Postmarketing Considerations for Drugs and Devices

FDLI's Introduction to Drug and Device Law and Regulation for Patient Organizations

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November 19, 2020

Topics Covered

- Postmarket Surveillance
  - Adverse Drug Event (ADE) Reporting and Pharmacovigilance
  - Medical Device Reporting (MDR)
- Recalls & Device Reports of Corrections and Removals
- Safety Communications
- Postapproval Changes and Supplements
  - Drugs (NDAs and ANDAs)
  - Devices (PMAs and 510(k)s)
- Risk/Benefit Health Risk Assessments

Postmarket Surveillance

Adverse Drug Event (ADE) Reporting and Pharmacovigilance

What is pharmacovigilance?

The science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems

FDA Drug Topic: An Overview of Pharmacovigilance in the Center for Drug Evaluation and Research (March 26, 2019) at 8 citing World Health Organization definition

FDA Adverse Event Reporting System (FAERS)

- Supports the FDA's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products
- Contains adverse event reports FDA has received from
  - Manufacturers (required)
  - Consumers and healthcare professionals (voluntary)

Adverse Drug Experience

- An adverse drug experience is “any adverse event associated with the use of a drug in humans, whether or not considered drug related,” including
  - In the course of use of the drug in professional practice
  - From drug overdose, whether accidental or intentional
  - From drug abuse
  - From drug withdrawal
  - Any failure of expected pharmacological action

(21 CFR § 314.80(a))

Post-Market 15-day Alert Reports

(21 CFR § 314.80(c)(1) and (e) for drugs; § 600.80 for biologics)

- Requirements for applicants
- A serious and unexpected adverse drug experience must be reported as soon as possible, within 15 calendar days of the learning of the event
  - 15-day Alert Reports are not required for an ADE obtained from a postmarketing study unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience
  - Applicants must then investigate the ADE and submit a follow-up report within 15 calendar days of receiving new information or as requested by the FDA
  - If no new information is discovered, applicant should retain records of the attempts to find additional information

Post-Market 15-day Alert Reports

- Reporting requirements also apply to nonapplicants
- Nonapplicants are those whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor
- Nonapplicant's obligations may be met by submission of reports to the applicant
- Nonapplicant that chooses to notify the applicant, rather than the FDA, of an ADE must do so within 5 calendar days of its initial receipt of the information

Post-Market 15-day Alert Reports

- Serious ADE:
  - Death
  - Life-threatening, i.e., places patient at *immediate* risk of death from ADE
  - Inpatient hospitalization or prolongation of existing hospitalization
  - Persistent or significant disability/incapacity
  - Congenital anomaly/birth defect
  - Also, important medical events that may not result in the above, but require medical or surgical intervention to prevent one of these outcomes

Post-Market 15-day Alert Reports

- Unexpected ADE:
- Not listed in the current labeling
  - Including events related to labeled events, but of greater severity or specificity
    - Hepatic necrosis would be unexpected because of greater severity if labeling only referred to elevated hepatic enzymes or hepatitis

Periodic ADE Reports (21 CFR § 314.80(c)(2))

- Quarterly, applicants must report each adverse drug experience not reported through 15-day Alert Reports for the first 3 years after application is approved
  - Quarterly reports submitted within 30 days of the end of the quarter
  - Reports required only on annual basis after the first 3 years
  - Annual reports submitted within 60 days of the anniversary date of approval of the application
  - FDA may extend or reestablish the quarterly requirement or change these deadlines upon written notice

- Requirements of Periodic Reports
  - Descriptive information including a narrative summary and analysis of the information in the report, analysis of 15-day Alert Reports from that reporting interval, and a history of actions taken since the last report because of ADEs
  - Individual case safety reports (ICSRs) for serious, expected, and nonserious adverse drug experiences

Adverse Event Reporting During the COVID-19 Pandemic

Type of Product	Type of Report(s)/Statutory or Regulatory Timeframe(s)	FDA Recommended Reporting During a Pandemic With High Employee Absenteeism
Approved NDA, ANDA, or BLA used for the pathogen causing the pandemic or the disease cause by the pathogen (whether or not included in the product labeling)	15-day Alert report, 15-day Alert report -follow up / 15 calendar days AND Reports to applicant (or licensed manufacturer) instead of FDA /5 calendar days	Submit
NDA, ANDA, or BLA approved within the prior three years	See above	Submit
All other approved drugs and biologics	See above	Submit death outcome reports. Store if necessary other serious outcome (non-death) reports.

Adverse Event Reporting During the COVID-19 Pandemic (cont.)

Type of Product	Type of Report(s)/Statutory or Regulatory Timeframe(s	FDA Recommended Reporting During a Pandemic With High Employee Absenteeism
All approved NDAs, ANDAs, and BLAs	Periodic adverse drug experience report/ Quarterly for 3 years from the date of U.S. approval of the application (or license) and then annually thereafter	Store if necessary

Causality in Adverse Events

- Adverse Event "is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment." Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting - ICH Harmonised Tripartite Guideline draft (July 18, 2003) at 3.
- § 314.80 (l) Disclaimer
  - A report or information submitted by an applicant does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event.
- FDA's Adverse Event Reporting System (FAERS)
  - FDA highlights the limitation of FAERS as being that it does not require that a causal relationship between a product and event be proven for it to be reported

How regulators use ADE Reports

- After a FAERS report is evaluated by a clinical reviewer, if a potential safety concern is identified, then further evaluation is performed
- If those further evaluations support the potential safety concern, FDA may take regulatory action to improve safety and protect the public health, such as:
  - Updating a product's labeling information,
  - Restricting the use of the drug,
  - Communicating new safety information to the public, or
  - Removing the product from the market
- Removal is rare and FDA's primary risk management tool is communicating through FDA-approved product labeling

Labeling Changes

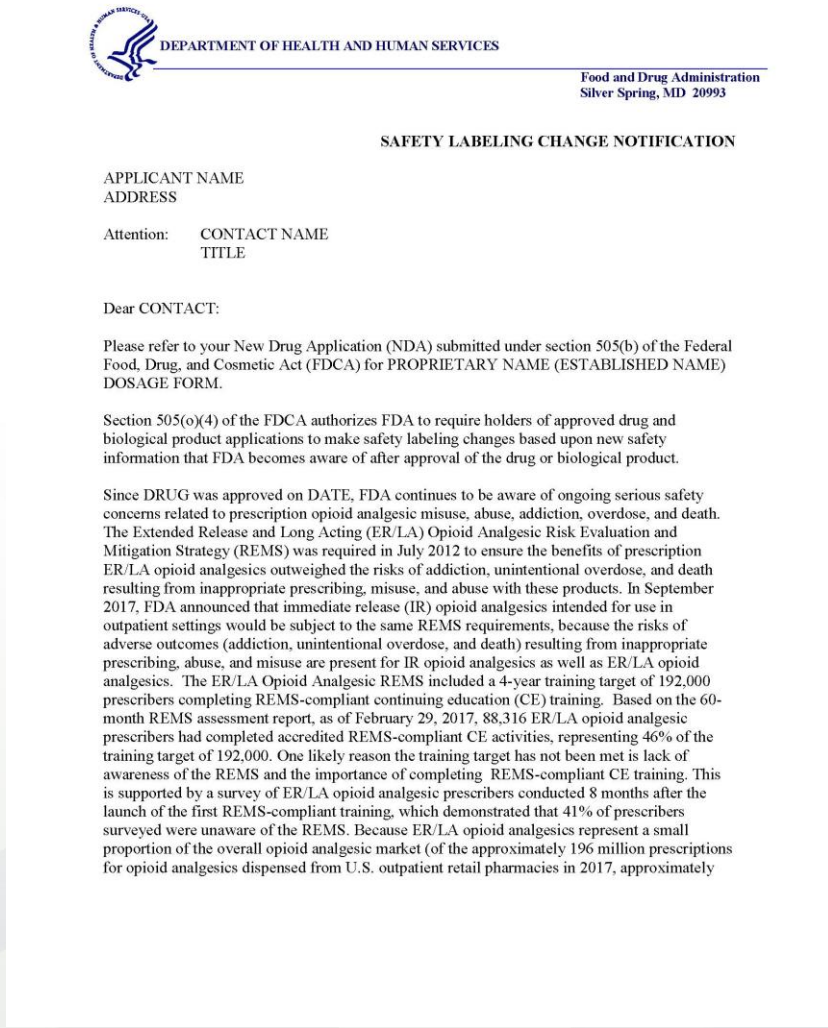
- § 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act") authorizes FDA to require and, if necessary, order labeling changes if FDA becomes aware of new safety information (NSI), which can originate from adverse event reports, that FDA believes should be included in the labeling of the drug
- NSI identifies a serious risk or an unexpected serious risk associated with use of the drug that FDA has become aware of since the drug was approved
- When FDA determines there is NSI that necessitates a labeling change, it will alert the applicant through a safety labeling change notification letter
  - Notification letters include proposed labeling changes

