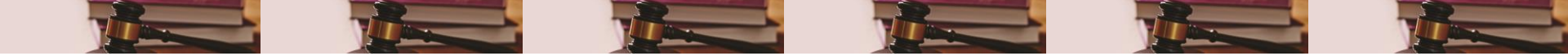

Post-Market Safety: Medical Device Safety Action Plan, Medical Device Safety Communications, and Post-Market Safety Reporting for Combination Products

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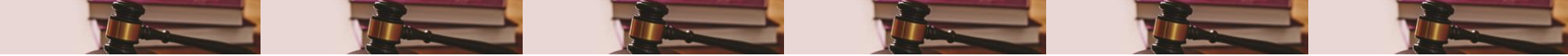
Panelists

Anne K. Miller, Principal Legal Counsel, Medtronic

Kristin Davenport, Of Counsel, Covington & Burling LLP

William A. McConagha, Partner, Sidley Austin LLP



Part I:
Post-Market Safety Reporting for Combination Products

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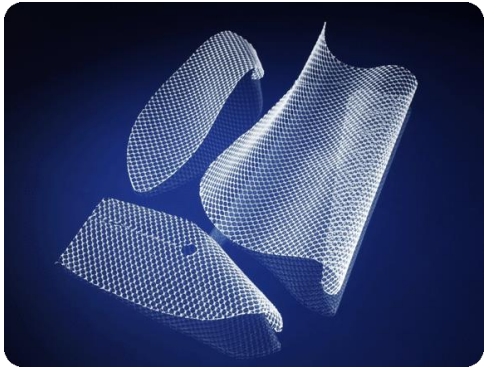
Coralite
BANDAGE
WITH NON-STICK PAD
ANTIBACTERIAL
First Aid Antiseptic on Pad
STERILE
Kills Germs
30



Jurisdiction Based on PMOA

- Lead center (CDER, CBER or CDRH) is assigned primary jurisdiction over a combination product based on the “Primary mode of action” (PMOA)
- Lead center conducts premarket review and remains primary point of contact for postmarket compliance
- Office of Combination Products (OCP)
  - Assigns Center with primary jurisdiction
  - Plays a coordinating role
  - Does not directly regulate

Safety Reporting Requirements for Combination Products

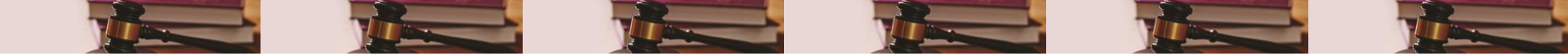
- December 2016 Final Rule applies to application holders for combination products
- Addresses requirements based on type of application holder:
  - **Combination product applicant:** product marketed under a single application or by separate applications held by the same entity
  - **Constituent part applicants**: constituent parts marketed under separate applications held by separate applicants
- Describes requirements in terms of application-based requirements and constituent part requirements (i.e., requirements for non-PMOA constituent part)
- FDA has issued Guidance documents on PMSR requirements for Combination Products:
  - March 2018 – Draft guidance "Postmarketing Safety Reporting for Combination Products" issued
  - April 2019 – Immediately in effect guidance "Compliance Policy for Combination Product Postmarketing Safety Reporting" issued
  - July 2019 – Final guidance "Postmarketing Safety Reporting for Combination Products" issued

Reporting Under Single Application

	Drug-Device **Drug App (eg, NDA)**	**Biologic-Device** **Biologics App (BLA)**	**Device-Drug** **Device App (eg, PMA)**	**Device-Biologic** **Device App (eg, PMA)**
Application type-based reporting	Full NDA reporting requirements	Full BLA reporting requirements	• **Full MDR reporting** • **Reports of corrections and removals**	• Full MDR reporting • Reports of corrections and removals
Constituent part-based reporting	• 5-day MDR reports • Malfunction reports • Reports of corrections and removals	• 5-day MDR reports • Malfunction reports • Reports of corrections and removals	• Field alert reports • 15-day reports	• BPDRs • 15-day reports

