POST-MARKET SURVEILLANCE: HOW FDA REGULATES YOUR MEDICAL PRODUCT AFTER LAUNCH

WHAT YOU NEED TO DO TO COMPLY WITH AGENCY RULES, AVOID LIABILITY, AND IMPLEMENT BEST PRACTICES

JUNE 28, 2019

Device Post-Market Surveillance Under CDRH & §522

Moderator: Christina Kuhn, Associate, Covington & Burling

Panelist: Kim Graul, Director, Post-Market Safety, Stryker

Panelist: Dr. Susan Alpert, Principal, SFA Regulatory, LLC

Device Post-Market Surveillance

June 28, 2019

COVINGTON

BEIJING BRUSSELS DUBAI FRANKFURT JOHANNESBURG LONDON LOS ANGELES
NEW YORK PALO ALTO SAN FRANCISCO SEOUL SHANGHAI WASHINGTON

www.cov.com

Postmarket Surveillance

- Postmarket surveillance is a collection of processes and activities the FDA uses to monitor the safety and effectiveness of medical devices once they are on the market
- CDRH Action Plans (2012, 2013, 2018):
  - Establish UDI system
  - Promote development of device registries
  - Modernize adverse event reporting
  - Develop NEST
  - Calibrate risk-benefit evaluation in pre- and post-market setting
  - Develop and use new methods for evidence generation and analysis; improve clarity around real world evidence

Postmarket Safety Mechanisms

- Medical Device Reporting
- Recalls (corrections and removals)
- Postmarket surveillance under 522
- Safety communications and emerging signals

2018 Medical Device Safety Action Plan

- FDA goal to be “first” regulator
  - Active surveillance of real world evidence
  - FDA research
  - Early public communications
- Specific initiatives
  - Women’s health
  - Surgical tools
  - Materials in implantable devices
  - Cybersecurity

Example: Women's Health

- **April 2019:** FDA ordered all manufacturers of surgical mesh intended for transvaginal repair of anterior compartment prolapse to stop selling and distributing their products
  - Required to continue follow-up in 522 studies
- **February 2019:** Safety Communication warning against use of thermography devices in place of mammography
  - Warning Letter issued to firm for marketing device as a sole screening device for breast cancer and other diseases
- **February 2019:** Safety Communication cautioning against use of robotically-assisted devices in women's health procedures
- **July 2018:** Safety Communication warning against use of Use of Energy-Based Devices to Perform Vaginal 'Rejuvenation' or Vaginal Cosmetic Procedures
  - Seven (7) "It's Come to Our Attention Letters" issued to manufacturers of these devices
- **April 2018:** Restrictions imposed by FDA on sale of Essure, a permanently implanted birth control device for women

Implantable Device Materials

- FDA has recognized a growing body of evidence suggesting that a small number of patients may have biological responses to certain materials in implantable or insertable devices (e.g., inflammatory reactions and tissue changes)
  - Some symptoms may not show up until several years following implantation and thus may not be detected in clinical studies
  - Currently available tests don't do enough to identify which people might be at risk of reaction to the material in a certain device
- Materials of interest:
  - Metals (2019 priority)
  - Animal materials
  - Innovative materials (e.g., nanoparticles, graphene)

FDA Activities on Metals/Potential Outcomes

- ❑ FDA Scientists Conducting Research
- ❑ "State-of-the-Science" White Paper
- ❑ Advisory Panel Meeting Fall 2019

- ➢ FDA safety communications
- ➢ Up-classification
- ➢ Recalls
- ➢ New boxed warnings
- ➢ More pre-market research
- ➢ More post-market studies

MDR Reportable Event

- Event that reporter becomes aware of information that reasonably suggests that the device:
  - User facilities:
    - has or may have caused or contributed to a death or serious injury
  - Manufacturers and importers:
    - may have caused or contributed to a death or serious injury
    - has malfunctioned and that device or a similar device marketed by the manufacturer or importer would be likely to cause or contributed to a death or serious injury if the malfunction were to recur

Reporting Requirements

Reporter	What to Report	Where	When
Manufacturer (Mfr)	Events that require remedial action to prevent an unreasonable risk of substantial harm	FDA	5 working days
	Events pursuant to FDA request	FDA	5 working days
	Deaths, serious injuries, malfunction	FDA	30 calendar days
	Supplemental reports	FDA	30 calendar days
Importer	Deaths and serious injuries	FDA and Mfr	30 calendar days
	Malfunctions	Mfr	30 calendar days
User Facility	Deaths	FDA	10 working days
	Serious injuries	Mfr	10 working days
	Annual Reports	FDA	January 1

