Post-Approval Issues

Introduction to Drug Law and Regulation Virtual Course

Tuesday, November 10, 2020
2:50 – 3:50 p.m.

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Disclaimer

The educational content was prepared by Nimi Chhina in her personal capacity. The opinions expressed in this presentation are the author's own and do not necessarily reflect the views of FDA or BioMarin or their affiliates.

Outline

- Pharmacovigilance and Adverse Drug Experience (ADE) Reports
- Annual and Other Reports
- FDA Drug Safety Activities
- Post-Approval Changes and Supplemental NDAs (sNDAs) and ANDAs
- Grounds for Withdrawal of Approval
- Medicare, Medicaid and Reimbursement Issues
- Drug Supply Chain Security Act (DSCSA) Product Tracing Requirements

Learning Objectives

- Understand regulatory requirements for post-approval safety reporting.
- Explain FDA's drug safety activities.
- Describe the regulatory framework for post approval changes and supplemental NDAs and ANDAs.
- Understand at a high-level:
  - Grounds for Withdrawal of Approval
  - Medicare, Medicaid and Reimbursement Issues
  - DSCSA Product Tracing Requirements

Ice-breaker

Ice-breaker

- Name, affiliation.
- Motivation for taking the course.
- How you feel this morning?
- Show-and-tell! Share what you know or think about post-approval safety issues?

Pharmacovigilance and Adverse Drug Experience (ADE) Reports

Pharmacovigilance

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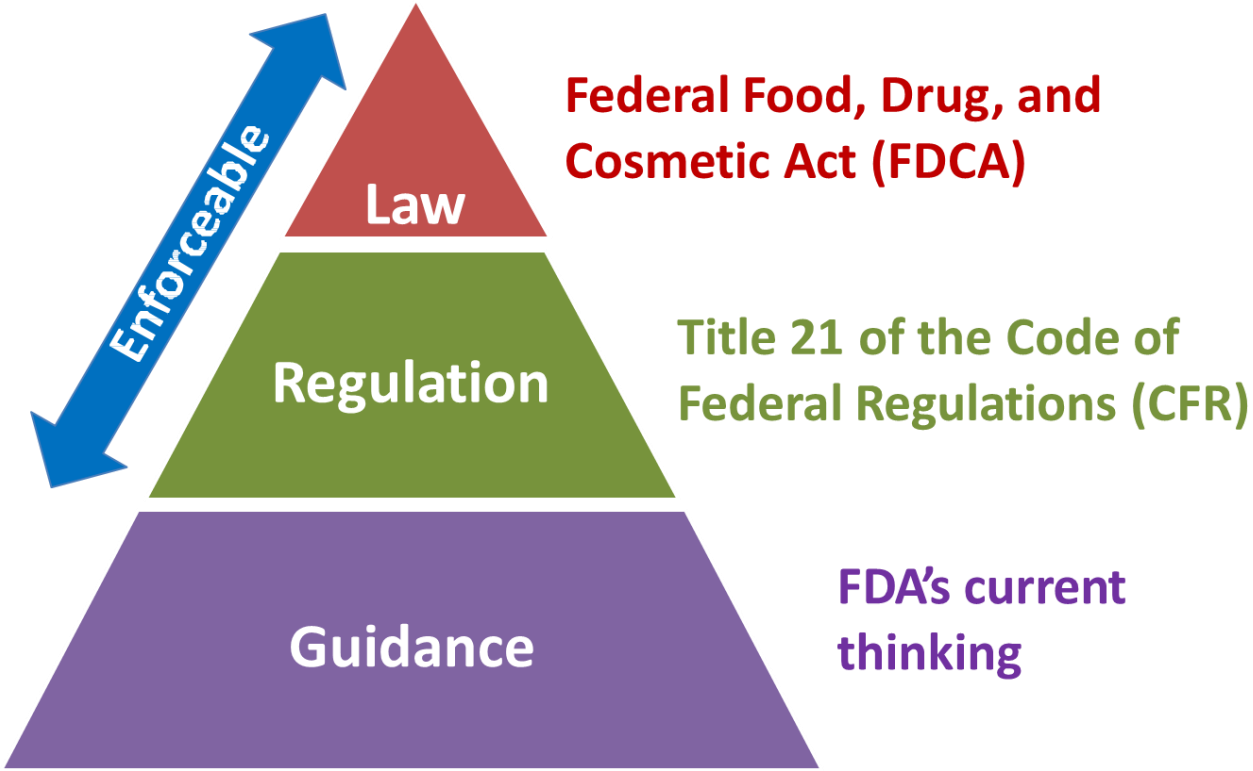
Pharmacovigilance

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

World Health Organization. The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. (2002).

Legal Framework



www.fda.gov

Postmarketing Adverse Drug Experience (PADE) Requirements:
Statutory Provisions / Regulations for Prescription Drug Products for Human Use

FDCA, Subchapter V, Part A, Section 505 (21 USC §355)	New drugs
21 CFR 310.305	New drugs: Records and reports concerning ADEs on marketed prescription drugs for human use without approved new drug applications
21 CFR 314.80	New drug applications: Postmarketing reporting of ADEs
21 CFR 314.81(b)(2)	New drug applications: Annual reports
21 CFR 314.90	New drug applications: Waivers
21 CFR 314.98	Abbreviated applications: Postmarketing reports
21 CFR 314.540	Accelerated approval of new drugs for serious of life-threatening illnesses: Postmarketing safety reporting
21 CFR 314.630	Approval of new drugs when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR Part 4, Subpart B	Postmarketing safety reporting for combination products

Source: CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018

Adverse Drug Experience as Defined by Regulation (21 CFR 314.80)

Any undesirable event that is associated with the use of a drug in humans, whether or not considered drug- related and occurs in the course of the use of a drug product in professional practice. This may include:

- Drug overdose
- Drug abuse
- Drug withdrawal
- Any failure of expected pharmacologic action

Federal Register - Code of Federal Regulations. ***21 CFR 314.80*** *(a)*

Serious Adverse Event/Experience

Results in any of these outcomes:

- Death
- Life-threatening adverse experience
- Inpatient hospitalization – new or prolonged
- Persistent/significant disability or incapacity
- Congenital birth defect
- Other serious: based upon appropriate medical judgment, these AEs may jeopardize the patient and require intervention to prevent a serious outcome

Federal Register - Code of Federal Regulations. ***21 CFR 314.80*** *(a)*

Postmarketing Safety Reporting Requirements

Postmarketing safety reports must be submitted to FDA for the following:

- **Expedited reports:** Both **serious** and **unexpected** adverse events from all sources (domestic and foreign)
  - Expedited Reporting
- **Non-expedited i.e. Periodic Adverse Experience Reports:** Domestic ***spontaneous*** adverse events that are:
  - Serious and expected
  - Non-serious and unexpected
  - Non-serious and expected
  - Quarterly for the first 3 years, then annually (for New Molecular Entity)

Federal Register - Code of Federal Regulations. ***21 CFR 314.80*** *(a)*

Written Procedures Must Address…

Surveillance	Receipt	Evaluation	Reporting

• Account for all sources
• Spontaneous
• Solicited
• Internet sources (firm-sponsored)
• Literature
 	
…and more!
	• ADE info
	  • Initial
	  • Follow-up
	
	• Receipt from ***any*** source
		• Seriousness
		• Expectedness
		• Relatedness
		
		• ADEs from ***any*** source
		
		• Follow-up procedures
			• 15-day Alert Reports
			• Non-expedited individual case safety reports (ICSRs)
			• Aggregate Reports
			• All info must be submitted electronically

Source: CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018

Annual and Other Reports

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Annual Reports

- 21 C.F.R. § 314.80(c)(2) (requiring adverse drug experience reports quarterly for the first three years after approval of the application and then annually).

- 21 C.F.R. § 314.81(b)(2) (requiring an annual report “within 60 days of the anniversary date of approval of the application”).

- 21 C.F.R. § 314.98(c) (requiring an annual report for ANDA’s).

Spontaneous Reports

- A communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority
- Describes a suspected adverse event(s)
- Passive and voluntary reports

Source: April 10, 2018 presentation on “An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System” by LTCDR Anne Tobenkin (OSE, CDER)

Aggregate Reports: Periodic

- Timing (based on FDA approval date)
  - Quarterly for 3 years (submit within 30 days of close of the quarter)
  - Annually thereafter (submit within 60 days of approval date)

- Contents
  - Narrative summary and analysis
  - 15-day ADEs: analysis
  - Periodic ADEs: line-listing and Form FDA 3500A for each ADE
  - Actions taken due to ADEs

- Formats: PADER, PSUR, PBRER
  - Electronic
    - Submit Periodic Report as PDF
    - Submit ICSRs as XML file via Electronic Submission Gateway

Other Information

- Submission of promotional materials
  - Representative copies at time of initial dissemination (Form 2253)
- Withdrawal of approved drug from sale
  - Notify FDA within 15 working days
  - Sole manufacturer of life supporting drug, life sustaining or intended to prevent serious disease or condition - must notify FDA at least 6-months before discontinuing manufacture
- Establishment registration (electronic)
  - Update annually; PDUFA fee
- Drug product listing (electronic)
  - Update every 6-months; PDUFA fee

Postmarketing AE Reporting During a Pandemic

FDA's revised final guidance issued on March 19, 2020 (updating 2012 guidance):

- FDA does not intend to object to companies that are unable to submit AE reports to the agency within the required timeframes as a result of pandemic-related employee absenteeism, **so long as they submit all delayed reports within six months of restoring their adverse event reporting processes "to their pre-pandemic state**."
- Companies should keep records of any AEs that have been stored and document when their reporting processes are restored.
- Companies should comply with normal reporting requirements during a pandemic for newly emerging product-related safety issues and product problems associated with AEs.
- Guidance does not apply to reporting obligations for investigational products.
- See table from guidance in next slide on FDA's approach to postmarketing safety reporting during a pandemic if normal processes of mandatory AE reporting are not feasible because of high employee absenteeism.