Compliance Dates

- In April 2019, FDA issued a compliance policy that affects the following requirements:
  - 21 CFR 4.102(c) and (d) (constituent part-based reporting requirements)
  - 21 CFR 4.104(b)(1) and (b)(2) (submission process for constituent part-based ICSRs)
  - 4.105(b) (recordkeeping requirements)
- **July 31, 2020** for constituent part-based reporting for Combination Product Applicants using FAERS and eMDR to report ICSRs
- **January 31, 2021** for constituent part-based reporting for Combination Product Applicants using VAERS to report ICSRs



Case Studies: Examples from FDA Guidance

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Example: Malfunction Report versus 15-Day Report (1/2)

- **Example**: Co-packaged drug and infusion set approved under an NDA.
- **Event**: A serious, unexpected adverse event related to over-infusion occurs. After submitting the 15-day report, the applicant determines that failure of the infusion set to meet its specifications could have caused or contributed to the event.
- **Reporting Requirement**: A malfunction report also must be submitted
  - Should be submitted as a supplement to the 15-day report, identified as a malfunction report.
  - FDA does not object to submitting the report within 30 (rather than 15) calendar days after the day the applicant becomes aware of the reportable malfunction.

Example: Malfunction Report versus 15-Day Report (2/2)

- **Example**: Co-packaged drug and syringe approved under an NDA.
- **Event**: Applicant receives a report that a medical professional noticed before use that the sterile barrier for a co-packaged syringe was compromised and discarded the syringe before using it on a patient. The breach in the sterile barrier would be likely to cause or contribute to a death or serious injury if it were to recur, e.g., infection that would require hospitalization.
- **Reporting Requirement**:
  - No 15-day report is required because there was no adverse event.
  - A malfunction report must be submitted within 30 calendar days after the day the applicant becomes aware of the reportable malfunction.

Foreign Malfunctions

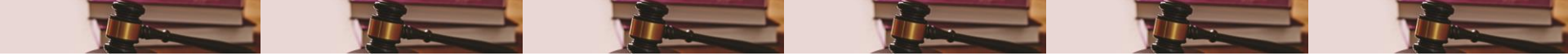
- **Example**: Inhaler + drug cartridge approved under NDA.
- **Event**: Foreign event involves otherwise reportable malfunction where a user is unable to deliver the dose. The foreign marketed inhaler is similar to the US inhaler.
- **Reporting Requirements**:
  - The applicant should submit a malfunction report if:
    - The inhaler has only minor differences (e.g., minor differences in the shape of the external housing) as compared to the inhaler used in the applicant's U.S.-marketed combination product; **and**
    - The malfunction is likely to occur in the U.S.-marketed combination product.
  - The applicant should not submit a malfunction report if:
    - The basic design and performance characteristics related to safety and effectiveness of the inhaler in the foreign-marketed product are different.
    - E.g., no malfunction report if blockage of the inhaler nozzle results from the actuator nozzle orifice having a significantly smaller diameter than the U.S.-marketed product, significantly altering performance of the foreign-marketed inhaler.

Drug Application Combination Product (1/2)

- **Example**: Sterile syringe pre-filled with an injectable drug, approved under an NDA.
- **Event**: Applicant receives a report that a user had difficulty pulling back the syringe plunger rod. When the user managed to pull the plunger back, the entire plunger came out, and the product sprayed into his eyes, causing temporary blindness and requiring medical intervention to prevent serious damage to his eyes. Potential blindness is not an expected adverse event discussed in the labeling.
- **Reporting Requirements**:
  - 15-day report because the event was both serious and unexpected (was not included in the product labeling).
  - Malfunction report because the report indicated that the device did not perform as intended, which resulted in temporary blindness. This reasonably suggests that the product or a similar product marketed by the applicant would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
  - No 5-day report required at this time because at the time of the initial report, insufficient information is available to the applicant to determine whether remedial action is necessary to prevent an unreasonable risk of substantial harm.
- Single report that includes information for 15-Day and Malfunction Report can be submitted within 15 calendar days.

