CDRH Post-Approval Update

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Director, Division of Epidemiology
Circulatory Devices Advisory Panel,
July 21, 2011
Post-Approval Studies:

Legal Authority

21 C.F.R. § 814.82

FDA may impose post-approval requirements at the time of approval of the PMA or by regulation subsequent to approval and may include:

(2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state the reason and the number of patients to be evaluated.

(9) Other requirements as FDA determines necessary to provide reasonable assurance of the safety and effectiveness of the device.
Need for Post-Approval Studies

- Gather essential postmarket information
- Longer-term performance including effects of re-treatments & product changes
- Real-world device performance (patients and clinicians)
- Learning curve effects and effectiveness of training programs
- Sub-group performance
- Outcomes of concern (safety and effectiveness)
Recent PAS Developments

2005    Established integrated CDRH PAS program

2005    Began raising scientific rigor of PAS

2006    Developed and instituted PAS tracking system

2006    Issued PAS Guidance

2007    Created PAS public website

2007    Instituted Advisory Panel

2008    Initiated BIMO inspections of PAS

2008    Increased focus on infrastructure building

2009    Increased focus on methods development

2010    MDEpiNet Initiative
Ongoing Studies Completed Studies

Detailed Study Protocol Descriptions:
- Study Population
- Sample Size (sites and patients)
- Study Endpoints
- Data Collection and Follow-up Visits

Final Data Summary:
- Number of Sites and Enrolled Patients
- Study Final Results
- Study Strengths and Limitations
- Recommended Labeling Changes

http://www.fda.gov/devicepostapprovalstudies

Food and Drug Administration
Division of Epidemiology
Post Approval Studies

- The new Center for Devices and Radiological Health (CDRH) Post-Approval Studies Program encompasses design, tracking, oversight, and review responsibilities for studies mandated as a condition of approval of a premarket approval (PMA) application. The program helps ensure that well-designed post-approval studies (PAS) are conducted effectively and efficiently and in the least burdensome manner.

- On January 1, 2005, the oversight responsibility was transferred to CDRH’s Office of Surveillance and Biometrics (OSB) and the PAS review functions were integrated into the medical device epidemiology program. Guidance on report format and content was developed to ensure optimal PAS reporting and review.

- CDRH has established a new automated tracking system that efficiently identifies the reporting status of active PAS studies ordered since January 1, 2005. This system represents CDRH’s effort to ensure that all PAS commitments are fulfilled in a timely manner. The effective tracking system is based on study timelines incorporated in study protocols and agreed upon by the CDRH and manufacturer.

- In addition to this internal tracking system, CDRH launched this publicly available webpage to keep all stakeholders informed of their progress. It displays not only the report status, but also study status (based on protocol-driven timelines) of each PAS.

### Post-Approval Study Commitment

<table>
<thead>
<tr>
<th>Application Number</th>
<th>Applicant Name</th>
<th>Device Name</th>
<th>Medical Specialty</th>
<th>Date PMA Approved</th>
<th>Study Name</th>
<th>Protocol Approved</th>
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Number of PAS for Original PMAs and Panel-Track Supplements

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Number Approved with PAS

# Individual PAS Requirements

Food and Drug Administration
Compliance with PAS Requirements

Issued 2005 to Present, N= 207

As of July 19, 2011

Food and Drug Administration
Division of Epidemiology
Reasons for “Progress Inadequate”, N=37

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<th>Follow-up</th>
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As of July 19, 2011

Food and Drug Administration
Labeling Change Requests Based on PAS Final Results

Calendar Year

Number

As of July 19, 2011

Food and Drug Administration

Division of Epidemiology
Number of Approved Cardiovascular Original PMAs and Panel-Track Supplements

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As of July 19, 2011

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Division of Epidemiology
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As of July 19, 2011
Focus on Infrastructure
CDRH Ongoing Registry Efforts

- Use existing registries for PAS studies and surveillance
  - INTERMACS (NIH, CMS, FDA)
  - Atrial Fibrillation Registry (ACC, HRS, STS)
  - American Joint Replacement Registry (AAOS)
  - Diagnostic and Therapeutic Bronchoscopy Registry (ACCP)
  - Uro-Gynecological Mesh Registry (U Mass; AUS)
  - IMPACT Registry (ACC)

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CDRH Ongoing Registry Efforts (cont)

- Use existing registries for discretionary studies
  - ICD Registry (ACC-NCDR)
  - Adult Cardio-Thoracic Database (STS)
  - Total Joint Replacement Registry (Kaiser)
  - Hospital for Special Surgeries Registry (Cornell)
  - OUS Orthopedic Registries (Australia, Denmark)

- Explore registry capabilities
  - Active surveillance: short-term and longitudinal
  - Linkages studies with Medicare claims data

- Advocate for registries

- Build methodological infrastructure for registries
Focus on Methods
Make better use of existing pre & post approval data

Integrate/combine when appropriate!