Postmarketing AE Reporting During a Pandemic

Table 1. FDA Approach to Postmarketing Safety Reporting During a Pandemic if Normal Processes of Mandatory Adverse Event Reporting Are Not Feasible Because of High Employee Absenteeism

Type of Product or Application	Type of Report(s)/Statutory or Regulatory Timeframe(s)[1]	FDA Recommended Reporting During a Pandemic With High Employee Absenteeism
Products with special concerns as specified by FDA (any product or application type below)[2]	As per regulation(s) and/or statute(s) relating to the FDA-specified product	Submit[3]
Prescription drug products marketed without an approved New Drug Application (NDA)	15-day Alert report, 15-day Alert report -follow up / 15 calendar days	Store if necessary[4]
Approved NDA, Approved Abbreviated New Drug Application (ANDA) 1. labeled indication for pathogen causing the pandemic 2. approved within prior three years	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	Approved NDA, Approved ANDA 1. Submit 2. Submit 3. Store if necessary
Approved Biologics License Application (BLA) 1. Pandemic vaccines 2. Biologics (vaccines or nonvaccines) approved within prior three years 3. Other biologics (vaccines or nonvaccines)		Approved BLA 1. Submit 2. Submit 3. Submit death outcome reports. Store if necessary other serious outcome (non-death) reports.
Approved NDA: all products	Periodic adverse drug experience report[5]/ Quarterly for 3 years from the date of U.S. approval of the application (or license) and then annually thereafter	Store if necessary
Approved ANDA: all products		
Approved BLA: all products		

Post-Approval Safety Reporting

Quiz

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Post-Approval Safety Reporting *Quiz*

True or False?

Expedited postmarketing safety reports must be submitted to FDA for all serious and expected adverse events.

Pharmacovigilance and FDA Drug Safety Activities

FDA Adverse Event Reporting (FAERS)

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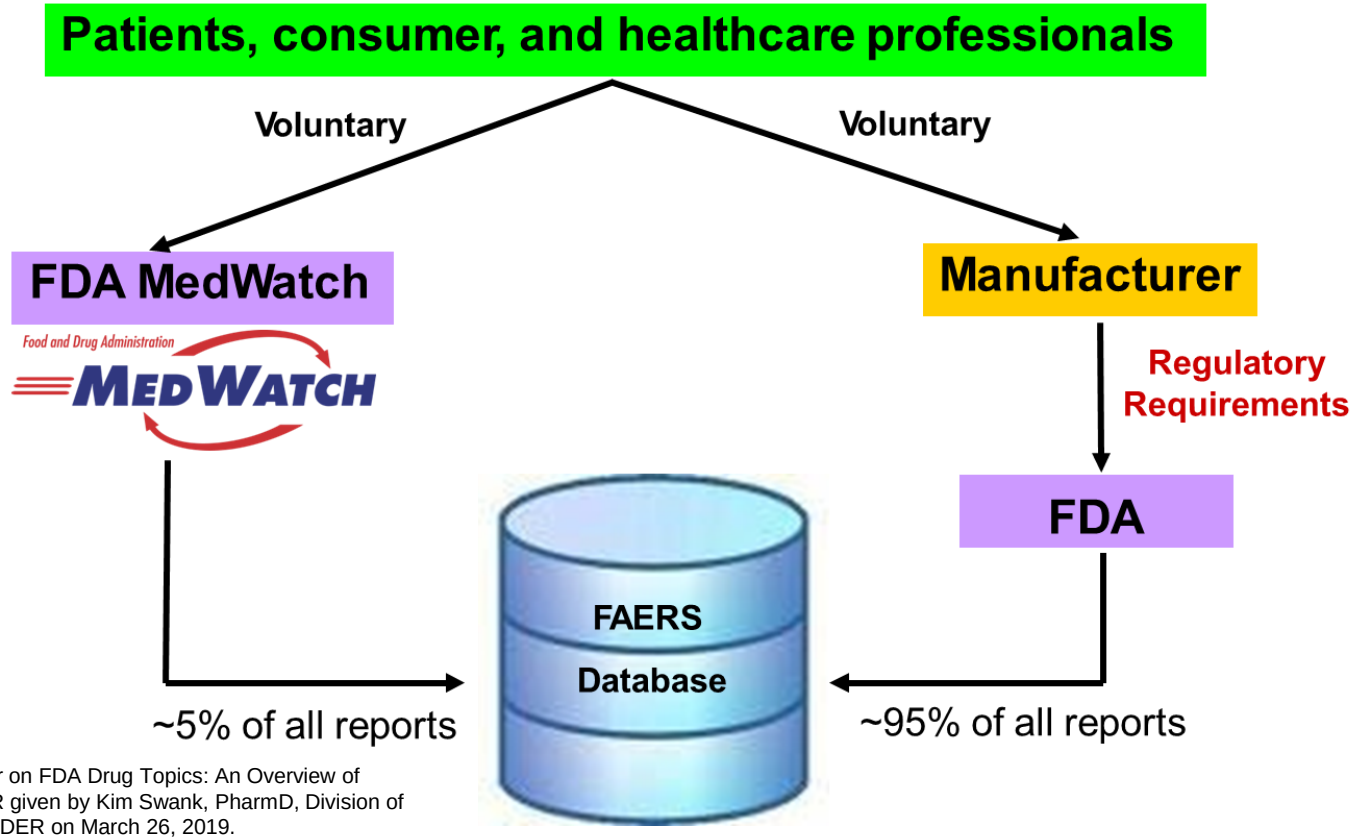
How Postmarketing Reports Get to FDA



Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

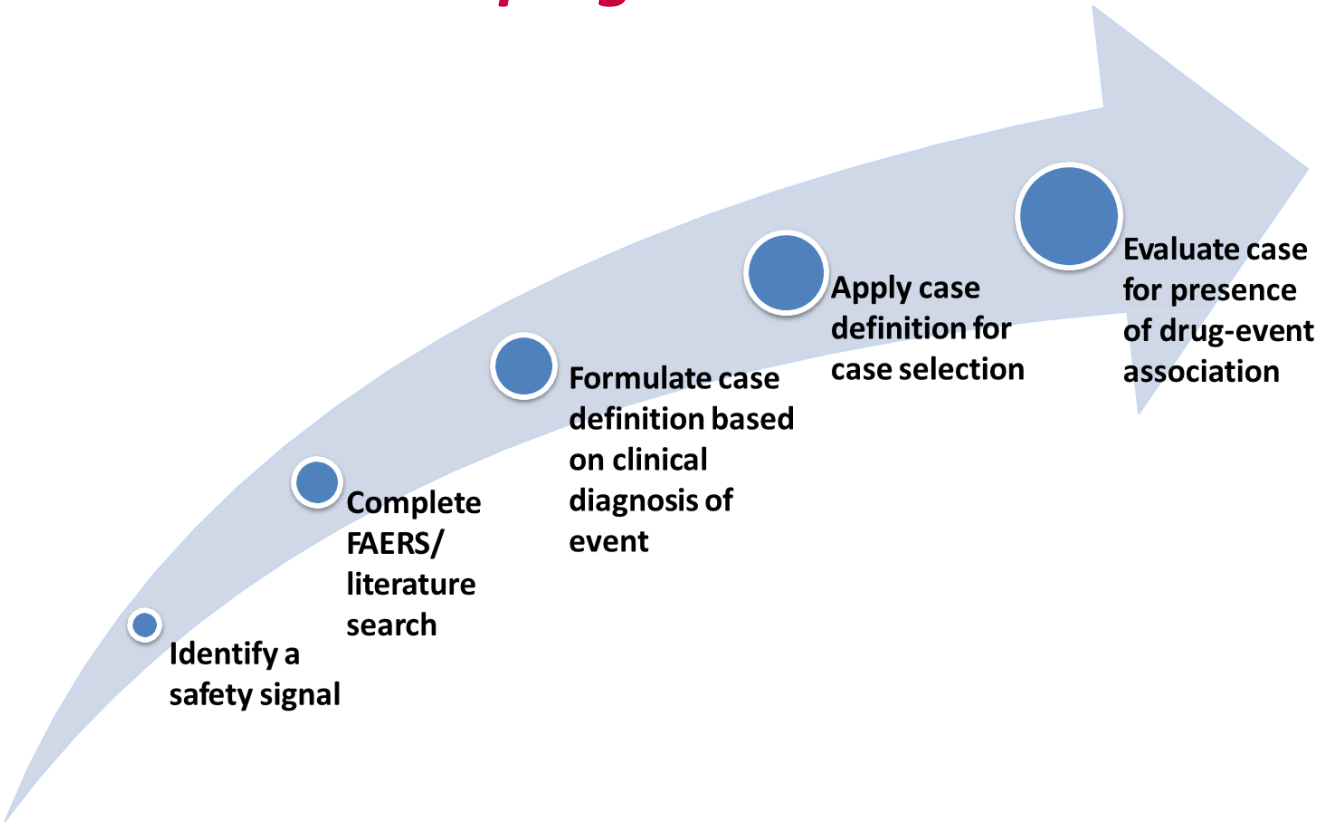
FDA Adverse Event Reporting (FAERS)

- FDA's computerized postmarketing safety surveillance database of spontaneous reports for drugs and therapeutic biologics.
  - Voluntary communication from an individual (e.g., healthcare professional, consumer).
  - Mandatory reporting requirements for manufacturers.
- Contains human drug and therapeutic biologic reports.
- Over 1.8 million new reports received in 2017.
- As of September 30, 2018, 16,470,915 million reports received since 1969.
- FDA uses FAERS data to monitor, identify and analyze adverse event and medication errors.
- FDA staff in CDER and CBER regularly examine the FAERS database as part of routine safety monitoring.
- When a safety signal is identified from FAERS data, it is further evaluated.

Source: Adapted from CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018.

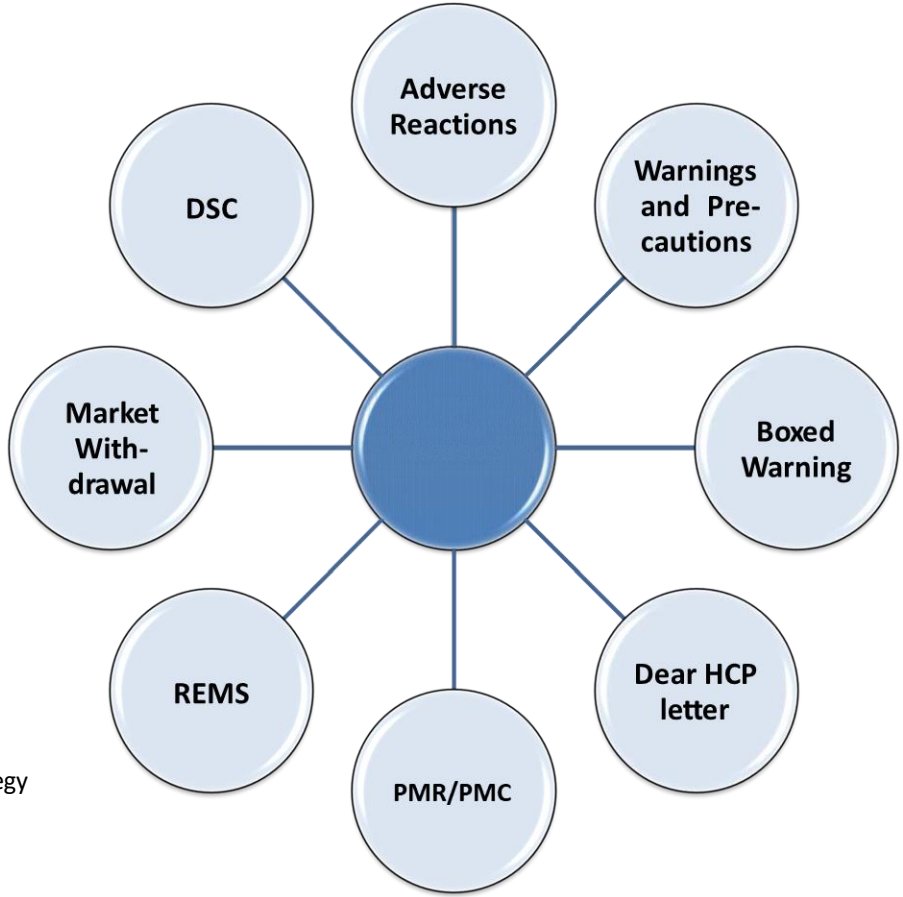
Case Series Development and Evaluation

Developing a Case Series



U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

Select sponsor and FDA actions



DSC = drug safety communication
REMS = risk evaluation and mitigation strategy
PMR = postmarketing requirement
PMC = postmarketing commitment

U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012.