Drug Application Combination Product (2/2)

- **Example**: Sterile syringe pre-filled with an injectable drug, approved under an NDA.
- **Event Continued**: Applicant determines that the syringe supplier made changes to the material of the plunger without notifying the applicant and that the new material alters the force needed to pull the plunger during use. Applicant now determines that:
  - remedial action (the removal of lots of the combination product that include the syringes with the new material) is necessary to prevent an unreasonable risk of substantial harm.
  - the change in material is inconsistent with a specification established in the application for the combination product.
- **Reporting Requirements**:
  - 5-day report within five working days of determining the remedial action is necessary.
  - FAR within three working days of receiving the information that the lots of the combination product were not meeting the specification established in the application.
  - Correction and removal report within 10 working days of initiating the product removal.
- **Additional Considerations**:
  - If the effect on the user's eyes had been expected → Malfunction report, but no 15-day report required.
  - If the removal was initiated within five working days of making the determination that a removal was necessary to prevent an unreasonable risk of substantial harm to the public health → Applicant could have submitted a single report to satisfy both the 5-day and correction/removal reporting requirements.
  - Applicant must continue to assess and submit 15-day reports as required for adverse events, even after the 5-day report is submitted.



Part II:
Medical Device Safety Action Plan and Safety Communications

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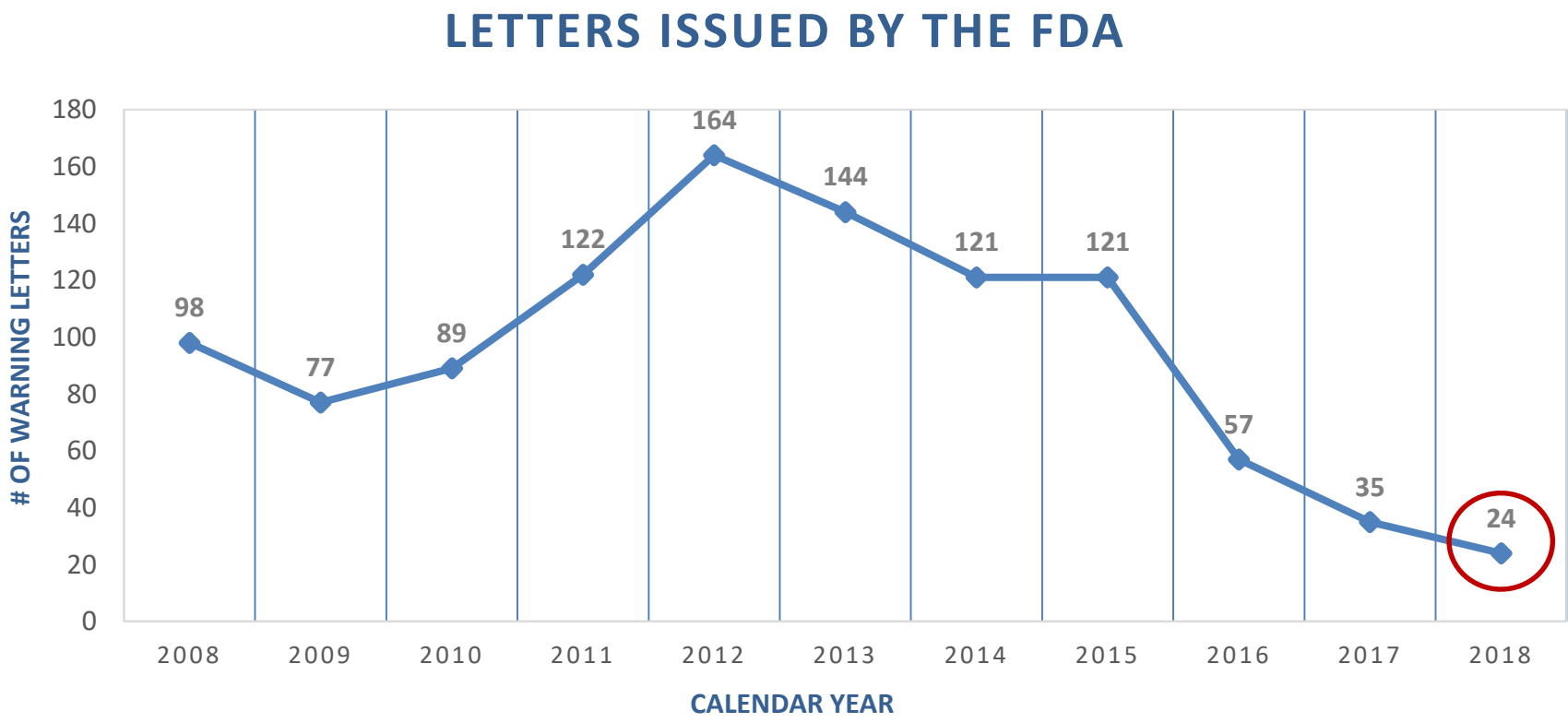
Enforcement Trend – Device Quality-Related WL's Down