Potential Pitfalls

- Not documenting and reporting MDRs from any source, including:
  - Social media
  - Literature
  - Servicing
  - Trade shows
  - Clinical trials
  - OUS
- Failure to report in timely manner, due to, e.g., employees failing to report internally
- MDR reportability decision making, including:
  - User error
  - Off-label use
  - Labeled adverse events

Regulatory and Policy Framework Governing Recalls

	Statute	**Regulations**
Voluntary recalls		21 C.F.R. Part 7*
Mandatory device recalls	FDCA § 518(e)	21 C.F.R. Part 810
Reports of corrections and removals	FDCA § 519(g)	21 C.F.R. Part 806

*Although published in the C.F.R, Part 7 is agency guidance

Recalls

- Voluntary recall: Firm's removal or correction of a marketed product that the FDA considers to be in violation of FDA and against which FDA would initiate legal action
- Mandatory recall : If FDA finds that there is a reasonable probability that a device would cause serious, adverse health consequences or death, FDA may require company to:
  - Cease distribution of device
  - Notify health professionals and user facilities to cease use of device
  - Recall device

Recall Classification

- Class I: there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death
- Class II: the use of, or exposure to, a violative product:
  - may cause temporary or medically reversible adverse health consequences, or
  - the probability of serious adverse health consequences is remote
- Class III: the use of, or exposure to, a violative product is not likely to cause adverse health consequences

Reports of Corrections or Removals

- Must report any correction or removal of a device if action was initiated to:
  - Reduce a risk to health posed by the device, or
  - Remedy a violation of the FDCA caused by the device which may present a risk to health
- Risk to health:
  - A reasonable probability that use of, or exposure to, the product will cause serious adverse health consequences or death, or
  - That use of, or exposure to, the product may cause:
    - temporary or medically reversible adverse health consequences, or
    - an outcome where the probability of serious adverse health consequences is remote
- Reports are required for Class I and II recalls

Common Pitfalls

- Allowing too much time to elapse between identifying a systemic issue and initiating a recall
- Lack of justification for why the recall was not initiated to reduce a risk to health
- Undertaking actions in the field without realizing these actions are "corrections" or "removals" that must be analyzed for reportability under Part 806
  - Distributing a "market bulletin" or "technical advisory"
  - Applying corrections, including inspection of product, during routine maintenance services

Conditions of PMA Approval

- FDA may impose postapproval requirements in approval order, including:
  - restriction of sale, distribution or use
  - continuing evaluation and periodic reporting on safety, effectiveness, and reliability of device for intended use (e.g., post-approval studies)
  - prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards or precautions important for the device's safe and effective use
  - at specified intervals, submission of periodic reports
- Postapproval (Annual) Reports:
  - Identification of certain changes
  - Bibliography and summary of information not previously submitted, including unpublished reports of data involving device or related devices and reports in scientific literature concerning device

Postmarket Surveillance Studies

- FDCA § 522; 21 C.F.R. Part 822
- Postmarket surveillance can be ordered at time of approval or anytime thereafter if following conditions are met:
  - failure of the device would be reasonably likely to have serious adverse health consequences; or
  - the device is intended to be implanted in the human body for more than one year; or
  - the device is expected to have significant use in pediatric populations; or
  - the device is intended to be a life sustaining or life supporting device used outside a device user facility

Postmarket Surveillance Studies

- Manufacturers must:
  - Submit a postmarket surveillance plan for approval within 30 days of receiving an order to conduct a postmarket surveillance study from FDA,
  - Commence surveillance no later than 15 months from date of order
- Device is misbranded under FDCA § 502(t) if requirements are not met

Warning Letters

- 2011 – 1 Letter to manufacturer of spinal system
- 2015 – 3 Letters to: manufacturer of exoskeleton device, manufacturer of skull prosthesis, and manufacturer of multiple hip implants
- 2018 – 3 Letters to 3 manufacturers of duodenoscopes all subject to same 522 study requirement

Safety Communications and Related Notices

- Safety issues communications through “Safety Communications” and recall notices published on FDA’s website
  - Previously, called Public Health Notifications
- Safety signals:
  - 2009-2010 Signal Escalation Pilot Program
  - Posting of drug potential safety signals pursuant to section 921 of FDAAA
  - Draft guidance “Public Notification of Emerging Postmarket Medical Device Signals” published Dec. 2015

What is an Emerging Signal?