Failure to Change Label

- If an applicant fails to update their label within the proper timeframe, FDA can bring enforcement action against the applicant, including:
  - Charges under § 505 of the FD&C Act - A responsible person may not introduce or deliver into interstate commerce the drug involved if the application holder is in violation of § 505(o) safety labeling changes requirements
  - Misbranding charges
  - Civil monetary penalties
  - Seizure of the product
  - Injunction

Example: Opioid Analgesic Products

- In June 2018, FDA sent letters to holders of approved NDAs for opioid analgesics, stating that “FDA continues to be aware of ongoing serious safety concerns related to prescription opioid analgesic misuse, abuse, addiction, overdose, and death.”
- FDA explained that data indicated a general lack of awareness of the REMS for this product class among prescribers
- FDA required new safety information regarding the REMS in the Boxed Warning and Warnings and Precautions sections of prescribing information



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

SAFETY LABELING CHANGE NOTIFICATION

APPLICANT NAME
ADDRESS

Attention: CONTACT NAME
TITLE

Dear CONTACT:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROPRIETARY NAME (ESTABLISHED NAME) DOSAGE FORM.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since DRUG was approved on DATE, FDA continues to be aware of ongoing serious safety concerns related to prescription opioid analgesic misuse, abuse, addiction, overdose, and death. The Extended Release and Long Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) was required in July 2012 to ensure the benefits of prescription ER/LA opioid analgesics outweighed the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse, and abuse with these products. In September 2017, FDA announced that immediate release (IR) opioid analgesics intended for use in outpatient settings would be subject to the same REMS requirements, because the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse are present for IR opioid analgesics as well as ER/LA opioid analgesics. The ER/LA Opioid Analgesic REMS included a 4-year training target of 192,000 prescribers completing REMS-compliant continuing education (CE) training. Based on the 60-month REMS assessment report, as of February 29, 2017, 88,316 ER/LA opioid analgesic prescribers had completed accredited REMS-compliant CE activities, representing 46% of the training target of 192,000. One likely reason the training target has not been met is lack of awareness of the REMS and the importance of completing REMS-compliant CE training. This is supported by a survey of ER/LA opioid analgesic prescribers conducted 8 months after the launch of the first REMS-compliant training, which demonstrated that 41% of prescribers surveyed were unaware of the REMS. Because ER/LA opioid analgesics represent a small proportion of the overall opioid analgesic market (of the approximately 196 million prescriptions for opioid analgesics dispensed from U.S. outpatient retail pharmacies in 2017, approximately

Medical Device Reporting (MDR)

Medical Device Reporting

- Goals of the MDR Regulations (21 CFR Part 803):
  - Identify and monitor adverse events and malfunctions
  - Detect and correct problems in a timely manner
  - Ensure that distributed devices are safe and effective
  - Keep FDA informed so that it may take action as needed

Guidance: Medical Device Reporting for Manufacturers (Nov. 2016) (the "MDR Guidance"): https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-reporting-manufacturers

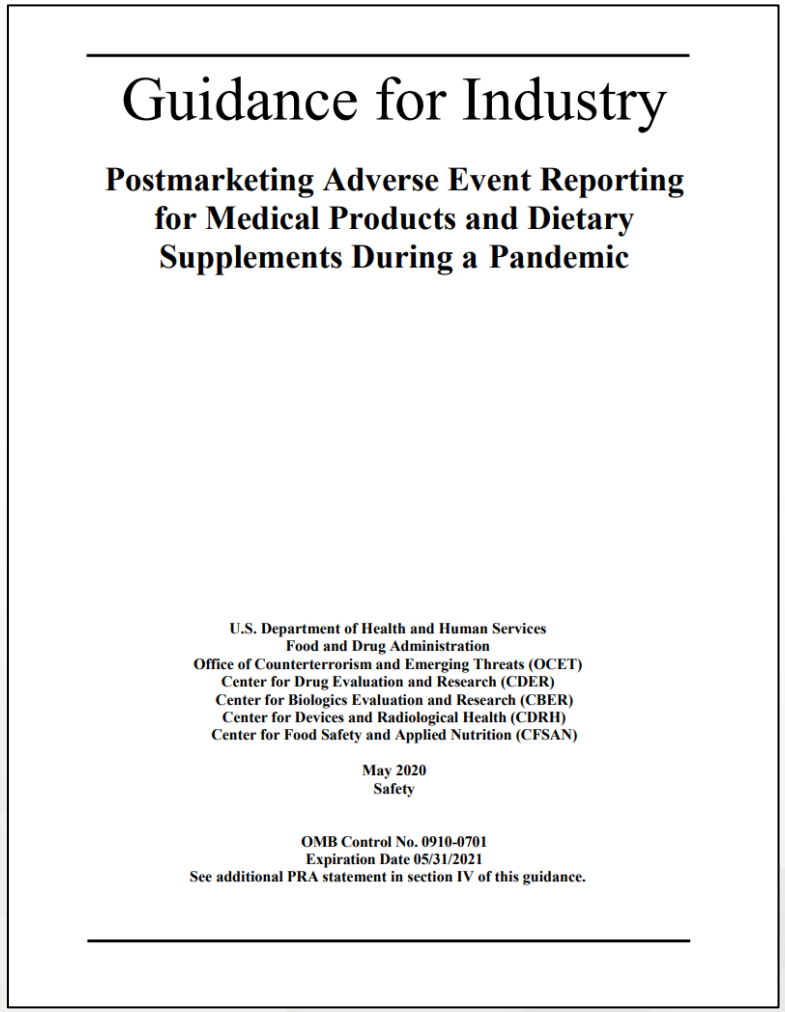
Medical Device Reporting

- Required under § 519(a)-(c) of the FD&C Act; 21 CFR Part 803
- Failure to meet requirements = Misbranding under § 502(t) of the FD&C Act
- Who must report
  - Manufacturers
  - Importers
  - User facilities (hospitals, ambulatory surgical facilities, nursing homes, outpatient diagnostic/treatment facilities, *etc*.; not physician's offices, school nurse offices and employee health units)
- Distributors do not have to report, but must maintain records

MDRs: What, to Whom, and When

Entity	Type of Event	Reported to	Reporting Timeline
Manufacturers	Remedial action needed	FDA	5 work days
	FDA request	FDA	5 work days
	Death	FDA	30 calendar days
	Serious Injury	FDA	30 calendar days
	Malfunction	FDA	30 calendar days
Importers	Death	FDA and manufacturer	30 calendar days
	Serious injury	FDA and manufacturer	30 calendar days
	Malfunction	Manufacturer	30 calendar days
User Facilities	Death	FDA and manufacturer	10 work days
	Serious injury	Manufacturer (FDA if mfr unknown)	10 work days
	Annual reports	FDA	Annually

MDRs: When to Submit During a Pandemic



Guidance for Industry

Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Counterterrorism and Emerging Threats (OCET)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)

May 2020
Safety

OMB Control No. 0910-0701
Expiration Date 05/31/2021
See additional PRA statement in section IV of this guidance.