FDA Mechanisms for Compliance

- FDA has been pursuing non-traditional mechanisms for compliance and regulatory action

- FDA is also taking a proactive approach to transparency and public communication of safety signals

- Examples:
  - Safety Communications / Letters to HCPs
  - Mandatory postmarket studies (522 studies)
  - Advisory committee meetings on postmarket issues
  - Requests for Additional Information (RFAIs)
  - Labeling changes
  - Voluntary recalls (trending up in recent years)

What's Behind the Trend?

- FDA Medical Device Safety Action Plan
  - Published April 2018
  - References the CDRH "Signal Management Program"

- Emerging Signals Guidance
  - Published December 2016
  - Signals can come from a number of sources (MDR, clinical studies and literature, administrative databases and registries, other health agencies)
  - FDA issues a public communication in response to a signal
  - FDA may or may not consult industry prior to initiating a public communication

- External Pressures
  - Plaintiffs bar
  - Investigative journalists
  - Public advocacy and patient groups

FDA Public Transparency

- Medical Device Safety Action Plan + Emerging Signals Guidance + External Pressures = FDA Public Transparency
- FDA transparency is evolving into a more established trend that will continue to impact industry decision-making
- FDA will communicate earlier in a demonstrable way in response to what it sees as a safety signal
- FDA may communicate before more robust information is known about a particular safety signal – updated communications are not uncommon
- The outcome can be less predictable
  - Labeling changes? 522 studies? Registry? Ad Comm meeting?

FDA's Public Communication of Signals

- Safety Communication: *"The FDA's analyses and recommendations for patients and health care providers about ongoing medical device safety issues."*
- Letters to Health Care Providers: *"Information for health care providers about the safe use of medical devices in medical facilities."*
- Alert the public or HCPs about a particular issue and may include instructions for patient management
- Can relate to a specific device or class of devices, single manufacturer or multiple manufacturers
- Source of the signal can be from multiple studies, a single study, MDR trend, directed 522 studies, or other sources of information
- FDA provides notice of the communication to the affected company/companies and may also link to the company's own communication but doesn't "vet" the communication in advance
- May or may not involve a recall – potentially creates confusion among HCPs

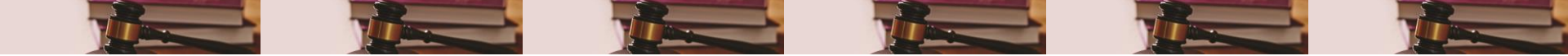
Examples

- Safety Communications:
  - FDA Alerts Providers and Patients to Check for Premature Battery Depletion in Certain Medtronic Pacemakers (May 7, 2019)
  - Use of the Stryker Wingspan Stent System Outside of Approved Indications Leads to an Increased Risk of Stroke or Death (April 25, 2019)
  - The FDA is Recommending Transition to Duodenoscopes with Innovative Designs to Enhance Safety (August 29, 2019)
  - Urgent / 11 Cybersecurity Vulnerabilities (October 1, 2019)
- Letters to HCPs:
  - Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality (January 17, 2019; updated August 7, 2019)
  - Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL) (February 6, 2019; superseded by communication on Allergan voluntary recall July 24, 2019)
  - Increased Rate of Mortality in Patients Receiving Abiomed Impella RP System (February 4, 2019; updated post-approval study results December 2, 2019)
  - Safe Use of Surgical Staplers and Staples (March 8, 2019)
- Where to find communications: FDA Home → Medical Devices → Medical Device Safety

Advisory Committee Meetings on Postmarket Safety

- In addition to public communications regarding safety signals, FDA is using advisory committees to vet postmarket issues

- Recent Examples:
  - Surgical staplers and staples (May 30, 2019)
  - Paclitaxil coated balloons and eluting stents (June 19-20, 2019)
  - Ethylene Oxide sterilization (November 6-7, 2019)
  - Metals in implants (November 13-14, 2019)



Questions?

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