Future of FAERS

- On October 29, 2019, FDA issued new draft guidance and supporting technical specification documents requiring sponsors to submit IND safety reports for serious and unexpected suspected adverse events to FAERS starting 24 months after the guidance is finalized.
- Currently, IND safety reports are submitted to FDA in electronic common technical document (eCTD) format using PDF files.
- Once the requirement is in effect, sponsors will be required to submit certain IND safety reports to FAERS instead of in eCTD format. There will be two options for submission:
  - Directly to FAERS via FDA's Electronic Submission Gateway (ESG).
  - Via the Safety Reporting Portal, a web-based submission system that feeds into FAERS.

FDA's Best Practices for Postmarket Safety Surveillance

- On November 6, 2019, the FDA posted a draft document titled "Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff" per mandate under the 21st Century Cures Act.
- CDER Director Janet Woodcock issued an accompanying Statement on the agency's safety surveillance efforts.
- 21st Century Cures Act revised a previous statutory requirement that generally required FDA to conduct routine safety analyses of drugs 18 months following approval or after 10,000 individuals have used the drug, whichever occurs later.
  - –Over time, FDA found these assessments to be largely redundant to FDA's existing surveillance practices.
  - –The assessments also did not provide sufficient flexibility to take a risk-based approach based on various factors; e.g. drugs for rare diseases never met the 10,000-individual use threshold triggering these analyses.
- Products subject to more extensive monitoring include: NMEs, original BLAs, biosimilars, first-in-class approvals, newly approved formulation(s), newly approved indication(s), extension into new patient populations, products with complex PK or PD characteristics, and products with complex compositions or manufacturing processes.
- FDA staff also monitor the safety of compounded products, even though they are not subject to FDA premarket review and approval, as well as homeopathic products.
- The extent and frequency of screening the FDA adverse event databases and the medical literature varies with the product type.

FDA Drug Safety Activities

Office of Surveillance and Epidemiology

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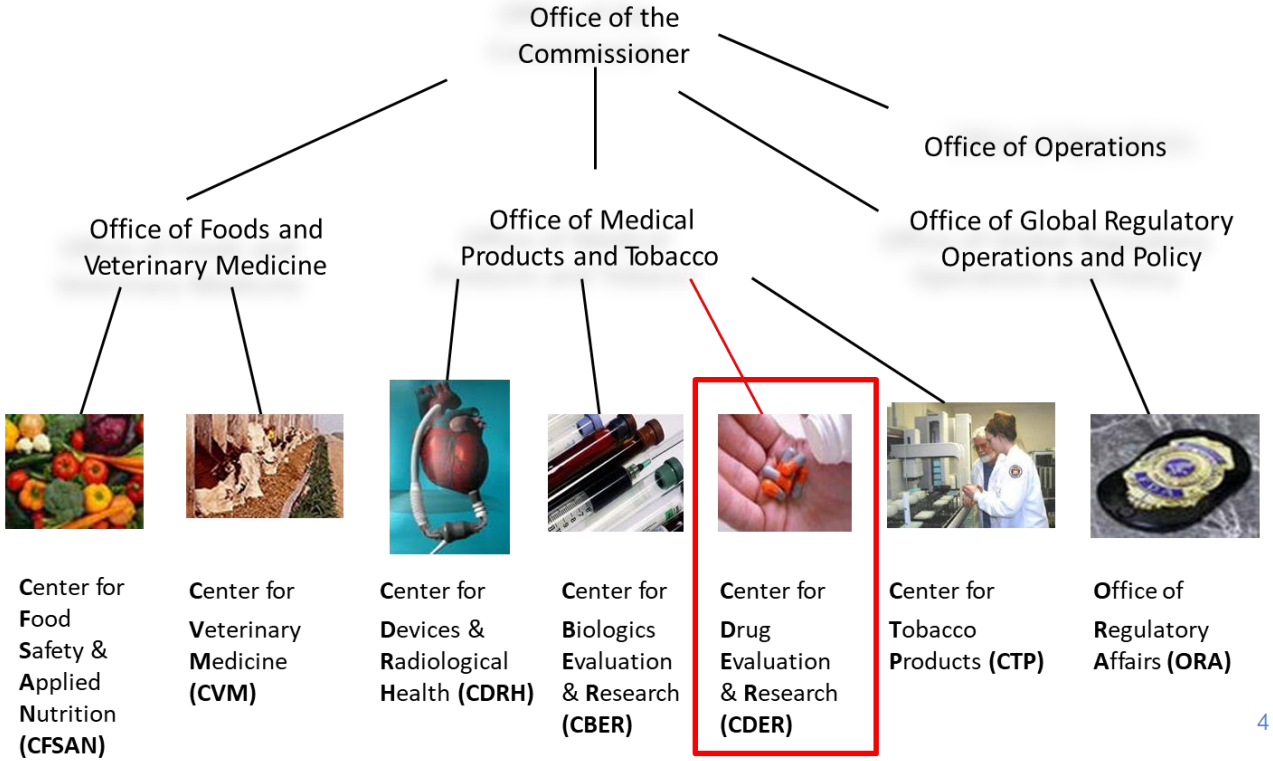