Type of Report(s) / Statutory or Regulatory Timeframe(s)	FDA Recommended Reporting During a Pandemic With High Employee Absenteeism
Manufacturer MDR to FDA / 5 work days	Submit
Manufacturer MDR to FDA / 30 calendar days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury or device malfunction
MDR from importer to manufacturer and FDA / 30 calendar days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury
MDR from user facility to manufacturer (and/or FDA) / 10 work days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury

MDR Reportable Event (Manufacturers & Importers)

- Reporting trigger: An event that manufacturers or importers becoming aware of that reasonably suggests that one of their marketed devices
  - May have caused or contributed to a death or serious injury, or
  - Has malfunctioned and such device or similar device marketed by manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur

- 21 CFR 803.3(o)

MDR: Key Definitions

- **Serious Injury**
  - Is life threatening;
  - Results in permanent impairment of a body function or permanent damage to body structure; or
  - Necessitates medical or surgical intervention to preclude permanent impairment or permanent damage.
- **Permanent**
  - Irreversible damage/impairment but excludes trivial damage/impairment, e.g., minor cosmetic damage.
  - Note: A life threatening injury is a serious injury, whether or not "temporary" (*see* MDR Guidance at 10).

- 21 CFR 803.3(w)

MDR: Key Definitions

- **Caused or Contributed**
  - A death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:
    - Failure
    - Malfunction
    - Improper or inadequate design
    - Manufacture
    - Labeling, or
    - User Error

- 21 CFR 803.3(c)

MDR: Key Definitions: Malfunctions

- **Malfunction**
  - The failure of device to meet its performance specifications or otherwise perform as intended
    - Performance specifications include all claims in the labeling

- 21 CFR 803.3(k)

MDR: Malfunctions

- Once a malfunction has caused a death or serious injury, it creates a presumption that any similar malfunction occurring thereafter is reportable, *i.e.*, death or serious injury is "likely." This presumption will continue until either the malfunction has caused or contributed to no further deaths or serious injuries for two years, or the manufacturer can show through valid data that the likelihood of another death or serious injury as a result of the malfunction is remote.

- MDR Guidance at 13

- The MDR Guidance helps define when a malfunction is reportable:
  - Change of a death or serious injury is not remote
  - Affects the device in a catastrophic manner that may lead to a death or serious injury
  - Failure of the device to perform its essential function and compromises the device's therapeutic, monitoring, or diagnostic effectiveness, which could cause or contribute to a death/serious injury
  - Involves a long-term implant or life-supporting or life-sustaining device
  - Requires a recall/remedial action

- MDR Guidance at 11

MDR: Malfunctions

- **Similar Device**:
  - Devices that have the same:
    - Basic design and performance characteristics related to device safety and effectiveness; and
    - Intended use and function; and
    - Device classification and product code
- **Other factors considered**:
  - Brand name
  - Common name
  - Whether the devices were introduced into commercial distribution under the same 510(k) or PMA

MDRs: Timing

- 30-day or 5-day reporting clock begins when the Company “becomes aware” of the reportable event
- **Becomes Aware:**
  - An employee becomes aware of the event
  - A management, supervisory, or complaint handling employee becomes aware of the event requiring *remedial action*

- 21 CFR 803.3(b)

5-Day MDRs

- Reports must be filed within 5 working days:
  - If the event necessitates **remedial action** to prevent an unreasonable risk of substantial harm to the public health
  - When the FDA has made a written request for the submission of a 5-day report

- 21 CFR 803.53

- **Becomes Aware:**
  - Begins the day after an employee with (1) **management or supervisory responsibilities** over persons with regulatory, scientific, or technical responsibilities, or (2) a **person whose duties relates to the collection and reporting of adverse events** **"**becomes aware" of the event.
  - Employees such as **non-technical staff** are not expected to recognize that an adverse event requires remedial action to prevent a risk of substantial harm to the public.
  - Reports must be filed within 5 working days after **any employee** learns of an FDA written request for a 5-day report.

- MDR Guidance at 16

5-Day MDRs

- **Remedial Action:**
  - Any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable event.

- 21 CFR 803.53

- FDA does not consider an action to correct only a single device involved in an MDR reportable event to be a remedial action.
- Can be based on any information, including
  - Occurrence of one or more MDR reportable events
  - Internal analyses, such as trend analyses, using appropriate statistical or other acceptable methodologies
- Remedial actions taken in response to an adverse event that would be considered a Class I recall ("reasonable probability that the use of, or exposure to" the device "will cause serious adverse health consequences or death") require 5-Day MDRs.

- MDR Guidance at 17

When an MDR is Not Required

- A device-related adverse event did not occur

  - 21 CFR 803.22(b)(1)

- Clinical personnel (e.g., a physician, nurse, risk manager, or biomedical engineer) reasonably concludes that
  - The device did not cause or contribute to a death or serious injury, or
  - A malfunction would not be likely to do so if it were to recur

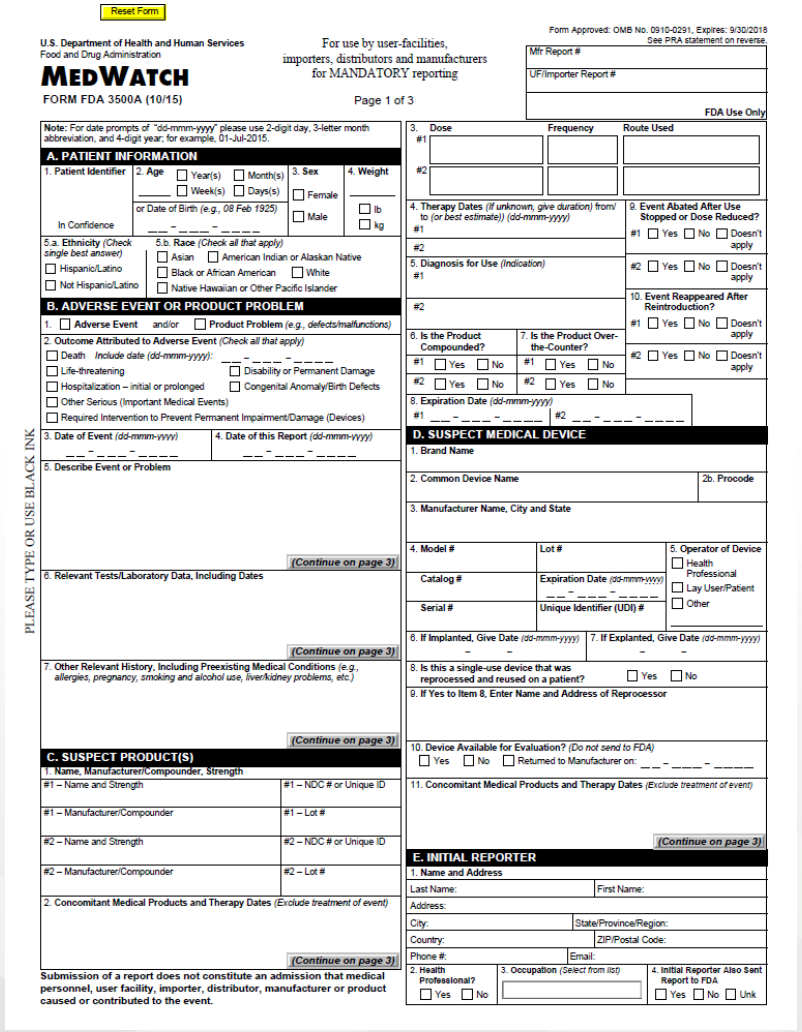
  - 21 CFR 803.20(c)(2)

- The firm did not manufacture/import the device and received the information in error

  - 21 CFR 803.22(b)(2)

MDR: Reporting Methods

- MedWatch, Form 3500A
- Manufacturers and Importers must submit electronically
- User Facilities
  - May submit electronically or on paper
  - Must also submit annual reports on Form 3419



Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (10/15)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Days(s) — or Date of Birth (e.g., 08 Feb 1925)
3. Sex — Female Male
4. Weight — lb kg
5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino
5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (Check all that apply)
Death Include date (dd-mmm-yyyy): ___ - ___ - ____
Life-threatening; Disability or Permanent Damage; Hospitalization – initial or prolonged; Congenital Anomaly/Birth Defects; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (dd-mmm-yyyy) ___ - ___ - ____
4. Date of this Report (dd-mmm-yyyy) ___ - ___ - ____
5. Describe Event or Problem
(Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. SUSPECT PRODUCT(S)

