The Total Product Life Cycle and the Dynamic Regulatory Environment of Medical Devices in the U.S.

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Medical Devices in the US

• In 2010, the medical device industry had $135.9 billion market in the US*

• 12% increase since 2005

• 6% of total healthcare industry

To Market... Drugs

Lab / Bench → IND → NDA → Post-marketing
Devices are Not the Same as Drugs

- Minor change in structure can alter drug properties – not always true for devices
- Implanted devices often in the body for extended time
- Discontinuing exposure to a device may be difficult
- Devices are susceptible to manufacturing tolerances and multiple types of mechanical failures
- Device use is dependent on the skills of the operator
- Difficult to blind a user to device exposure
Different Premarket Requirements

- Multiple premarket RCTs atypical
- Broader interpretation of “valid scientific evidence”
- Devices can reach market with only non-clinical testing
To Market... Devices

Devices
- Lab / Bench
- IDE
- PMA
- Post-marketing

Drugs
- Lab / Bench
- IND
- NDA
- Post-marketing
Devices have Class(I)

• Class I
  – “General controls” are sufficient to ensure safety and effectiveness
  – Substantially equivalent to device already marketed
  – May be exempt from premarket notification

  – Examples include mechanical wheelchairs, arsenic test, dental handpieces
Devices have Class(II)

- Class II
  - “Special controls” are sufficient to ensure safety and effectiveness
  - Substantially equivalent to device already marketed
  - May be exempt from premarket notification

- Examples include many hospital beds, coils for filling neurovascular aneurysms, most ventilators
Devices have Class(III)

• Class III
  – Supports or sustains human life - or -
  – Is of substantial importance in preventing impairment of human health – or -
  – Presents a potential, unreasonable risk of illness or injury
  – Approximately 10% of medical devices
  – Examples include breast implants, hip implants, pacemakers
Postmarketing Requirements

- Inspections (Quality Systems Regulation)
- Recalls, Corrections, Removals
- Reporting Adverse Events
- Post-Approval Studies (PAS)
- Postmarket Surveillance Studies (522)
Postmarketing Surveillance

• Adverse event reporting
  – Monitoring of individual reports
  – Data mining

http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm
Importance of Medical Device Research

- Length of use
- Learning curve for procedures
- Community or “real-world” use
- Subgroup information
- User training and location of use
Importance of Medical Device Research

• Cleared vs. approved devices
• Combination products

• Reduction of adverse events
• Rare events
Framework for Research

Sedrakyan, 2010
Challenges of Studying Medical Devices

• Similar to drugs, but distinct differences
• Lack of unique identification
• Multiple modes of failure
• Combination of products used
• Adverse event capture
Challenges of Studying Medical Devices (2)

- Modification of device over time
- Removal or revision surgery
- Incomplete documentation of procedure location
Division of Epidemiology

Oversight of Mandated Postmarketing Studies
• Post-Approval Studies
• Postmarket Surveillance Studies

Leadership in Regulatory Science Efforts
• Epidemiology Regulatory Science Program

CDRH Epidemiology Expertise
• Premarket reviews
• Center working groups
• Consults
Post-Approval Studies (PAS)

- Class III, PMA devices
- Ordered at time of approval
- Authority under CFR Title 21 Section 814.82
  (a) FDA may impose post-approval requirements at the time of approval of the PMA ...
  (2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. . .
Postmarket Surveillance Study (522)

- Public health question for any class II or class III device which meets one of the following criteria
  - failure of the device would be reasonably likely to have a serious adverse health consequence
  - expected to have significant use in pediatric populations
  - intended to be implanted in the body for more than one year
  - intended to be a life-supporting device used outside of a user facility
Current Study Paradigm

• 164 Active PAS
• 185 Active 522
• Studies are founded on good science, are timely and provide useful results
• All include major study design elements
  – Protocol with primary hypothesis, statistical analysis, etc.
• Stress collaboration between epidemiologists at FDA and industry
• Often de novo data collection
Identifying Obstacles and Opportunities for Recruitment and Retention in Clinical Research

The Food and Drug Administration’s (FDA’s) mission is to promote and protect the public health by helping safe and effective drugs, biologic products, and medical devices reach the market in a timely way and increasing public access to accurate, science-based health information. Additionally, FDA monitors medical products to ensure they remain safe and effective after they are approved. Prior to approval, medical products are evaluated based on a small population relative to the number of people who will eventually use the product. Thus, tasked with the responsibility of ensuring high-quality clinical research throughout the total product lifecycle, FDA is interested in identifying obstacles and opportunities for recruitment and retention in clinical research that may affect the accuracy and completeness of clinical research data.