**Office of the Commissioner undergoing reorg.

CDER

Office of Translational Sciences

Office of New Drugs

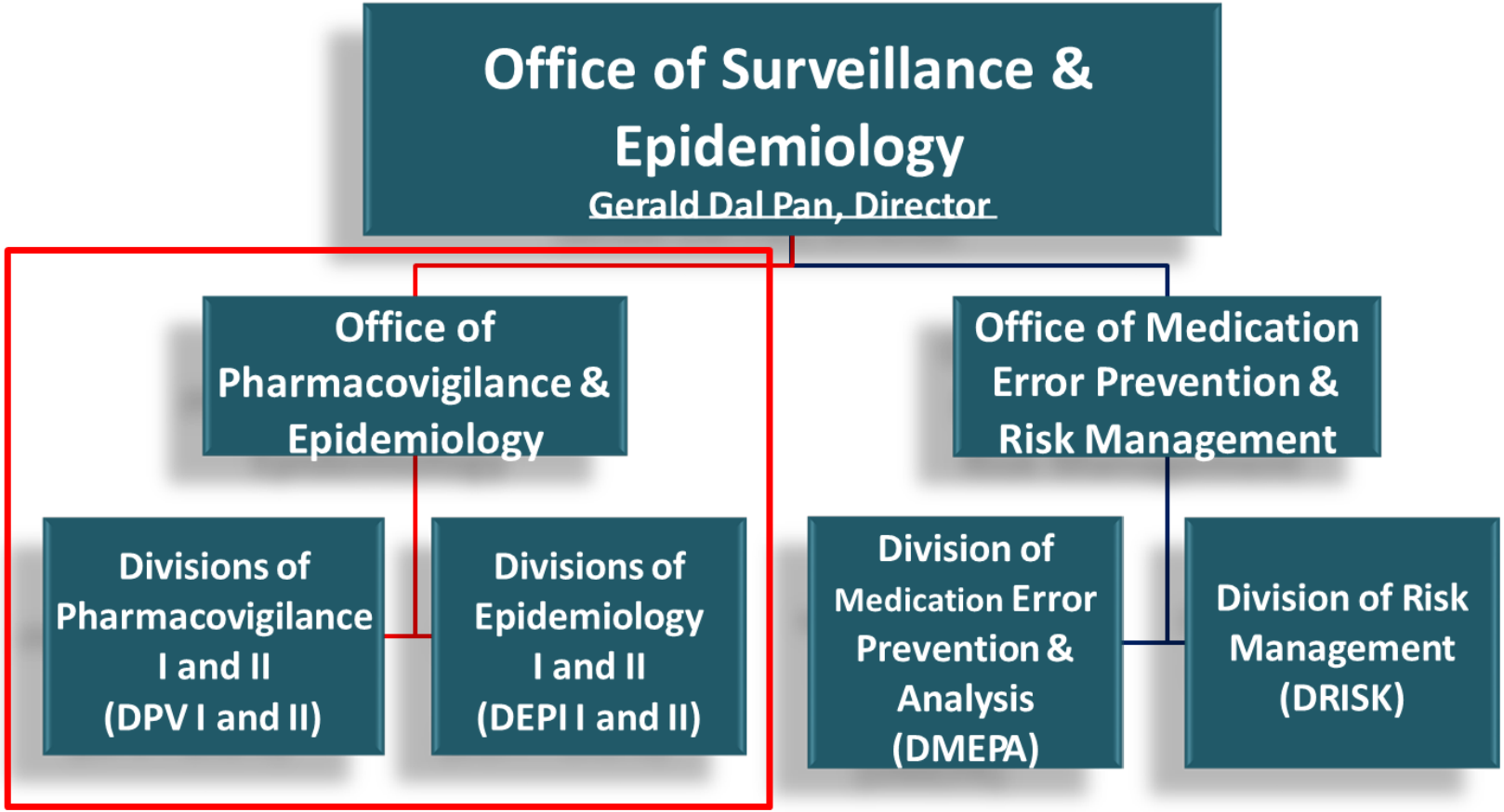
Office of Generic Drugs

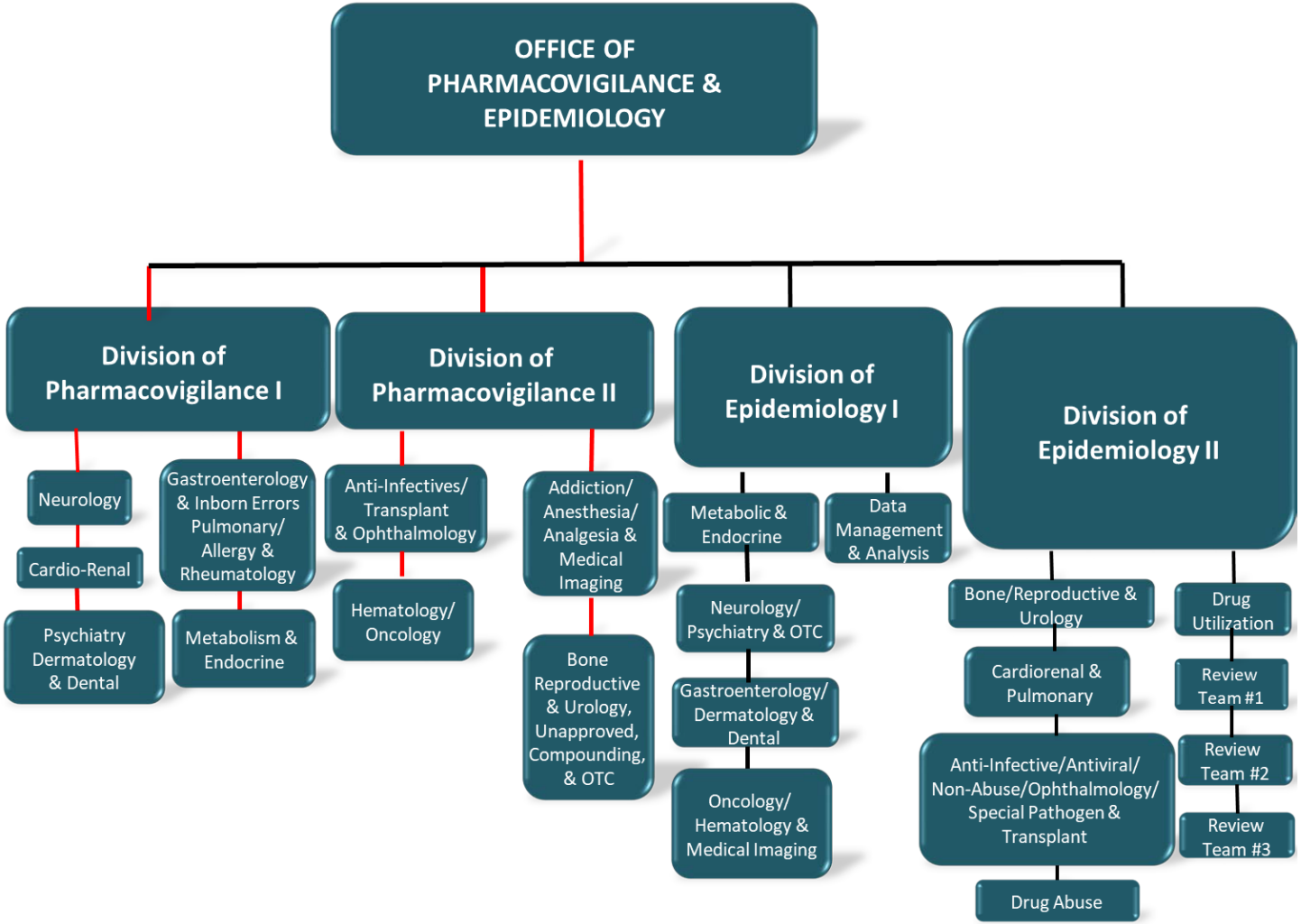
Office of Pharmaceutical Quality

Office of Compliance

Office of Surveillance and Epidemiology

**Several Offices in CDER undergoing reorg.


Office of Surveillance & Epidemiology
Gerald Dal Pan, Director
Office of Pharmacovigilance & Epidemiology
Office of Medication Error Prevention & Risk Management
Divisions of Pharmacovigilance I and II (DPV I and II)
Divisions of Epidemiology I and II (DEPI I and II)
Division of Medication Error Prevention & Analysis (DMEPA)
Division of Risk Management (DRISK)


OFFICE OF PHARMACOVIGILANCE & EPIDEMIOLOGY
Division of Pharmacovigilance I
Division of Pharmacovigilance II
Division of Epidemiology I
Division of Epidemiology II
Neurology
Cardio-Renal
Psychiatry Dermatology & Dental
Gastroenterology & Inborn Errors Pulmonary/ Allergy & Rheumatology
Metabolism & Endocrine
Anti-Infectives/ Transplant & Ophthalmology
Hematology/ Oncology
Addiction/ Anesthesia/ Analgesia & Medical Imaging
Bone Reproductive & Urology, Unapproved, Compounding, & OTC
Metabolic & Endocrine
Data Management & Analysis
Neurology/ Psychiatry & OTC
Gastroenterology/ Dermatology & Dental
Oncology/ Hematology & Medical Imaging
Bone/Reproductive & Urology
Cardiorenal & Pulmonary
Anti-Infective/Antiviral/ Non-Abuse/Ophthalmology/ Special Pathogen & Transplant
Drug Abuse
Drug Utilization
Review Team #1
Review Team #2
Review Team #3

Office of Surveillance and Epidemiology
Who are they?

Safety Evaluators and Medical Officers: Group of mostly pharmacists and physicians

- Provide clinical expertise in various therapeutic areas such as dermatology, oncology, neurology, etc.
- Review the weekly FAERS “inbox” for newly received individual case safety reports

Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

Office of Surveillance and Epidemiology
What do they do?

- Advance public health by detecting safety signals from all available data sources
- Evaluate the safety of drugs
- Identification of reporting trends, possible risk factors, at risk populations, etc.
- Collaborate with other divisions (i.e., DEPI, DMEPA, DRISK)
- Recommend regulatory actions
- Communicate relevant safety information

Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

Office of Surveillance and Epidemiology

Why does DPV exist?

JAMA | Original Investigation

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

- Among 222 novel therapeutics approved by FDA from 2001- 2010, 32% were affected by a postmarket safety event:
  - New boxed warning
  - Withdrawal due to safety issue
  - FDA safety communication

- Variables associated with higher rates of events:
  - **Biologics**
  - Psychiatric therapeutics
  - Accelerated approval
  - Near-regulatory deadline approval

Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

FDA Drug Safety Activities

Sentinel Initiative

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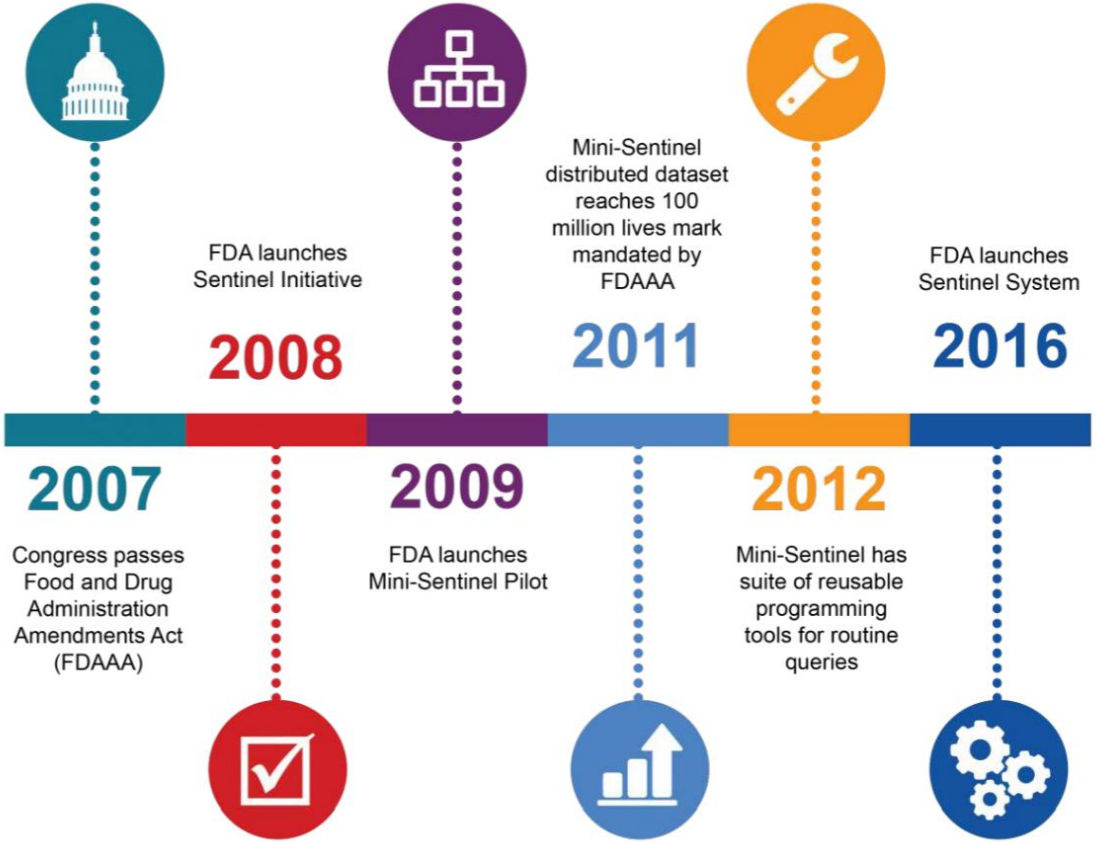
Sentinel Initiative

- FDA's medical product safety surveillance system created in response to a Congressional mandate
- Primarily electronic healthcare & administrative claims data
- Based on a distributed data network & common data model
- National medical product monitoring system
- 17 data partners with 178 million members with pharmacy and medical coverage
- Distributed system where data partners retain physical control of data to protect privacy and security

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Timeline of the Sentinel Initiative



Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

What kinds of questions can Sentinel answer?

- Number of tablets of X dispensed to outpatients in 2015?
- Fraction of patients who filled a prescription for X who also filled a prescription for Y?
- Risk of a problem among patients dispensed both drug X and drug Y compared to patients dispensed drug X and drug Z?

