior years, less follow-up may be needed. Alternatively, if stent thrombosis rates continue to increase, longer-term follow-up or specific labeling changes may be appropriate.
- The statistical plan should include planned descriptive statistics on certain subgroups of interest including:
  - Lesions in the setting of acute ST elevation myocardial infarction
  - Within 36 hours of non-STEMI ACS
  - Long lesions (multiple overlapping stents)
  - Bifurcation lesions
  - Patients with diabetes, renal insufficiency
  - Patients with 3 vessel disease
  - LM lesions
  - CTO
  - SVG
  - Post-brachytherapy
  - ISR (BMS), if not included in an additional study
  - Post-DES
  - LV dysfunction
- Case report forms should capture patient compliance with prescribed antiplatelet therapy and significant bleeding complications

- FDA is open to the inclusion of nested registry studies to support additional indications, such as for long lesions (multiple overlapping stents) or 2 vessel disease.