Recruitment mechanisms should encourage enrollment of a study group that is representative of the intended use populations. Strategies addressing opportunities for improvement include clinician and patient education and using best practices for eligibility, screening, and targeted recruitment. It is important that the composition of the study population is related to the question being addressed in a scientific study because disease incidence, prevalence, mortality, and the occurrence of adverse events may differ by sex, age, racial and ethnic groups, and other characteristics. A variety of factors affect study progress, including subject-related, investigator-related, and protocol-related factors. Following study subjects can also be a challenge. Differential losses to follow-up may introduce biases that can limit the validity and generalizability of study results.

Valuable information regarding barriers and opportunities can be obtained from those with “hands-on” research experience. The critical role of clinical research coordinators (CRCs) is widely recognized. The CRC’s responsibilities include ensuring compliance with the protocol, identifying
Future PAS

• Traditional prospective and retrospective studies not always feasible
  – Lack of identification
  – Lack of documentation
  – Lack of adverse event capturing

• Goal of leveraging existing resources (registries, administrative data, etc) so that existing infrastructure is fully utilized/integrated into postmarket
Future 522

• Have infrastructure available to address many questions by leveraging existing resources
• Integrate this program into wider Signal Management framework – as one option for evaluating signals
  – Some questions answered by FDA, others by industry, others by greater stakeholder community
Working Groups

• Scientific/Methodologic
• Guidance/Standards
• Specific Program
• Specific Device Area
Regulatory Science Research

• Epidemiology Regulatory Science Program
• Data Mining
• Pilot projects with Medicare/Medicaid
• Sentinel Initiative
• Medical Device Epidemiology Network
• Registries
• OUS Data
Emergency Department Visits for Medical Device-Associated Adverse Events Among Children

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KEY WORDS: medical device, adverse events, emergency department

ABBRÉVIATIONS
MDAE—medical device-associated adverse event
NEISS—National Electronic Injury Surveillance System
AIP—all injury program
FDA—Food and Drug Administration
CPSC—Consumer Product Safety Commission
ED—emergency department
CI—confidence interval
CDRH—Center for Devices and Radiological Health

WHAT’S KNOWN ON THIS SUBJECT: To our knowledge, national estimates and characterization of MDAEs in the pediatric population have not been reported.

WHAT THIS STUDY ADDS: The authors characterized the first national estimates of MDAEs from EDs in the pediatric population. The scope and severity of these MDAEs underscore the need for more-intensive preventive efforts.

abstract

OBJECTIVES: The purposes of this study were to provide national estimates of emergency department (ED) visits for medical device-associated adverse events (MDAEs) in the pediatric population and to characterize these events further.

METHODS: ED medical record reports from the National Electronic Injury Surveillance System All Injury Program database from January 1, 2004, through December 21, 2005, were reviewed. MDAEs among pediatric patients were identified, and data were abstracted. National estimates for pediatric MDAEs were determined according to medical specialty, device category and class, injury diagnosis, and patient characteristics and outcome.

RESULTS: The total estimated number of pediatric MDAEs during the 24-month period was 144,799 (95% confidence interval: 113,051–183,903), involving devices from 13 medical specialties. Contact lenses accounted for most MDAEs (23%), followed by hypodermic needles (8%). The distribution of MDAEs according to medical specialty varied according to age subgroup. The most-relevant types of injuries in-
Data Availability Today

- Medical Device Reports
- De Novo Data Collection
- Device-Based Registries
- Claims Data
- Electronic Healthcare Records
- Disease-Based Registries
- Other Sources
Common MDR Issues

• Majority of reports are from the Manufacturer
• Quality Voluntary Reports are needed for complete picture of device problems
• Often Voluntary Reports are missing vital information or are not detailed.
• Serious injury or death
• Medical/surgical intervention required?
• What type of potential human factors were involved in device problems
Sentinel Initiative – a national electronic safety monitoring system

A national electronic system that will transform FDA’s ability to track the safety of drugs, biologics, medical devices--and ultimately all FDA-regulated products once they reach the market--is now on the horizon. Launched in May 2008 by FDA, the Sentinel Initiative aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products.

Monitoring the safety of its regulated products is a major part of FDA’s mission to protect public health. The Sentinel System would enable FDA to actively query diverse automated healthcare data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.