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Summary: The Sentinel System

- Sentinel is FDA's national medical product monitoring system
- Uses a common data model and a distributed database
- Generates real world evidence to inform clinical decision-making
- Multiple ways to stay informed and active
  - Sentinel website: https://www.sentinelinitiative.org/
  - Annual Public Workshop: https://healthpolicy.duke.edu/events/eleventh-annual-sentinel-initiative-public-workshop

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

FDA Safety Activties: Risk Assessment and Risk Management

New safety information

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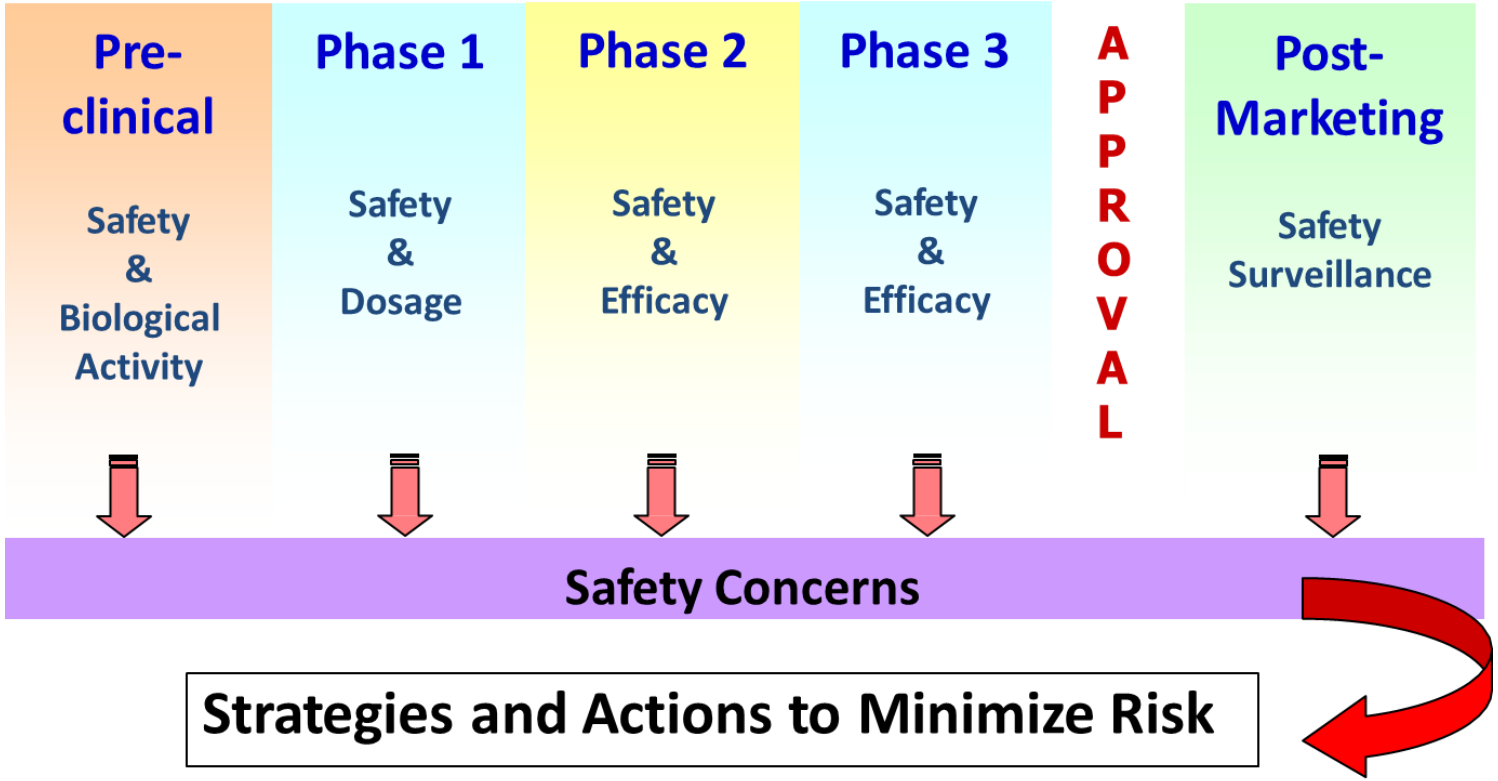
Safety in the Lifecycle of FDA-regulated Products



Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

Premarket vs Postmarket Safety Data

Limitations of Premarket Clinical Trials

- Small size of patient population
- Narrow population/indication
- Short duration versus chronic use
- Lack of adequate ascertainment and classification of adverse events
- Comorbidities
  - Hepatic or renal failure
  - Other serious medical conditions
  - Use of concomitant medications

Benefits of Postmarket Safety Reporting

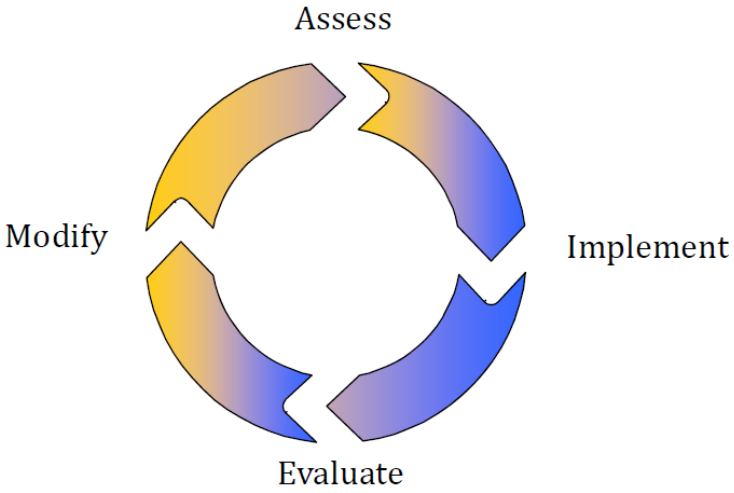
- Low frequency/rare adverse events
- AEs from entire population/all indications
- Drug-drug/food interactions
- Detect ↑ severity of known reactions
- Direct engagement of HCPs/consumers
- Chronic/long-term use
- Misuse or abuse
- Increased frequency/severity of expected AEs
- Medication errors; e.g. packaging, labeling

Singh S et al. Trials. 2012;13:138
Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm
Source: April 10, 2018 presentation on "An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System" by LTCDR Anne Tobenkin (OSE, CDER)

What is Risk Management?

Risk Management Concept

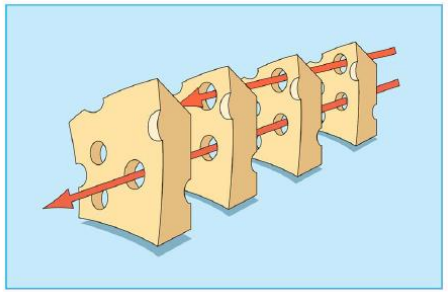
Risk assessment + Risk minimization = Risk management



Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Risk mitigation

- Risk mitigation is often accomplished by introduction of a series of steps or processes that lower likelihood of unsafe use
  - May reinforce good clinical practices
  - May introduce new risk mitigation measures
  - May include administrative checks to support risk mitigation efforts
- Each intervention that is part of risk mitigation may introduce some level of burden



Adapted from: Reason J. Human Error: Models and Management. *British Medical Journal* 2000

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

The foundation of risk management

Product safety issues are typically managed through:

- Labeling is the cornerstone of risk management and the foundation for the risk management of products

- Routine reporting requirements allows us to continually assess the benefit risk profile of the product

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Why do we need additional risk management tools?

In a small number of drugs/biologics, additional measures are necessary to mitigate risks and preserve benefits.

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

FDA Safety Activities

FDA's authority to require post-market studies or trials

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Post-marketing Studies and Clinical Trials

- Studies conducted after licensure
- Agreed upon between the applicant and FDA
- Intended to further refine the safety, efficacy, or optimize use of the drug
- To ensure consistency and reliability of the product quality

Post-Marketing Requirement (PMR)

- In 2007, Section 901, in Title IX of FDAAA created section 505(o) of the FD&C Act which authorized FDA to require postmarketing studies or clinical trials for assessing or identifying a “serious risk” at the time of approval or after approval if FDA becomes aware of new safety information (21 CFR subpart H).
- FDAAA states that studies and clinical trials may be required for one of three purposes:
  - To assess a known serious risk related to the use of the drug,
  - To assess signals of serious risk related to the use of the drug, or
  - To identify an unexpected serious risk when available data indicate the potential for a serious risk.
- Reporting requirements
  - A timetable of completion
  - Periodic reports on the status of the study, including whether any difficulties in completing the study
  - Periodic report on the status of the clinical trial

Post-Marketing Commitment (PMC)

- Studies and clinical trials the applicants have agreed to conduct, but not required (Section 506B of the Act).
- For drug and biologic quality studies , including manufacturing, stability, and immunogenicity studies that do not have a primary safety endpoint.
- The applicant has agreed with FDA to conduct.

PMC/PMR Reporting Requirements

- Section 130(a) of Title I of the Food and Drug Administration Modernization Act of 1997 (FDAMA) added a new provision (section 506B) to the FD&C Act which mandates **applicants to report annually on the status of PMRs and reportable PMCs**, and obligated FDA to make certain information about these PMRs/PMCs is publicly available.
- **506B-Reportable PMC:** Postmarketing studies or clinical trials concerning **clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology** that applicants and the FDA have agreed, in writing, to conduct; and applicants are required to report on these PMCs in their PMR/PMC annual report (21 CFR 314.81(b)(2)(vii)(a), 21 CFR 601.70(b), and Section 506B the FD&C Act, Reports of Postmarketing Studies)
- **Non-506B Non-Reportable PMCs** – Any **CMC study**, agreed, in writing, to be conducted, to assess drug or biologic product quality data that was not required for approval; yet, the review committee felt was necessary to provide complete quality information; in addition, these commitments are not subject to 506B's reporting requirements.

Recent FDA Guidance

- On October 24, 2019, FDA issued draft guidance titled on “Postmarketing Studies and Clinical Trials—Implementation of 1 Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.”
- This draft guidance revises and replaces the April 2011 draft guidance on the implementation of section 505(o)(3) of the FD&C Act, which authorizes FDA to require postmarketing studies.
- The revised draft guidance affirms FDA’s new authority to mandate postmarketing studies to assess diminished efficacy, in accordance with a provision in the 2018 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act)
- While the SUPPORT Act focuses on opioids and other controlled substances, FDA notes that “at this time, the agency does not intend to treat controlled substances differently than other….”
- The original postmarket requirement authority was enacted as part of the 2007 FDA Amendments Act (FDAAA), and focused exclusively on safety issues.
- FDAAA also authorized FDA to develop the Sentinel system, and the mandatory postmarket study authority was explicitly linked to that effort.
- FDA and the Sentinel team have launched a formal active surveillance tool, called ARIA (Active Risk Identification and Analysis)
- Per FDA, the draft guidance is being revised to include the factors that the agency considers when determining whether a postmarketing study or clinical trial will be required for a drug or biologic, or whether postmarketing reports and the agency’s ARIA system are sufficient to assess a product’s risks in the postmarket setting.
- The revised draft guidance provides four examples of clinical trials to assess risks related to “failure of expected pharmacological action, including reduced effectiveness”— all of which are from non-opioid drug classes— therefore underscoring the broad scope of FDA’s new authority to require trials for reduced effectiveness in updated draft guidance.