1. Name, Manufacturer/Compounder, Strength

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

2. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

PLEASE TYPE OR USE BLACK INK

3. Dose / Frequency / Route Used — #1, #2
4. Therapy Dates (If unknown, give duration) from/to (or best estimate)) (dd-mmm-yyyy) — #1, #2
5. Diagnosis for Use (Indication) — #1, #2
6. Is the Product Compounded? — #1 Yes No; #2 Yes No
7. Is the Product Over-the-Counter? — #1 Yes No; #2 Yes No
8. Expiration Date (dd-mmm-yyyy) — #1 ___ - ___ - ____; #2 ___ - ___ - ____
9. Event Abated After Use Stopped or Dose Reduced? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
10. Event Reappeared After Reintroduction? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name — 2b. Procode
3. Manufacturer Name, City and State
4. Model # — Lot # — 5. Operator of Device: Health Professional; Lay User/Patient; Other
Catalog # — Expiration Date (dd-mmm-yyyy) ___ - ___ - ____
Serial # — Unique Identifier (UDI) #
6. If Implanted, Give Date (dd-mmm-yyyy) — 7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on: ___ - ___ - ____
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

E. INITIAL REPORTER

1. Name and Address
Last Name: — First Name:
Address:
City: — State/Province/Region:
Country: — ZIP/Postal Code:
Phone #: — Email:
2. Health Professional? Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA Yes No Unk

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MDRs are Not Admissions

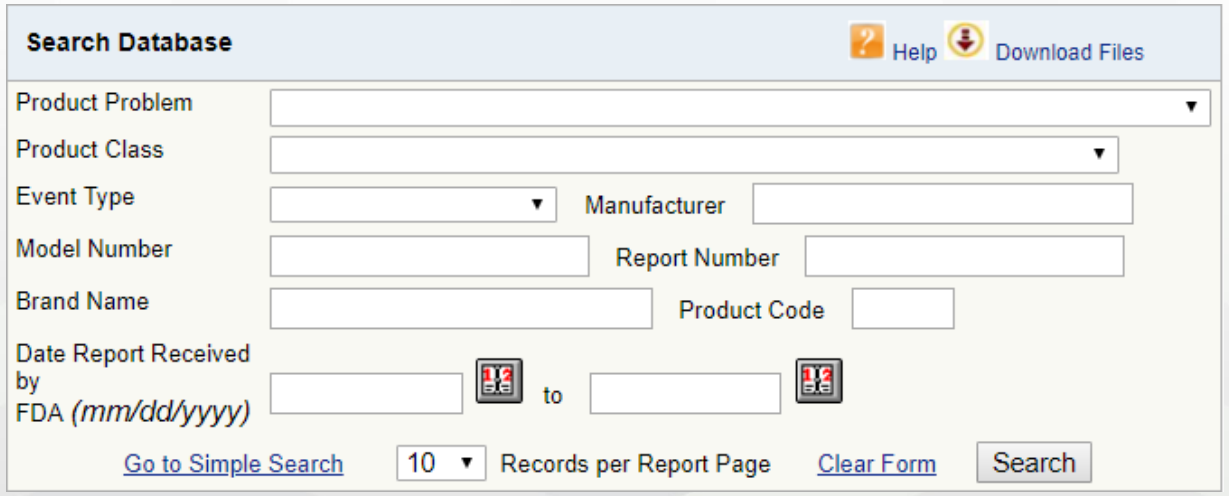
- An MDR “is not necessarily an admission that the device, or you or your employees, caused or contributed to the reportable event.”

- 21 CFR 803.16

Public Availability of MDRs

- MDRs are publicly viewable in FDA's MAUDE database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
- Redactions:
  - Trade Secrets
  - Confidential Information
  - Personal Information
  - Medical Information

- 21 CFR 803.9



Investigation of Complaints of Adverse Events

- Manufacturers have the responsibility to inform **all employees** to **immediately** forward adverse event information to appropriate persons
- Employees should be **trained** to identify, collect, and report complaints to the formally designated complaint handling unit
- All complaints of adverse events must be investigated, but not all must be reported
- **Investigations of complaints** of adverse events should be conducted for the purpose of gathering enough evidence to support the decision to submit or not to submit an MDR report. This should be done in a **timely manner**
- **Level of effort** to obtain additional information depends on the **nature and severity** of the event reported, and a "good faith effort" to obtain information should be made (and should not focus only on the number of attempts to obtain such information)

- MDR Guidance

MDR Procedures

- Required to develop, maintain, and implement written MDR procedures that provide for:
  - Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements, **including device-related complaints**
  - A **standardized review process or procedure** (based on the MDR regulation) for determining whether or not an event is an MDR reportable event; and
  - Timely transmission of complete reports to FDA

- 21 CFR 803.17(a)

MDR Procedures

- Procedures must also include documentation and recordkeeping requirements for, as applicable to manufacturers
  - Information that was evaluated to determine if an event was reportable;
  - All medical device reports and information submitted to FDA;
  - Systems to ensure access to information that facilitate timely follow-up and inspection by FDA.

- 21 CFR 803.17(b)

MDR Files

- Establish and maintain complete MDR files, either in written or electronic form
- Identify the files prominently as MDR files
- May be maintained as part of complaint files if prominently identified as MDR files
- A record of a complaint investigation must be documented in the complaint file
- The files should include a record of each attempt to obtain information, and the nature of the response of the reporter. If MDR information cannot be obtained, an explanation of why it was not possible to obtain the required MDR information must be documented. The information should demonstrate that a **reasonable attempt** to follow up and obtain the relevant information.

- MDR Guidance at 24

MDR Files

- Must be maintained for **two years** from the date of the event or a period equivalent to the **expected life of the device**, whichever is greater

  - 21 CFR 803.18(c)

- **Expected life of the device:**
  - The time that a device is expected to remain functional after it is placed into use

  - 21 CFR 803.3

Examples - Is an MDR Required?

[Survey: Yes / No / Maybe]

- A device manufacturer receives notice that:
  - a user of the device had died in a car crash;
  - based upon an alert provided by the device, the user received a dangerously high dose of medication;
  - a user has been incorrectly setting the device's alert parameters, and as a consequence, the patient did not receive medication in a timely manner and suffered permanent brain damage;

Examples - Is an MDR Required?

[Survey: Yes / No / Maybe]

- A device manufacturer receives notice that:
  - a user of the device used the device off-label, contrary to warnings in the instructions for use, and as a consequence suffered a serious injury;
  - a physician observed damage in the manufacturer's catheter prior to use, and as a result was able to utilize a back-up device in time such that the patient does not suffer injury;
  - a surgeon observed the device fractured in the patient's body during surgery, but was able to quickly remove the fragments without injury to the patient.

Recalls & Medical Device Reports of Corrections and Removals

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Recalls (Drugs & Devices)

Recalls

- Goals:
  - Remove or correct products that violate laws administered by FDA
  - Protect the public health and well-being from products that present a risk of injury or are otherwise defective

Recalls

- Mandatory recall, § 518(e) of the FD&C Act [device only]
  - Reasonable probability that device would cause serious, adverse health consequences or death
  - Rarely used
  - Misbranding under § 502(t)
- Voluntary recall, 21 CFR Part 7 (not a misbranding, but important)
  - Recall: firm's removal or correction of marketed product that FDA considers to be in violation of the laws and against which FDA would initiate legal action; excludes market withdrawal and stock recovery
    - Market withdrawal, *e.g.*, normal stock rotation practices, routine equipment adjustments and repairs
    - Stock recovery, *e.g.*, product is on premises owned by, or under the control of, the firm and no portion of the lot has been released for sale or use

Recalls

- FDA's role in a recall is overseeing the company's strategy, classifying the recall, and assessing the adequacy of the recall
- 3 recall classifications assigned by FDA
  - Class I: reasonable probability that use of, or exposure to, a violative product will cause serious adverse health consequences or death
  - Class II: use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
  - Class III: use of, or exposure to, a violative product is not likely to cause adverse health consequences

Recalls

- FDA draft guidance – Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C (April 2019)
  - Be “recall ready”
    - Identify appropriate personnel
    - Train personnel – consider mock recalls
    - Establish recall communications plan
    - Identify any reporting requirements
    - Use adequate product coding
    - Maintain distribution records

Recall Strategy

- Considerations:
  - Results of a Health Hazard Evaluation
  - Ease of identifying the product
  - Degree to which the issue is obvious
  - Degree to which the product remains unused in the market
  - Availability of essential products
- Elements to address
  - Depth of recall (wholesale, retail, consumer)
  - Public warnings
  - Effectiveness checks