- "Public Notification of Emerging Postmarket Medical Device Signals" guidance (Dec. 2016)
- New information:
  - that supports a new causal association or new aspect of a known association between a device and an adverse event
  - for which the agency has conducted an initial evaluation and determined that the information has the potential to impact patient management decisions and/or the known benefit-risk profile of the device

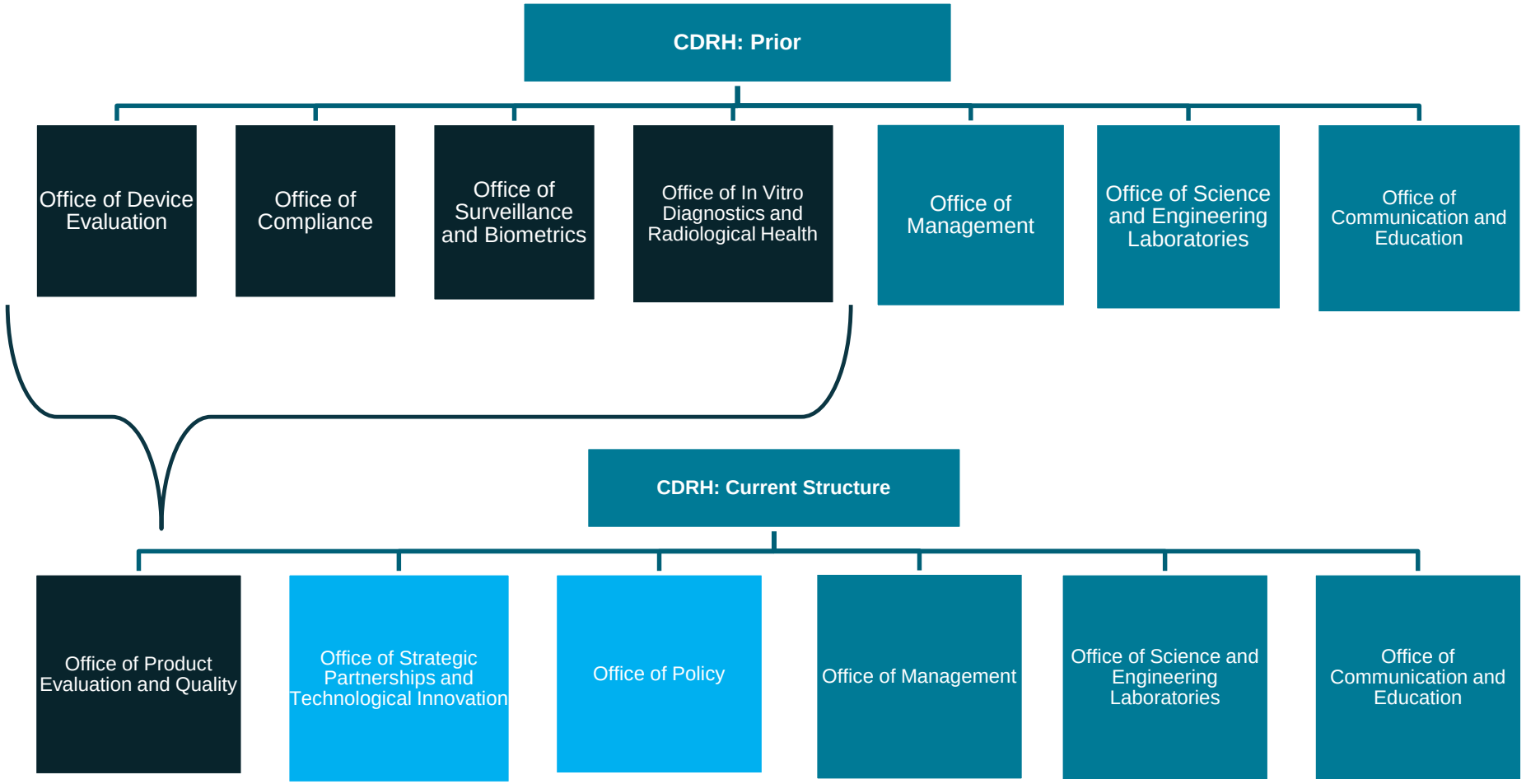
When is an Emerging Signal Published?

- Factors include:
  - Likelihood of the event
  - Severity, duration and reversibility of the event
  - Magnitude of the benefit of the device
  - Quality of data and strength of evidence of a causal relationship
  - Extent of patient exposure
  - Impact on vulnerable populations
  - Potential for preventing, monitoring or mitigating risk
  - Availability of alternative therapies
  - Implications for similar or related devices

Emerging Signals: Open Issues

- Data sources and methodologies
- Impact on prescribing and use
- Extrapolation across multiple products
- Speed and nature of FDA investigation
- FDA follow-up and corrections
- Industry notice and involvement
- Off-label information
- Expected manufacturer response
- Potential for products liability lawsuits
- Appropriateness of acting through guidance

CDRH Reorganization



Office of Product Evaluation and Quality