Recent FDA Guidance

- On October 20, 2020, FDA issued the draft guidance for industry entitled, "Annual Status Report Information and Other Submissions for Postmarketing Requirements and Commitments: Using Forms FDA 3988 and FDA 3989."
- This guidance is intended for industry applicants who are required to report annually on the status of postmarketing studies and clinical trials for human drug and biological products under section 506B of the FD&C.
- Use of Forms FDA 3988 and 3989 is optional, but, "FDA encourages their use because the forms should facilitate FDA management and review of the applicant's submissions, as well as enhance the accuracy of data within FDA's electronic document archiving systems" used to create PMR and PMC annual reports and to update data quarterly on the FDA's Postmarket Requirements and Commitments public web page.
- The guidance does not apply to postmarketing studies or clinical trials that are not subject to the criteria of PMR/PMC reporting as outlined in section 506B of the FD&C.

Other Post-Marketing Requirements

- Risk evaluation and mitigation strategies (REMS). Required under certain circumstances (Sections 505-1 and 505(o)(4) of the Act)
- Safety related labeling changes (SLC)
- Pediatric studies (21CFR314.55)
  - Assessment required for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration
  - To assess the safety and effectiveness of the drug product for the claimed indications
  - For all relevant pediatric subpopulation

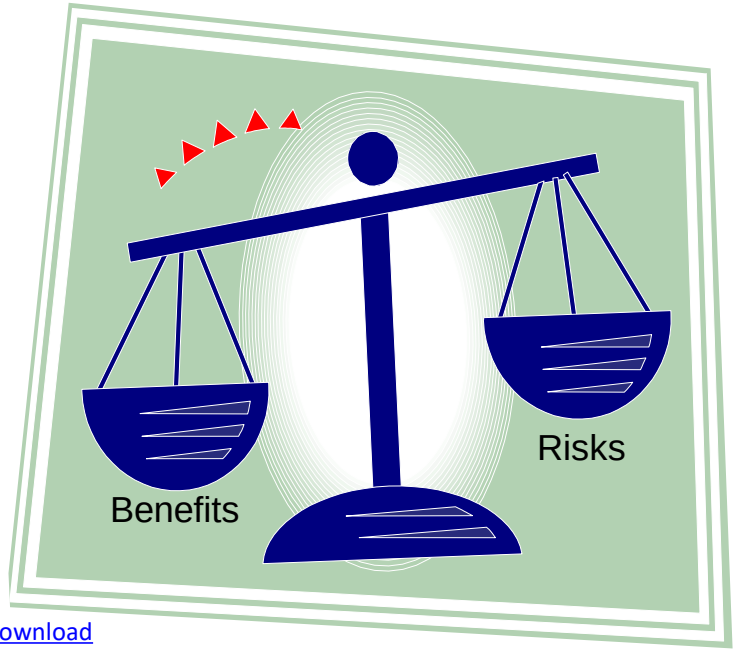
Risk Assessment and Risk Management

Overview of REMS authorities

FDLI

Risk Evaluation and Mitigation Strategy (REMS)

- A required risk management plan that uses risk mitigation strategies beyond FDA-approved FDA professional labeling.
- FDA Amendments Act of 2007 (FDAAA) (Section 505-1 of the FD&C Act) authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
  - *FDA does not directly regulate healthcare professionals or patients who may be impacted by a REMS.*
- Applies to NDAs, BLAs, and ANDAs.
- A required risk management plan that uses risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks.
- REMS can be required pre- or post-approval if FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks.



Source: Slides from CDER SBIA Webinar on REMS available at link: https://www.fda.gov/media/105565/download

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

REMS: Key Points

- Drug sponsors develop REMS programs, FDA reviews and approves them
- REMS programs can be designed for a single drug or a class of drugs
- Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs

Source: Slides from CDER SBIA Webinar on REMS available at link: https://www.fda.gov/media/105565/download

FDA Drug Safety Activties

Quiz

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Quiz

True or False

Both PMRs and PMCs are required by law.

Post-Approval Changes and Supplemental applications

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Post-Approval Changes/Supplements

21 CFR 314.70

- NDA/ANDA holder must notify FDA about any “change in a condition established in an approved application beyond the variations already provided for” in application
- Assess whether advance approval is needed to implement change
- Fact-specific analysis

Reporting Categories and Types of Supplements Related to Changes

- **Prior Approval Supplement (PAS) – Major:** Changes requiring supplement submission and approval prior to distribution of the product made using the change
  - Changes in formulation, manufacturing process, packaging materials

- **Changes Being Effected in 30 days (CBE-30) – Moderate:** Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change
  - Packaging change that doesn't affect drug quality

- **Changes Being Effected – Immediate (CBE) – Moderate:** Based on experience with a particular type of change, …on particular assurances that the proposed change has been appropriately submitted (to the Agency)…. the product made using the change may be distributed immediately upon receipt of the supplement by FDA
  - Addition of specification, certain labeling changes to improve safe use

- **Annual Report Reportable Changes – Minor:** Changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
  - Delete color; adopt compendial change

Types of Postapproval Changes

- **Components and composition**
  - Any changes in the quantitative or qualitative formulation, including inactive ingredients, are considered to be major changes
  - Deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report.
- **Manufacturing sites:** If a drug maker changes to a manufacturing site other than those specified in the approved application, CDER must be notified. These sites can include those used to:
  - Manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates
  - Package drug products
  - Label drug products
  - Test components, drug product containers, closures, packaging materials, in-process materials, or drug products.
- **Manufacturing processes:** Reporting category depends on potential for adverse effects on identity, strength, quality, purity, or potency of a drug product
  - When there is substantial potential for adverse effect regardless of direct testing of the substance for conformance with the approved specification, the change must be submitted to the FDA in a prior approval supplement.
- **Specifications:** Changes from approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance.
- **Container closure system:** Typically, a change to or in the packaging component will only result in a new or revised specification for the packaging component. In this case, only the reporting category for the packaging change needs to be considered.
  - Potential for adverse effect on the identity, strength, quality, purity, or potency of the drug's safety or effectiveness is generally dependent on the following:
    - Drug's route of administration
    - Performance of the container closure system
    - Likelihood of interaction between the packaging component and the dosage form.
- **Labeling:** A change in a drug's labeling includes changes in Package insert; Package labeling; Container label
  - All promotional labeling and advertising must be promptly revised to be consistent with any labeling change(s) implemented.
  - All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.
- **Multiple Related Changes:** If an applicant has multiple related changes that fall into different recommended reporting categories, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

Labeling Changes

Labeling Changes

FDA must be informed before distribution of the product with the labeling changes

- Labeling changes that require supplement submission and prior approval before distribution
- Labeling changes that require supplement submission but may be distributed prior to approval
- Labeling changes requiring submission in an annual report
  - Examples: Editorial changes
- Advertisements and promotional labeling

Changes to the Drug Substance/Drug Product

- If the drug product changes substantially and is no longer the same drug, then a new NDA will be required.
- Discuss with FDA to determine if the proposed change will change the drug to require a new NDA.
- Develop change management protocols

Evaluating Changes: Tools For Change Management

- Comparability Studies
- Risk Evaluation
- Use of Standards
- Bridging studies
- Post-marketing commitments (e.g., Assessment of long term effects of the changes)

Emerging Concepts in Managing Change

- **ICH Q12:** Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (DRAFT Guidance Issued November 16, 2017. Public commenting period ended in December 2018; Expected to complete step 4 in the 2nd half of 2019)
- **Established conditions:** ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority
  - Implicit and Explicit Established Conditions
  - Identification of Established Conditions
  - Revision of Established Conditions

Post-Approval Changes: Summary

- Expect change
- Post-approval changes should be made with caution
- Prior approved comparability protocols can help managing changes
- Nature of the change determines the reporting category
- Early interactions with the FDA will help in designing comparability studies
- Appropriate use of change management tools may increase regulatory predictability

Source: https://www.asgct.org/ASGCT/media/about/Approved-Vatsan-ASGCT-2019.pdf

Post-Approval Changes

Quiz

Quiz

True or False

A major facility change that could introduce contaminations or cross-contaminations should be submitted as a PAS.

Source: https://www.asgct.org/ASGCT/media/about/Approved-Vatsan-ASGCT-2019.pdf

Grounds for Withdrawal of Approval

Mandatory Withdrawal

- Safety - clinical or other evidence shows drug unsafe
- Safety - based on new clinical evidence not in NDA or known to FDA that drug “is not shown to be safe”
  - E.g., VIOXX Cox-2 NSAID (2004)
  - E.g., Seldane (following Allegra approval)
  - E.g., Avastin for breast cancer (2011)
- Effectiveness - new evidence shows lack of substantial evidence of effectiveness
- Failure to file required patent information
- Application includes untrue statement of material fact
  - E.g., KV Pharmaceutical (1998)

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Discretionary Withdrawal

- Failure to have system for maintaining required records, to permit access to records, or to file required reports
- New information: serious manufacturing deficiencies and not corrected within reasonable time after written notice
- New information: labeling is false or misleading and not corrected within reasonable time after written notice
  - Generic MiraLax (Rx/OTC marketing) (October 2008)

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Regulatory Considerations for Withdrawal of Approval

- Legal authority uncertain (but not challenged)
  - Failure to submit bioavailability or bioequivalence data
  - Failure to explain omission of investigation or other information pertinent to evaluation of drug (omission itself not basis for withdrawal)
  - Good laboratory practice violations
  - Informed consent/Institutional Review Board (IRB) violations
  - Refusal to permit inspection (applicant or contract research organization)

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Other Considerations for Withdrawal

- "Voluntary" – applicant request
  - Product no longer marketed (*e.g.*, Redux)
  - Failure to meet post-marketing endpoints (*e.g.*, Iressa, Oforta, one indication for Celebrex)
- "Voluntary" – FDA request
  - Safety issues with post-market trial (e.g., Mylotarg, Meridia)
- Citizen Petition
  - Raising alleged safety concerns
  - Confusion over product names
- "Imminent hazard" to public health
  - Summary suspension with opportunity for expedited hearing
  - HHS Secretary's decision - only used once (late 1970s)
- Agency "mistake" (*American Therapeutics* case)

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Other Considerations for Withdrawal Contd.