Health Hazard Evaluation

- An evaluation conducted by FDA of the health hazard presented by a product. Includes, but may not be limited to, consideration of the following factors:
  - Whether any disease or injuries have already occurred from the use of the product.
  - Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard. Any conclusion shall be supported as completely as possible by scientific documentation and/or statements that the conclusion is the opinion of the individual(s) making the health hazard determination.
  - Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk.
  - Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed.
  - Assessment of the likelihood of occurrence of the hazard.
  - Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

Public Warnings

- Alerts the public that a product being recalled presents a serious hazard to health.
- Reserved for urgent situations where other means for preventing use of the recalled product appear inadequate (21 CFR § 7.42(b)(2)).
  - Note: The FDA has other authorities to disseminate information. For example, under 21 U.S.C. § 375(b), the Secretary may disseminate information about FDA regulated products in situations that the Secretary determines involve "imminent danger to health or gross deception of the consumer."
- The FDA will ordinarily issue such a public warning, in consultation with the recalling firm.
- If the recalling firm decides to issue its own public warning, it submits to FDA its proposed public warning and plan for distribution for review and comment.
- A firm's recall strategy will specify whether a public warning is needed and whether it will issue as:
  - A general public warning through the general news media (national or local, as appropriate); or
  - Public warning through specialized news media (e.g., professional or trade press, or to specific segments of the population such as physicians, hospitals, etc).

Public Availability of Recalls

- Recalls are posted weekly in FDA's enforcement reports, located at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports.
- Device recalls are reported publicly in FDA's Medical Device Recalls database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm
- Drug recalls can also be found on FDA's "Drug Recalls" webpage: https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls
- Recalls of Biologics can also be found on FDA's "Recalls (Biologics)" webpage: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/recalls-biologics

Reports of Corrections and Removals (Medical Devices)

Corrections and Removals (21 CFR Part 806)

- **Goals**:
  - Ensure that FDA has current and complete information regarding actions taken to reduce risks to health caused by devices
  - Improve FDA's ability to evaluate device-related problems and to take prompt action against potentially dangerous devices

Threshold for Part 806 Reporting

- Any **correction** or **removal** of a device that is initiated to:
  - Reduce a **risk to health** posed by the device; or
  - Remedy a violation of the Federal Food, Drug, and Cosmetic Act by the device which may present a **risk to health**

  - 21 CFR 806.10(a)

- **Risk to Health**
  - Reasonable probability that use of, or exposure to, the product will cause **serious adverse health consequences** or **death**; or
  - 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 consequences** is remote

  - 21 CFR 806.2(k)

- "**Risk to Health**" tracks the definition of **Class I and II recalls** under 21 CFR Part 7 (voluntary recalls). Therefore, Part 806 Reports are **required** for Class I and II recalls.

Threshold for Reporting

- The following do not have to be reported under Part 806:
  - **Stock Recoveries:**
    - A correction or removal of a device that has not been marketed or that has not left the direct control of the manufacturer.
    - Device is located on the premises owned, or under the control of, the manufacturer, and no portion of the lot, model, code, or other relevant unit involved in the corrective or removal action has been released for sale or use.
  - **Market Withdrawals:**
    - A correction or removal of a distributed device that involves a minor violation of the act that would not be subject to legal action by FDA or that involves no violation of the act.
    - Examples: Normal stock rotation practices.
  - **Routine Servicing:**
    - Regulatory scheduled maintenance, including the replacement of parts at the end of their normal life expectancy.
    - Examples: Calibration, replacement of batteries, and responses to normal wear and tear.
  - Actions taken to improve the performance or quality of a device but that do not reduce a risk to health or remedy a violation of the act.
  - A similar report has been filed under Part 803 or Part 1004.

- 21 CFR 806.1(b); 21 CFR 806.10(f)

Timeline for Reporting & Where to Report

- When to report: Within 10 working days of initiating the correction/removal (issue exists regarding when an action is initiated)
- Where to report:
  - FDA's eSubmitter system, or
  - By e-mail to your FDA's Office of Regulatory Affairs (ORA) Division Recall Coordinator (DRC).
    - Foreign manufacturers and importers must e-mail the report to the DRC where their U.S. agent is located.

Content of Part 806 Report

- Registration number, date of report, and sequence number (e.g., 1234567-11/7/2019-001-R)
- Name, address, and telephone number of manufacturer/importer and information for entity submitting the report, if different
- Brand, common, and classification name of the device
- Marketing status of the device and listing number
- UDI or model/catalogue/code number+lot or s/n
- Description of event causing recall and corrective actions taken or to be taken
- Any injuries or illness that have occurred; MDR numbers
- Total number of devices subject to the correction or removal
- Date of manufacture or distribution and expiration date or expected life
- Consignee list, including the name, address and phone number of all domestic and foreign consignees; dates and number of devices distributed to each consignee
- Copy of all communications regarding the recall
- Statement explaining why any required information is not available and when it will be submitted

- 21 CFR 806.10(c)

Records of corrections and removals not required to be reported

- Keep records of corrections or removals, including those not required to be reported to FDA
- Records shall be retained for a period of 2 years beyond the expected life of the device, even if the manufacturer or importer has ceased to manufacture or import the device
- Records of corrections and removals not required to be reported to FDA shall contain:
  - The brand name, common or usual name, classification, name and product code if known, and the intended use of the device
  - UDI, or the device identifier, UPC, model, catalog, or code number, the manufacturing lot or serial number, or other identification number
  - A description of the event(s) giving rise to the information reported and the corrective or removal action that has been, and is expected to be taken
  - Justification for not reporting the correction or removal action to FDA, which shall contain conclusion and any follow-ups, and be reviewed and evaluated by a designated person
  - Copy of all communications regarding the correction or removal

- 21 CFR 806.20

Part 806 Not Necessarily an Admission

- A submitted report does not necessarily reflect a conclusion by the manufacturer that the report of information constitutes an admission that the device cause or contributed to a death or serious injury
- A manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the device caused or contributed to a death or serious injury

- 21 CFR 806.10(e)

Safety Communications

GOODWIN

Overview of Safety Communications

- Safety Communication/Public Health Notification/Physician Communication
  - "A Public Health Notification was an important message to the health care community describing a risk associated with the use of a medical device and providing recommendations to avoid or reduce the risk. They were published until 2009 when they were replaced with Safety Communications."
  - Safety communications often result from evaluation of safety signals
    - CDRH Signal Management Program established in October 2012
      - To ensure consistency, efficiency, accountability and transparency in how CDRH evaluates and addresses signals related to marketed medical devices

Example of FDA Safety Communication

- Safety Communication Example
  - Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy (April 17, 2014)
    - Aimed at health care providers, medical professional associations, cancer advocacy organizations, health care facilities/hospitals, women with symptomatic uterine fibroids who are considering surgical options, and manufacturers of devices used for minimally invasive surgeries
    - "Based on currently available information, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids."
      - Risk of spreading unsuspected cancerous tissue, uterine sarcomas, beyond the uterus
      - Estimated 1 in 350 women undergoing hysterectomy or myomectomy for treatment of fibroids is found to have an unsuspected uterine sarcoma

Example of FDA Safety Communication

- Other actions by FDA :
  - Instructed manufacturers to review labeling for accurate risk information for patients and providers
  - Convened a public meeting of the Obstetrics and Gynecological Medical Device Advisory Committee to discuss
    - Clinical role of laparoscopic power morcellation in the treatment of uterine fibroids
    - Whether surgical techniques and/or use of accessories can enhance safe and effective use of these devices
    - Whether a Boxed Warning related to the risk of cancer spread should be required
  - To continue to review adverse event reports, peer-reviewed scientific literature, and information from patients, health care providers, professional societies, and manufacturers

Example of FDA Safety Communication

- Updated by the FDA on February 25, 2020.
  - The FDA continues to recommend limiting the use of laparoscopic power morcellation to certain appropriately selected women undergoing myomectomy or hysterectomy.
  - In addition, FDA recommends performing laparoscopic power morcellation for myomectomy or hysterectomy only with a tissue containment system, legally marketed in the U.S. for use during laparoscopic power morcellation and performing these procedures only in appropriately selected patients.
    - Tissue containment systems used during laparoscopic power morcellation are intended to isolate and contain tissue that is considered benign.
    - Based on bench and animal testing, use of a containment system confines morcellated tissue within the containment system.