Sentinel will be developed and implemented in stages. As the system is envisioned, data would continue to be managed by its owners and

http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
News of Today

• ARRA, HITECH
• 125 million lives in mini-Sentinel
• Establishment of MDEpiNet
• UDI Proposed Rule
Automated Surveillance to Detect Postprocedure Safety Signals of Approved Cardiovascular Devices

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Monitoring the safety of approved medical products is of vital public health importance, given that in clinical practice such medical products are often used in numbers far greater and in patient populations more diverse than when studied in premarket evaluations and clinical trials. Within the broad range of medical products, implantable medical devices represent high-risk products that are uniquely challenging to monitor because there is little consensus regarding the most appropriate methods to account for the complex interactions among devices, medications, patients, and implanting physicians. In addition, the lack of unique medical device identifiers challenges the effective use of administrative claims data and electronic health records as a primary data source to evaluate manufacturer-specific device safety.

To support clinical research and quality-improvement efforts, detailed clinical registries have been established in recent years at the state, regional, and national levels for many high-risk implantable medical devices, which may provide unique opportunities to prospectively monitor the safety of such devices. The Massachusetts statewide coronary intervention registry was established in 2003 to monitor the quality of care of hospitals and physicians in the state. This registry is a mandatory clinical outcomes registry based on the

Context Ensuring the safety of medical devices challenges current surveillance approaches, which rely heavily on voluntary reporting of adverse events. Automated surveillance of clinical registries may provide early warnings in the postmarket evaluation of medical device safety.

Objective To determine whether automated safety surveillance of clinical registries using a computerized tool can provide early warnings regarding the safety of new cardiovascular devices.

Design, Setting, and Patients Prospective propensity-matched cohort analysis of 7 newly introduced cardiovascular devices, using clinical data captured in the Massachusetts implementation of the National Cardiovascular Data Registry CathPCI Registry for all adult patients undergoing percutaneous coronary intervention from April 2003 through September 2007 in Massachusetts.

Main Outcome Measure Presence of any safety alert, triggered if the cumulative observed risk for a given device exceeded the upper 95% confidence interval (CI) of comparator control device. Predefined sensitivity analyses assessed robustness of alerts when triggered.

Results We evaluated 74,427 consecutive interventional coronary procedures. Three of 21 safety analyses triggered sustained alerts in 2 implantable devices. Patients receiving Taxus Express2 drug-eluting stents experienced a 1.28-fold increased risk of postprocedural myocardial infarction (2.87% vs 2.25%; absolute risk increase, 0.62% [95% CI, 0.25%-0.99%]) and a 1.21-fold increased risk of major adverse cardiac events (4.24% vs 3.56%; absolute increase, 0.74% [95% CI, 0.29%-1.19%]) compared with those receiving alternative drug-eluting stents. Patients receiving Angio-Seal STS vascular closure devices experienced a 1.51-fold increased risk of major vascular complications (1.09% vs 0.72%; absolute increase, 0.37% [95% CI, 0.03%-0.71%]) compared with those receiving alternative vascular closure devices. Sensitivity analyses confirmed increased risk following use of the Taxus Express2 stent but not the Angio-Seal STS device.

Conclusion Automated prospective surveillance of clinical registries is feasible and can identify low-frequency safety signals for new cardiovascular devices.

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News of Tomorrow

• Evaluation of UDI within claims and electronic healthcare records
• Linkage of device registries with other healthcare data sources
• Use of distributed data networks for surveillance
Tomorrow’s Data

- Less De Novo Collection
- Increased Use of Registries, Claims, Electronic Healthcare Records

- Need for improved methodologies and better understanding for secondary data analysis
Rethinking Analytical Strategies for Surveillance of Medical Devices

The Case of Hip Arthroplasty

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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 is 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
In the Future

• Postmarket infrastructure allows most evaluation via automatic data collection
• Rare instances when additional data are needed – e.g. patient surveys disease-based registries
• Continued innovation and utilization of novel methodologies to better understand performance and clinical outcomes of medical devices
Data of the Future

• Allows ongoing evaluation of postmarket landscape to provide evidence for benefit-risk balance of newly developed devices

• Infrastructure and novel methodologies systematically developed and enhanced
FDA

GOVERNMENT/ACADEMIA

Enhance Regulatory Decision-Making

Scientific Research

PARTNERING FOR THE PUBLIC HEALTH

IMPROVE HEALTHCARE

Expedite Medical Product Development

PATIENTS/SOCIETIES/PAYERS

INDUSTRY
Looking forward with Medical Device Epidemiology

- Advancement of Methods
- Strategic Infrastructure Development
- Integrate Regulatory, Academic and Industry Efforts
- Consortia and Think Tanks
Knowledge Management throughout TPLC

- **Systematic** identification and of all relevant data
- **Innovative** analytical methods development and application
- **Dynamic** integration, synthesis and evaluation of data