FDA Perspectives of Clinical Trials in Interventional Cardiology: US FDA

Angela Smith
Acting Chief
Interventional Cardiology Devices Branch
ODE/CDRH
US Food and Drug Administration

TCT ASIA PACIFIC
April 24, 2008
Objectives

- Provide background on US medical device regulation
- Discuss FDA Perspectives of Interventional Cardiology Clinical Trials
  - Drug Eluting Stents (DES)
  - Cardiac Occluders
US Regulation of Medical Devices

- Risk based classification
- Defines level of oversight
- Class I, II and III devices
- Regulatory submissions
  - Premarket notification [510(k)]
  - Premarket Approval (PMA)
  - Investigational Device Exemption (IDE)
  - Humanitarian Device Exemption (HDE)
Device Classification

- **Class I: common, low risk devices**
  - General controls
  - Most exempt from premarket submission

- **Class II: more complex, higher risk**
  - General and special controls
  - Premarket Notification [510(k)]

- **Class III: most complex, highest risk**
  - General controls and premarket approval
  - Most require Premarket Application [PMA]
Drug Eluting Stents
Study Objectives

- Determine safety and effectiveness endpoint rates (Death, MI, Revascularization)
- Evaluate impact of stent thrombosis
- Assess adjunctive antiplatelet therapy (APT)
Study Design

- Randomized Controlled Trial for new DES
- Non-randomized design can potentially be used to expand original indications:
  - Additional stent diameters
  - Additional stent lengths
  - Direct stenting
  - Chronic total occlusions
- Other indications likely to require some randomization: AMI and LM & 3VD disease
RCT Designs

- Superiority Study
  - DES vs. BMS
  - Investigational DES vs. approved DES
  - Superiority margin should be clinically meaningful

- Non-inferiority Study
  - compared to DES
  - “Delta” for equivalency should be clinically meaningful
  - Care should be taken to avoid “outcome drift” in successive non-inferiority studies
Endpoints for DES Trials

Clinical Endpoints (device oriented):

- Composite endpoint allows for assessment of safety with a reasonable sample size
- Cardiac death + target vessel MI + TLR at 12 months
- While not powered for individual components, FDA looks closely at each outcome independently
Endpoints for DES Trials

- Imaging Endpoints
  - % Diameter Stenosis
  - Late Lumen Loss
  - Provide quantitative data on stent performance
  - Provide greater sensitivity of outcomes
  - Utilized in addition to clinical endpoints

- Angio/IVUS captured in separate study or after 12-month clinical visit due to impact on revascularization rates
Endpoints for DES Trials

Use of Multiple Endpoints
- Composite/co-primary clinical and imaging endpoints
- Adjustment for correlation between endpoints
- Preservation of type I error
- Study success = meeting both endpoints

Additional Evaluations:
- Angio
  - stent apposition
- IVUS
  - peri-stent phenomena
  - stent fractures
Sample Size Considerations

- Dependent on technology (i.e., novel vs. generational)
- Driven by safety
- For NME: Ability to detect catastrophic events that occur at a 1% rate with an upper 95% CI of 1.4% with 2000 patients
- Not all patients need to be part of randomized trial
- Smaller sample size may be appropriate if evaluating less novel technology
Post Approval Studies

Assessment of unanticipated risks or rare occurrences in real-world patient populations

Follow-up up to 5 years post-implant

Evaluate Stent Thrombosis
- Detect a 1% increased rate in each 12 month period with 95% confidence for on-label patients

Evaluate cardiac death plus MI
- On-label patients pooled with pre-approval pivotal cohort

Evaluate use outside of labeled indication
US FDA has published a draft guidance and a companion document for evaluation of DES:


Currently open for comments

Workshop to be held on April 29 to obtain comment and discussion
Cardiac Occluders
Cardiac Occluders

US Approved Devices:
- PDA (1)
- ASD (2)
- VSD [muscular only] (2)
- PFO (none)

2 approved ASD: non-randomized studies with surgical control

Now randomization to approved device would be appropriate
Trial Design Considerations

- Evaluate both pediatric and adult populations
- Each patient population has unique profile for interpretation of results
- Challenges with designing and completing trials for PFO (stroke)
  - Off-label use
  - Lack of consistently accepted medical therapy
  - Definitions for TIA and stroke
  - Risks not well characterized
Trial designs for PFO occluders

- Prospective, multicenter study
- Patients with at least one stroke/TIA in the presence of PFO
- No other identifiable cause for stroke
- Randomized Control Trial
  - Treatment of index stroke vs. recurrent stroke on meds
  - Randomization: device + meds vs. meds
- Outreach to clinical community to develop clinical studies for new devices, new indications
Conclusions

- US FDA uses a risk-based classification for medical devices
- RCT needed for novel DES
- Other study designs may be appropriate to expand indications
- There are challenges with designing and completing cardiac occluder studies, but RCT are necessary
- FDA is open to creative trial designs, just interact with us early and often!
Contact Information

Angela Smith
Acting Chief, ICDB
240-276-4188
angela.smith@fda.hhs.gov