Example of FDA Drug Safety Communication

- In February 2020, FDA requested the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market because of concerns about the risk of cancer
  - "We are taking this action because we believe that the risks of lorcaserin outweigh its benefits based on our completed review of results from a randomized clinical trial assessing safety"

- FDA instructed patients to stop taking the product, talk to a health care professional about alternatives, and dispose of unused medication
- FDA instructed health care providers to stop prescribing and dispensing the product and contact patients currently taking the product
- Additional Drug Safety Communications are available at https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications.

Postapproval Changes to Drugs and Devices

Changes to an Approved Drug (NDAs and ANDAs)

Supplements and Other Changes to an Approved NDA

- 21 CFR 314.70 sets out the processes for the holder of an approved NDA to notify FDA of changes to the product (some of which require FDA approval)
- FDA categorizes supplements after preliminary review as one of the following:
  - Efficacy - A supplement to an approved application proposing to make one or more related changes from among the following changes to product labeling:
    - Add or modify an indication or claim;
    - Revise the dose or dose regimen;
    - Provide for a new route of administration;
    - Make a comparative efficacy claim naming another drug product;
    - Significantly alter the intended patient population;
    - Incorporate other information based on at least one adequate and well-controlled clinical study
  - Labeling – A supplement that contains labeling changes only
  - Manufacturing – A change(s) to the manufacturing process, including product testing or changes to the facility(ies) involved in the manufacturing of the product (may include labeling changes as well)

(FDA SOPP 8401.2)

Major Changes

- A "major change" is any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors relate to the safety and efficacy of the drug product
- A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product (a "Prior Approval Supplement")
- Review timeline of 4 months

Examples of Major Changes

- Major labeling changes, such as changes to a Medication Guide, or changes to the Highlights of Prescribing Information (other than minor editorial changes that may be submitted as part of an annual report)
- Changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved NDA
- Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type or composition of a packaging component that may affect the impurity profile of the drug product

Moderate Changes

- A "moderate change" is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety and effectiveness of a drug product
- Two types of moderate changes:
  - One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change (a "Supplement - Changes Being Effected in 30 Days" or "CBE-30")
  - FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (a "Supplement - Changes Being Effected" or "CBE")
- Review timeline of 6 months
- For a CBE-30, FDA will inform the applicant within 30 days if a prior approval supplement is required or if information is missing
- For a CBE, the product can be distributed once FDA receives the supplement

Examples of Moderate Changes

- Supplement - Changes Being Effected in 30 Days
  - A change in the container closure system that does not affect the quality of the drug product
  - Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements
  - Note that labeling supplements are classified as either PAS or CBE

- Supplement – Changes Being Effected
  - Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess
  - A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another
  - Certain labeling changes to reflect newly acquired information (e.g., adding or strengthening a contraindication, warning or precaution; adding or strengthening a statement about drug abuse, dependence, psychological effect, or overdosage; deleting false or misleading indications or use or claims of effectiveness)

Minor Changes

- A change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product
- These changes must be described in the next Annual Report for the product

- Examples include:
  - The deletion or reduction of an ingredient intended to affect only the color of the drug product
  - Replacement of equipment with that of the same design and operating principles (except for changes that would require a CBE-30 or CBE)
  - A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form

Supplement Actions

- FDA will approve or issue a complete response for PAS
- For CBE-30 and CBE, the drug product manufactured using the proposed change can be distributed unless FDA orders the applicant to cease distribution
- Applicants should work to resolve deficiencies cited in a CRL

Changes to a PMA-Approved Device

Ongoing Monitoring of Device Performance

- Conditions of PMA Approval
  - PMA supplements
  - Annual reports
  - Postapproval studies
- Other mechanisms to handle changes
  - Document to file:
    - For “trivial” changes, such as an editorial change to a standard operating procedure
  - Submit a new PMA:
    - Consider consultation with the review office:
      - A design change causes a different intended use, mode of operation, and technological basis of operation
      - Change in patient population
      - A design change that is so significant that a new generation of the device will be developed
- A primary indicator of it or what type of PMA submission is needed is the nature of the data, if any, that is needed to demonstrate the safety and effectiveness of the changes.

PMA Supplements – Overview

- Required before making any change affecting the safety or effectiveness of the device unless FDA has advised that an alternate type of submission is permitted for a particular change
- Examples:
  - When unanticipated adverse effects increase in incidence or device failures necessitate a labeling, manufacturing or device modification
  - If the device is to be modified and animal or clinical testing is necessary to demonstrate safety and efficacy
- Multiple types of PMA Supplements

Contents of PMA Supplements

- Limited to information needed to support the change
- Identification of each change for which approval is being requested
- An explanation of the reason for each change
- Supporting data for each change
- A new summary is only required in certain situations (e.g., new indications for use)

Types of PMA Supplements

- PMA Panel-Track Supplement (21 CFR § 814.39(c))
- 180-Day PMA Supplement (21 CFR § 814.39(a))
  - PMA Manufacturing Site Change Supplement (21 CFR § 814.39(a)(3))
- Real Time Supplement
- Special PMA Supplement – Changes Being Effected (21 CFR § 814.39(d))
- 30-Day Notice and 135-Day PMA Supplement (21 CFR § 814.39(f))
- Periodic (Annual) Report (21 CFR § 814.39(e))
  - For certain types of change specified by FDA

PMA Panel-Track Supplement

- For changes that request a significant change in design or performance of the device, or a new indication for use of the device
- Substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness
- A full PMA review which may include a review by an outside advisory panel will be required

180-Day PMA Supplements

- For certain types of significant changes that affect the safety and effectiveness of the device
- For significant change in components, materials, design, specification, software, color additives, or labeling
- Require in-depth FDA review and approval prior to implementation of the change
- Generally speaking, the clinical data provided in support of the approval should still be applicable in supporting the approval of the changed device. In most cases, only new preclinical testing is needed to support safety and effectiveness.

Real-Time Review of PMA Supplements

- Change the review priority for PMA Supplements needing a short review but may spend a long time waiting in the FDA review queue. Applicant requests and FDA determines whether to grant a meeting or similar forum to jointly review and determine the status of the supplement.
- A mechanism to conduct document review with the Company interactively (e.g., face-to-face, videoconference, teleconference)
- Includes minor changes that can be expected within a product line, including changes to:
  - Device design
  - Software
  - Instructions for use, warnings, or precautions or other labeling that does not affect the indications or contraindications
  - Sterilization and packaging methods
- A minor change should not be one that is:
  - Expected for that device type
  - Validated according to scientific principles FDA has relied on in previous reviews and accepted test methods or procedures for devices of that type, wherever applicable, such an a FDA-recognized standard or guidance document
  - Adequately support by preclinical or animal testing with no new clinical data
  - Typically involving review within a single scientific discipline
- *See* FDA's guidance entitled "Real-Time Premarket Approval Application (PMA) Supplements" (December 2019)

Special PMA Supplement – Changes Being Effected

- For changes that enhance the safety of the device or the safety in the use of the device
  - Add or strengthen a contraindication, warning, precaution, or information about an adverse reaction
  - Add or strengthen an instruction intended to enhance the safe use of the device
  - Delete misleading, false, or unsupported indications
  - Addition of a new specification or test method in QC or manufacturing
- May be placed into effect prior to receipt of a written FDA order (but after the applicant receives specific acknowledgement from the FDA that the application qualifies as a “Special PMA Supplement – Changes Being Effected.”

30 Day Notice / 135 Day Supplements

- PMA Supplements for Manufacturing Changes
  - Change to the manufacturing process, or changes in method of manufacture
  - Changes to reduce manufacturing and/or labor cost
  - Changes to reduce manufacturing time
  - Changes to reduce waste
  - Changes to compensate for a change in suppliers of raw material or components
- Change should not alter performance or design specifications (designated physical or chemical specifications) of the finished device
- 30-Day Notice Submission Contents
  - Description of the change
  - Reason for the change
  - Rationale for submission
  - Summary of data supporting the change
  - Statement of compliance with FDA's QSR regulation
  - Any other necessary supporting data
- If the 30-Day Notice is not adequate, within 30 days of receipt, FDA will inform the applicant that a 135-Day PMA Supplement is needed, and will describe additional information or action that is required for acceptance of that change.
- *See* FDA's Guidance entitled "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes" (December 2019).