- Advisory Committee recommendation
  - Darvon/Darvocet (propoxyphene) (1/09)
    - AdCom voted to withdraw approval based on safety issues
    - FDA (July 2009): no withdrawal – strengthened label, Medication Guide, additional safety study
    - FDA (Nov. 2010): based on new data, requested withdrawal; manufacturer agreed
  - Vicodin, Percocet (narcotics + acetaminophen) (6/09)
    - AdCom voted to withdraw approval; no FDA action yet

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Other Considerations for Withdrawal Contd.

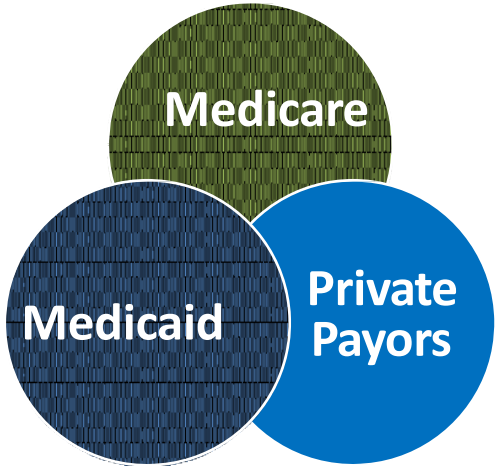
- "Administrative Reconsideration"
  - Spear Pharmaceuticals – fluorouracil ANDA approved April 11, 2008
    - Valeant Citizen Petition (denied); lawsuit against FDA
    - FDA announced reconsideration May 14, 2008 due to "outstanding questions regarding this approval"
    - Approval stayed until May 30, 2008 (Spear agreed to stay)
    - No indication what issues were uncovered
    - No additional delay in approval beyond May 30, 2008

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Medicare, Medicaid and Reimbursement Issues

FDLI

The Health Insurance Market



Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

What is Medicare?

Simple ABCD…

- **Part A** covers inpatient hospital stays, skilled nursing facility stays, home health visits (some also covered under Part B), and hospice care, and **accounted for 34%** of benefit spending in 2013. Part A benefits are subject to a deductible **($1,216 per benefit period in 2014**) and coinsurance.

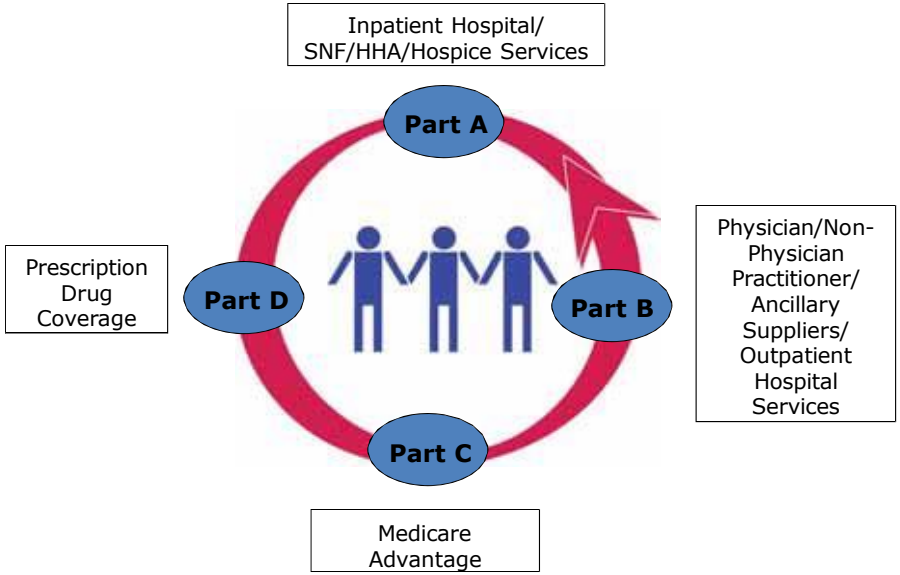
- **Part B** covers physician visits, outpatient hospital services, DME, some drugs, diagnostic services and accounted for **25% of benefit spending in 2013**. Part B benefits are subject to a deductible **($147 in 2014**), and cost sharing for most services.

- **Part C** refers to the Medicare Advantage program, through which beneficiaries can enroll in a private health plan, such as a health maintenance organization (HMO), and receive all Medicare-covered benefits. Payments to Medicare Advantage plans accounted for 25% of benefit spending in 2012.

- **Part D** is the voluntary outpatient prescription drug benefit, with additional subsidies for beneficiaries with low incomes and modest assets. The Part D benefit is offered through private plans that contract with Medicare, both stand- alone prescription drug plans (PDPs) and Medicare Advantage prescription drug plans (MA-PDs). In 2013, Part D accounted **for 11% of benefit spending.**

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

What is Medicare?



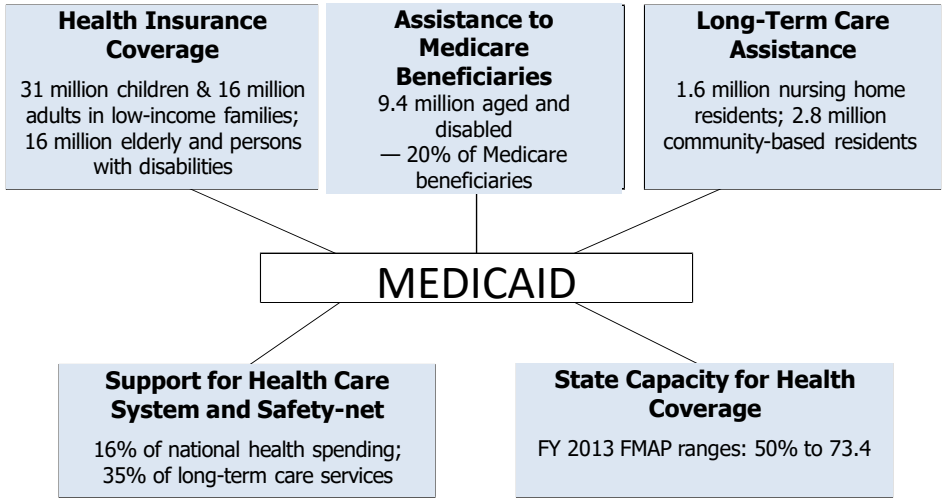
Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare Part D

- Prescription Drug Benefit
- Created by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003
- Commenced January 1, 2006
- Private entities contract with the federal government to offer prescription drug benefits
- CMS makes capitated (per member, per month) payments to the plan sponsor to manage drug benefits

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicaid – Basics



Sources: Kaiser Commission on Medicaid and the Uninsured, March 2013; and link:
https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicaid Basics: Benefits

Mandatory

- Physician services
- Lab and x-ray services
- Inpatient hospital
- Outpatient Hospital
- EPSDT for individuals under 21
- Family planning
- Rural and federally qualified health center (FQHC) services
- Nurse midwife services
- Nursing facility (NF) services for individuals 21 and over
- Home health for certain populations

Expansion Medicaid

- Essential Health Benefits

Optional

- Prescription drugs
- Clinic services
- Dental services, dentures
- Physical therapy and rehab
- Prosthetic devices, eyeglasses
- Primary care case management
- Intermediate care facilities for the mentally retarded (ICF/MR) services
- Inpatient psychiatric care for individuals under 21
- Personal care services
- Hospice services
- Alcohol and Drug Treatment

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Simple Reimbursement Model

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Payment Systems

- Cost Basis
- Prospective Payment (“Mini-bundle”)
- Fee Schedules

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

New Payment Systems

- Risk Transfer and Capitation
- Bundled Payment (“Episode of Care”)
- Shared Savings

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Drug Supply Chain Security Act (DSCSA) Product Tracing Requirements

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Overview of the DSCSA

Source: See DSCSA resources slide in back-up

Title II: Drug Supply Chain Security Act (DSCSA) adds new sections in the Federal FD&C Act

- 581 – Definitions
- 582 – Requirements (product tracing, product identification, verification)
- 583 – Standards for licensure of WDs
- 584 – Standards for licensure of 3PLs
- 585 – Uniform national policy

DSCSA Major Provisions

- Product tracing (*by 2015 lot-level, by 2023 package-level*)
- Product verification
  - Quarantine and investigation (steps for detection and response)
  - Notification, recordkeeping
- Product identification (*applied to product beginning 2017*)
- Wholesale distributor and Third-party logistics provider standards for licensure
- Enhanced system (*electronic, interoperable system to trace products at the package-level by 2023*)
- Penalties
- National uniform policy

Source: See DSCSA resources slide in back-up

Verification

- No later than 1/1/2015, manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) shall establish systems and processes to be able to comply with the verification requirements
  - Must be able to respond to verification requests from Secretary about suspect product
  - Quarantine and investigate suspect product to determine if illegitimate product (includes validating applicable TI and TH)
  - Notify trading partners and FDA of illegitimate product (within 24 hours of determination)
  - Respond to notifications of illegitimate product
  - Recordkeeping
- Verification requirements change once product is serialized. (starting in 2017 for manufacturers, 2018 for repackagers, 2019 for wholesale distributors and 2020 for dispensers)

Source: See DSCSA resources slide in back-up

Product identification (Serialization)

- Put a unique product identifier on certain prescription drug packages
  - Manufacturers (No later than 11/27/2017)
  - Repackagers (No later than 11/27/2018)

- Product identifier consists of
  - National Drug Code
  - Serial number
  - Lot Number
  - Expiration Date

Standardized numerical identifier

- Data Carrier – 2D bar code

Source: See DSCSA resources slide in back-up

After products are serialized

- Only buy and sell products encoded with product identifiers *(unless grandfathered under section 582(a)(5))*
  - Repackagers (beginning 11/27/2018)
  - Wholesale distributor (beginning 11/27/2019)
  - Dispensers (beginning 11/27/2020)
- Verification product at the package level, including the standardized numerical identifier *(NDC and serial number)*
  **see respective sections of 582 for specific verification requirements*
  - Manufacturers: starting 11/27/2017
  - Repackagers: starting 11/27/2018
  - Wholesale distributors: starting 11/27/2019
  - Dispensers: starting 11/27/2020
- Enhanced product tracing by 2023 at the package-level

Source: See DSCSA resources slide in back-up

Thanks and Questions

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Back-up Slides

FDLI

Approval vs. Marketing

Once a drug is approved, license holders MUST receive, evaluate, and report all adverse drug experiences (ADEs) to FDA, even if the biologic is not marketed.