Use Simultaneous:

- Meta-analysis
- Network meta-analysis
- Cross-design synthesis

• Bayes factors
Rethinking Analytical Strategies for Surveillance of Medical Devices

The Case of Hip Arthroplasty

Sharon-Lise Normand, PhD, Danica Marinac-Dabic, MD, PhD, Art Sedrakyan, MD, PhD, and Ronald Kaczmarek, MD, MPH

Background: Randomized trials that sometimes serve as the basis for device approval are small, short term, and generalizable to an increasingly smaller percentage of patients. Some of the most common and challenging devices are those used in hip replacement. Artificial hips are implanted in thousands to alleviate pain caused by noninflammatory joint disease and to restore patient mobility. During 2004 in the United States, although 68% of hospital stays for partial or total hip replacements were for those aged 65 years and older, younger patients will account for 52% by 2030.

Methods: Using hierarchical modeling, we propose a framework for combining information from premarket and postmarket settings. Our key assumption is that device performance characteristics and outcomes obtained from 1 cohort are related to device characteristics and outcomes of the same or similar devices observed in other cohorts. We illustrate methods by jointly modeling Harris Hip Scores (HHSs) and revision-success data from 1851 subjects who participated in 3 pivotal randomized or observational studies of artificial hips.

Results and Conclusions: Subjects participating in randomized studies had better 2-year HHS than those in observational studies (posterior mean increase in HHS = 4.1, posterior standard deviation = 0.6). Patients implanted with ceramic-on-polyethylene hip used in 1 study had higher 2-year HHS than those implanted with a different ceramic-on-polyethylene hip in another study (mean difference = 4.2, standard deviation = 0.6). Our approach is feasible and will advance regulatory science using a transparent and dynamic new paradigm for knowledge management throughout the total product life cycle.

Key Words: crossdesign synthesis, network meta-analysis, Bayesian hierarchical models, posterior distributions

Current approaches for integrating clinical information in clinical trials and real-world settings of medical devices require updating. This need arises due to the recognition of at least 2 facts. First, randomized controlled trials (RCTs), when serving as the basis for new device approval, are small, short term, and are generalizable to an increasingly smaller percentage of patients. The reasons for decreased generalizability are 2-fold: (1) the population is aging, having more chronic diseases, and comprising a larger portion of routine practice yet are often excluded from trials and (2) the increasing inclusion of less sick patients who are less likely to benefit.

Second, postmarket studies are often voluntary, have design limitations, and are difficult to execute. Although these problems are not new, they have become increasingly important during the last decade because device technology is changing at a rapid pace, therapies are used outside their intended populations, and more representative groups of patients are likely to have differential responses to the same therapy. A broader more inclusive group of patients means wider ranges of disease severity, of sociodemographic characteristics, of genetic characteristics, and of health-related behaviors. Consequently, the device effectiveness will be more heterogeneous.

Some of the most common and challenging devices are those used in hip replacement. A total hip replacement involves cutting off the top of the femur, inserting a stem (with a femoral ball) into the femur, and replacing the hip's socket, which will articulate with the femoral ball. Patient enrollment and retention in the pre or postapproval study setting pose unique problems in assessing hip replacement systems because long-term follow-up, generally 10 years postimplantation, is required. Blinding and allocation concealment in RCTs are difficult, and the numerous potential comparators requires very large numbers of patients to be studied. Device
Focus on Strategic Partnership
To bridge evidentiary gaps and develop datasets and innovative methodological approaches for conducting analytic studies to improve FDA understanding of safety and effectiveness of medical devices throughout their life cycle through formal leverage of expertise from academia and other stakeholders.
MDEpiNet conceptual framework

- Systematic appraisal of all available evidence
- New real world studies to fill the gaps
- Research consortium development
- Translate the results for regulatory decision making and dissemination for patients and physicians

Combined Evidence

Food and Drug Administration Division of Epidemiology
MDEpiNet – Unique Role

Will provide tools such as:

- Study design for distributed network based research
- Advanced analytical overall methods such as multilevel analyses (hospital, surgeon, patient)
- Advanced analytical methods for confounding adjustment - propensity scores, instrumental variables
- Cross design syntheses and Bayesian methods
- Help strengthen relationships and stakeholder development
Upcoming Epidemiology Outreach Efforts

- IDEAL/TPLC Conference  Dec 2011
- 522 Studies Conference   Mar 2012
- MDEpiNet Conference      Apr 2012
- PAS Studies Conference  May 2012
- Registries Conference      Jun 2012
Thank you!

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