Periodic (Annual) Reports

- Required at one (1) year increments from approval date (unless otherwise specified) in the PMA approval order.
- Unless FDA otherwise specifies:
  - Submissions must identify changes made to the device that do not affect safety or effectiveness
  - Submissions must provide a bibliography and summary of research involving the device or a similar device
  - Submissions also must summarize reports in scientific literature concerning the device
- *See* FDA's Guidance entitled "Annual Reports for Approved Premarket Approval Applications (PMA)"

Postapproval Studies

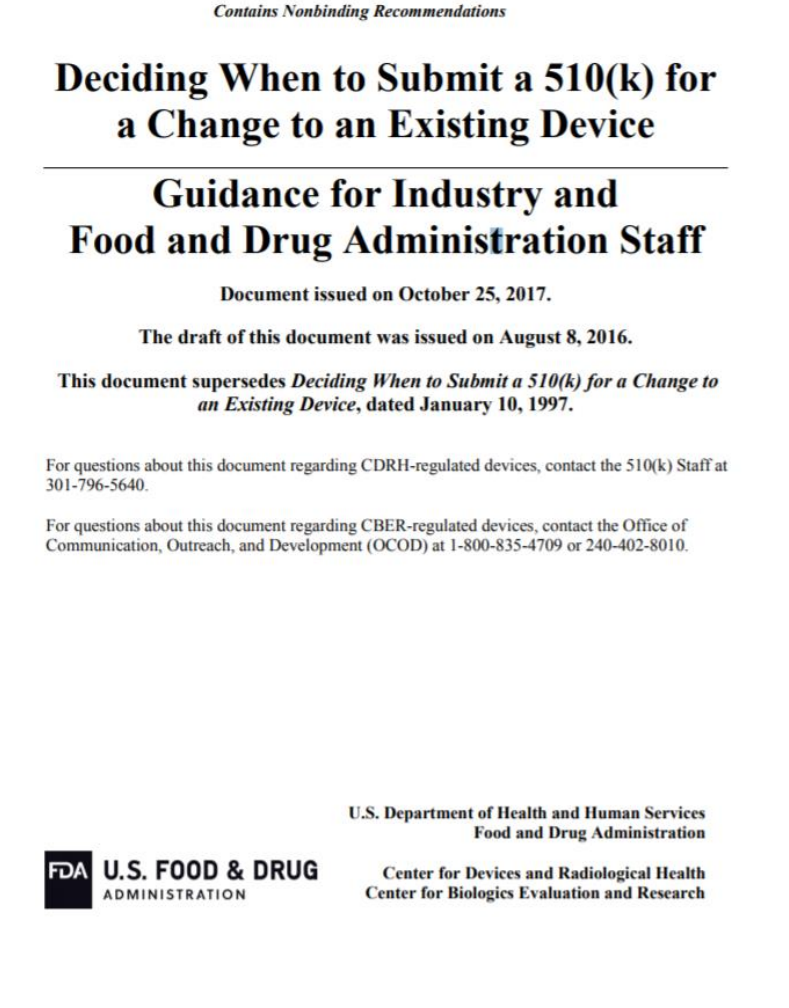
- Section 513(a)(3)(C) provides:
  - In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.
- May be required under 21 CFR § 814.82(a)(2):
  - Postapproval requirements may include as a condition to approval of the device: continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.
  - FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.
- Potential results of a failure to comply with post approval study requirements:
  - Postmarket surveillance under Section 522 of the FD&C Act (21 CFR Part 822)
  - Withdrawal of approval of the PMA under § 515(e) of the FD&C Act (21 CFR § 815.46(a))
  - Civil money penalties
    - A significant or knowing failure to report information about a post-approval study; or
    - Such failure constitutes a risk to public health

Changes to a 510(k) Cleared Device

Core Principles

- FDA's approach to 510(k) modifications has two goals:
  - Ensure patients and providers have timely access to modified devices; and
  - Provide flexibility for industry and FDA to enable innovation and ensure effective public health oversight of modified devices
- Bases for FDA's Policy for 510(k) modifications:
  - 21 CFR § 807.81(a)(3):
    - A new 510(k) is required for significant changes or modifications in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that required a 510(k):
      - A change or modification that could significantly affect the safety or effectiveness of the device
      - A major change or modification in the intended use of the device
  - 21 CFR § 820.30(i):
    - **Design changes**: Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation

FDA's 510(k) Modification Guidances



Contains Nonbinding Recommendations

Deciding When to Submit a 510(k) for a Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

This document supersedes *Deciding When to Submit a 510(k) for a Change to an Existing Device*, dated January 10, 1997.

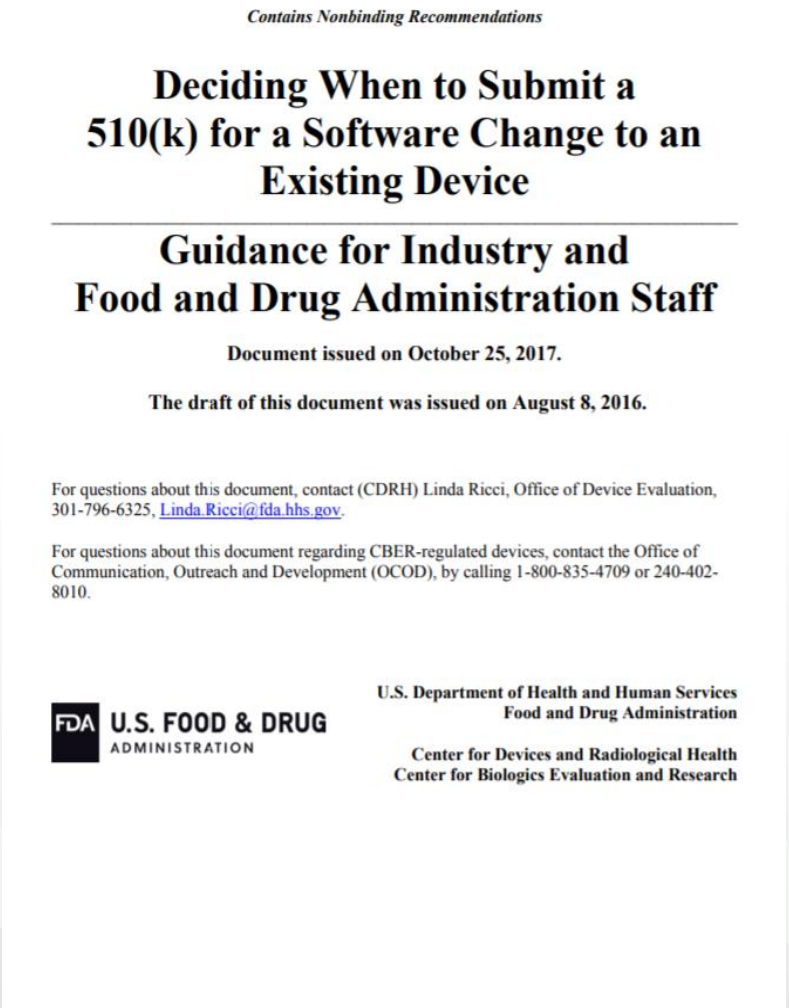
For questions about this document regarding CDRH-regulated devices, contact the 510(k) Staff at 301-796-5640.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research



Contains Nonbinding Recommendations

Deciding When to Submit a 510(k) for a Software Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

For questions about this document, contact (CDRH) Linda Ricci, Office of Device Evaluation, 301-796-6325, Linda.Ricci@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Guiding Principles

1. **Changes made with intent to significant affect safety or effectiveness**
   - Likely require a 510(k)
   - Example: To significantly improve clinical outcomes, to mitigate a known risk, in response to adverse events, etc.
   - **Note:** Modifications to address a violation or recall have additional considerations. *See* the following guidances:
     - *Blue Book Memorandum K95-1, 510(k) Requirements During Firm-Initiated Recalls*
     - *Distinguishing Medical Device Recalls for Medical Device Enhancements*
2. **Initial risk-based assessment**
   - A risk-based should first be conducted by a manufacturer when determining whether a change or modification could significantly affect the safety or effectiveness of a device
   - Should identify and analyze all new risks and changes in existing risks resulting from the device change, and lead to an initial decision whether or not submission of a new 510(k) is required

Guiding Principles (cont.)

3. **Unintended consequences of changes should be considered**
4. **Use of risk management**
   - Intended to leverage manufacturers' existing risk processes to determine when change requires a 510(k)
   - Risk terminology primarily based on ISO 14971
   - Both safety & effectiveness should be considered
5. **Verification and validation activities**
   - Risk-based determination not to submit should be confirmed by verification and validation (V&V)
   - Any unexpected results should prompt reconsiderations of prior decisions that submission of a new 510(k) is not required
6. **Evaluating simultaneous changes**
   - Changes should be assessed both separately and in the aggregate

Guiding Principles (cont.)

7. **Appropriate comparative device and cumulative effect of changes**
   - Compare the modified device to unmodified device as most recently cleared by FDA
   - For purposes of determining whether a 510(k) is needed, changes should not be compared to other predicate devices
8. **Document design changes** (as required by FDA's Quality System Regulation)
9. **510(k) submission for modified devices**
   - For a new 510(k) for a device with multiple changes, describe:
     - All changes that trigger the requirement for submission of a new 510(k)
     - Describe those other changes since the most recently cleared 510(k) that would have been documented as part of the first 510(k)
10. **Substantial equivalence determinations**
    - A SE determination is not assured through following the recommendations in the guidances

Determining When to Submit a 510(k) for a Change to an Existing Device – Flowcharts

- Flowcharts (not intended to be read in isolation)
  - Chart A: Labeling changes
  - Chart B: Technology, engineering, or performance changes for non-IVDs
  - Chart C: Material Changes for non-IVDs
  - Chart D: Technology, engineering, performance, or material changes for IVDs

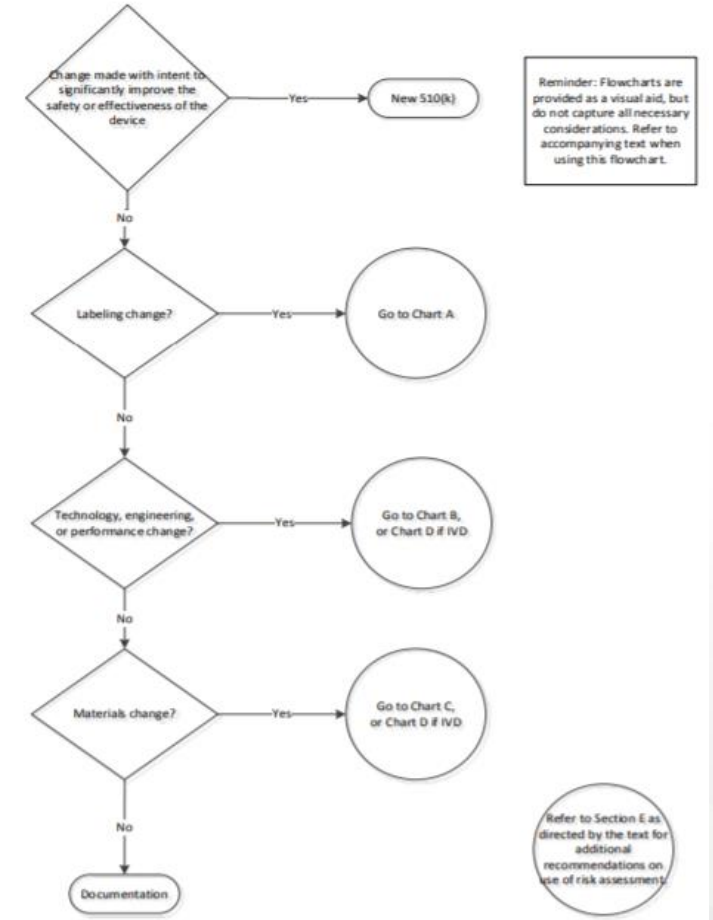


Figure 1 - Main Flowchart

Risk/Benefit Health Risk Assessments for Drugs and Devices and When to Take Action or Raise Issues to the FDA

FDA Benefit-Risk Assessments for Medical Devices

- FDA's "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions" explains how FDA assesses benefits and risks in making decisions on safety issues for approved or cleared products
- The Agency aims to consider the benefit-risk profile of a device to prevent unintended adverse impacts on patients (e.g., shortages of medically necessary devices)
- FDA will consider "relevant and reliable evidence and data available to the Agency," including patient input, and may request additional data to help assess these factors when making a decision

Potential Benefit Factors to Consider

- Type of benefit (e.g., effect on treatment plan; impact on survival)
- Magnitude of benefit
- Likelihood of patients experiencing one or more benefits
- Duration of effects
- Patient perspective on benefit
- Benefit factors for healthcare professionals or caregivers (e.g., reduction in procedural time; improvements in utility for practitioners with varying skill levels)
- Medical necessity

Potential Risk Factors to Consider

- Severity of harm
  - Medical device-related deaths and serious injuries
  - Medical device-related non-serious adverse events
  - Medical device-related events without reported harm
- Likelihood of risk
- Distribution of nonconforming devices
- Duration of exposure to population
- False-positive or false-negative results
- Patient tolerance of risk
- Risk factors for healthcare professionals

Example: Recall and potential shortage of a high benefit implantable coated device with low additional risk

- An implantable coated device was developed which reduced thrombosis by more than 80%.
- There were three field complaints for a malfunction in the device's first few months of wide scale commercial use. This malfunction represented an anticipated failure mode that appeared to be occurring more frequently than expected. During these events associated with the malfunction, blood loss occurred, but no serious injuries occurred. The manufacturer submitted MDRs for these events.
- Removal of the product from the field would have resulted in cancellation of hundreds of surgeries.
- Company determined that the product required a correction/removal that needed to be reported to FDA.
- Company proposed sending a customer communication with a supplement to the labeling and continued monitoring of the event.

Example Benefit-Risk Assessment (cont.)

- Benefits
  - High likelihood of benefit for patient population
  - No comparable treatment options
  - No indication that the malfunction affected the device's reduction of thrombosis
- Risks
  - No serious adverse events reported with malfunctions
  - Severity of risk appeared to be low
  - 3000 devices implanted (so likelihood of risk was low)
- Patient perspective
  - Patients appreciate benefit, even those who were informed about the increased incidence of AEs

Example Benefit-Risk Assessment (cont.)

- Uncertainty: Unclear if the AE rate would increase
- Mitigation: FDA reviewed the manufacturer's risk management information and proposed communication/labeling supplement
- Patient impact: Surgeries would be delayed or patients would be treated with a less beneficial device
- Decision: FDA found the benefits to be high and the risks to be low. FDA conducted a Health Hazard Evaluation and classified this as a Class II recall.

FDA Signal Escalation

- *See* FDA's Guidance entitled "Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals").
- Sources:
  - MDRs
  - MedSun Network reports
  - Data from mandated postmarket studies
  - Clinical trials or data published in the scientific literature
  - Epidemiological research, including evaluation of administrative databases
  - Health care claims data or registries
  - Inquiries or investigations from global, federal, or state health agencies

Risk Evaluation and Minimization Strategy (REMS)

- FDA can require a REMS for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks

- A REMS focuses on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event

- Manufacturers must periodically submit REMS assessment reports to FDA that includes analysis, findings, and conclusions related to whether the REMS is meetings its goals and what, if any, modification may be needed

Creating a REMS

- FDA determines that a REMS is necessary, specifies the requirements and approves the specific programs—it is up to the medication's manufacturer to develop and implement the program
- A REMS includes
  - A risk mitigation goal
  - Information communicated to and/or required activities to be undertaken by participants who prescribe, dispense or take the medication
    - Communicate to patients (e.g., Medication guide, a patient package insert)
    - Communicate to healthcare providers, pharmacists, and healthcare settings
    - Required activities or clinical interventions (Elements to Assure Safe Use (ETASU))
      - Specific training/certification for those that administer and/or dispense the drug
      - Drug dispensed only in certain healthcare settings and/or safe use conditions
      - Each patient using the drug be enrolled in a registry and/or subject to monitoring

Questions?

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