Source: CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018

Oversight of PV contractors

- Any PADE activities can be outsourced to a third party (e.g. vendor, contractor, consultant, or other pharmacovigilance provider)

- However, the applicant or non-applicant named on the label remains responsible for compliance

Source: CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018

Business Partners

- Joint development & marketing of drugs
- Contract manufacturers
- Drug safety data generated needs to be collected and exchanged between partnering firms (any source of ADEs)
- Laws and regulations govern the exchange, review, & reporting of safety data

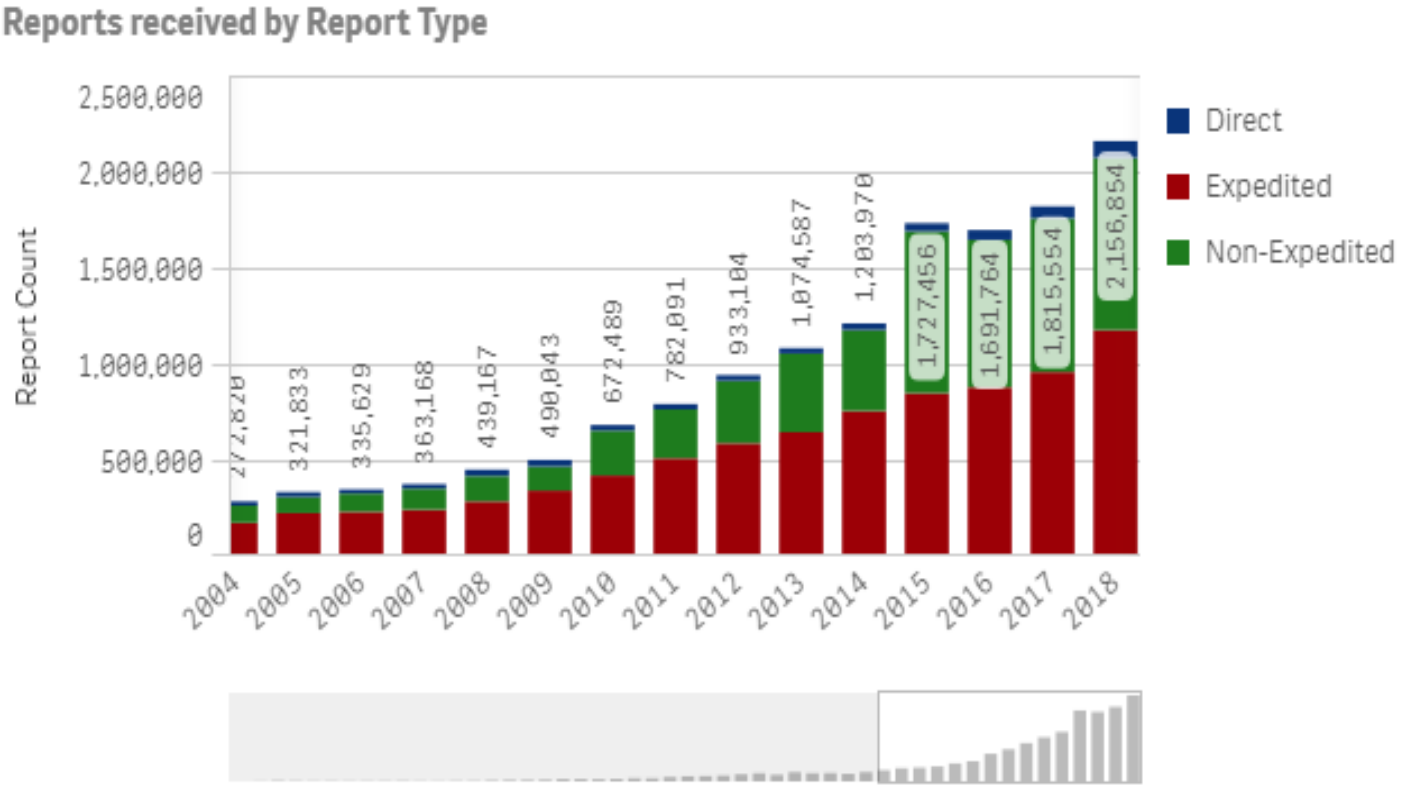
Source: CDER SBIA Webinar on Postmarketing Drug Safety and Inspection Readiness given on June 19, 2018

Best Applications of FAERS

- Events that are linked to specific diagnoses
- Events with a serious outcome that rarely occur in an untreated population
- Events with a short-to-moderate latency period following exposure
- “Safety signal” generation and descriptive case series

Source: April 10, 2018 presentation on “An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System” by LTCDR Anne Tobenkin (OSE, CDER)

Number of Adverse Event Reports Entered into FAERS



Data as of December 31, 2018

Source: CDER DDI Webinar on FDA Drug Topics: An Overview of Pharmacovigilance in CDER given by Kim Swank, PharmD, Division of Pharmacovigilance, OSE, CDER on March 26, 2019.

FAERS Strengths

- Can report even if causality is uncertain
- Less restrictive than clinical trials
  - Reports can be submitted for any drug, old and new
  - Entire US population is “eligible”
- Reports emerge from usual healthcare settings
  - Patient and prescriber population more heterogeneous
  - All stages of treated disease
  - Longer duration of use
  - Captures “off-label” use, including diagnosis and dose
  - Co-morbidities, concomitant products and procedures
- *Includes all marketed products, uses, and patient populations
- *Especially good for rare events and events that occur shortly after exposure

Source: April 10, 2018 presentation on “An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System” by LTCDR Anne Tobenkin (OSE, CDER)
**Source: Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

FAERS Limitations

- Passive, voluntary surveillance
- Underreporting occurs and is variable from drug to drug and over time
  - Some literature cites 1-10%
  - Actual is unknown so FDA does not assume extent
- Reporting bias exists
- *Dependent on report quality
- Quality of the reports is variable and often incomplete
- Duplicate reporting of the same case occurs
- Not population-based data source
  - Can not reliably estimate incidence or prevalence
  - Numerator uncertain, denominator can only be projected from drug utilization data
- *Cannot estimate incidence (underreporting)
- *Can include adverse events that could also be manifestations of the disease for which the drug is indicated

Source: April 10, 2018 presentation on "An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System" by LTCDR Anne Tobenkin (OSE, CDER)
**Source: Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

Sentinel Uses Secondary Data

- Patient interaction with the U.S. healthcare system generates data
- Why is data collected?
  - Payment/billing
  - Document clinical care
  - Physician decision support
  - Recordkeeping
  - Registries
- Data provide rich source of information for patient safety evaluations

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Sentinel Captures Billions of Encounters with the Healthcare System

- Populations with well-defined person-time for which most medically-attended events are known
- 223 million members*, 2000-2016
  - 178 million members* with medical and pharmacy benefits
- 43 million people currently accruing new data
- 425 million person-years of observation time

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Data is Collected for Several Purposes

Administrative Data

- Collected for transactional recordkeeping, reimbursement

Clinical Data

- Collected to document elements of clinical care and support physician decision-making

Registries

- Collected to provide information on a specific population of interest

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Scientific Partners Bring Expertise
Data Partners Respond to Queries

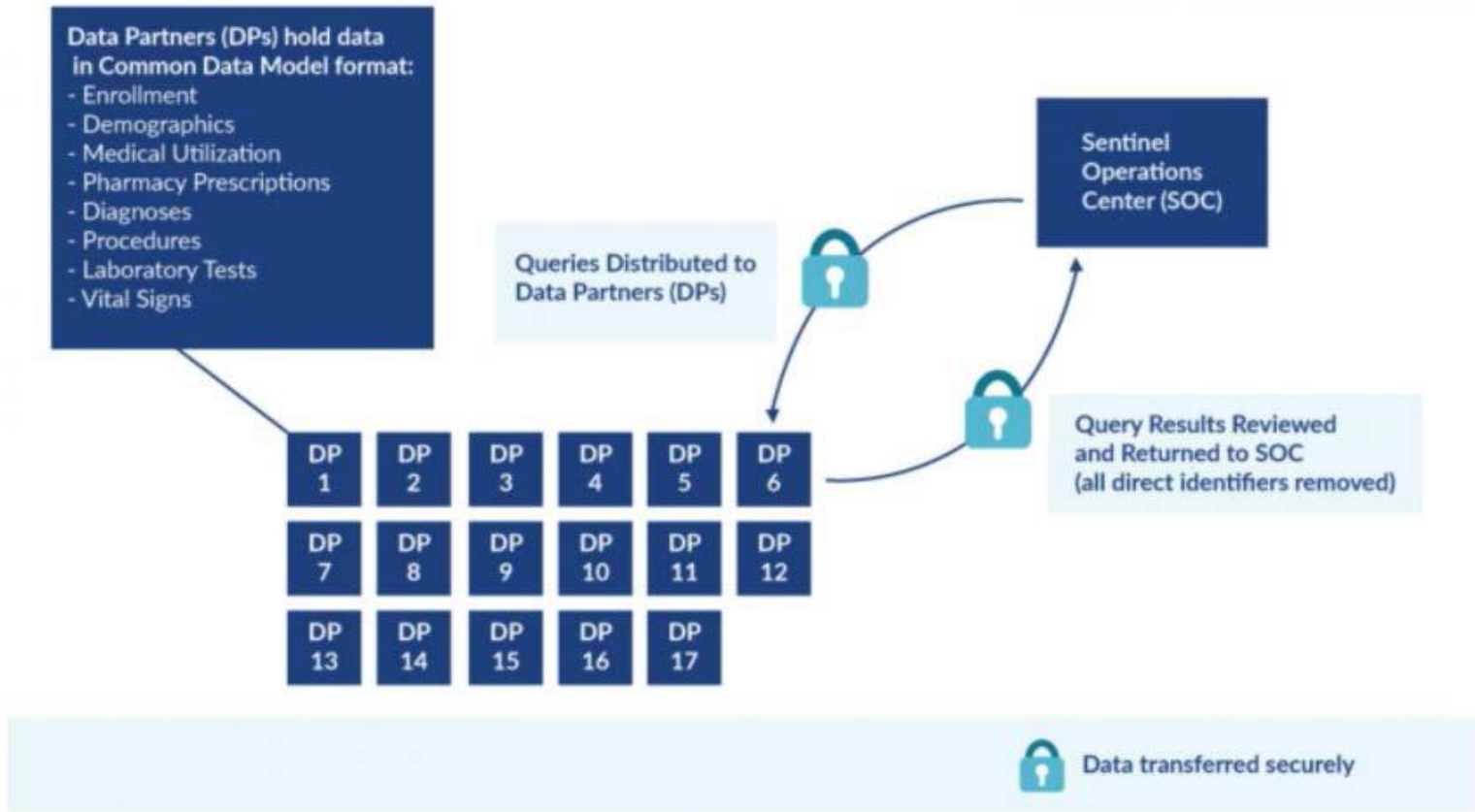
Lead – HPHC Institute

Data and scientific partners

Scientific partners

Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Sentinel Distributed Database Ensures Data Security



Source: FDA's Sentinel Webpage access Sep 9, 2019 at link: https://www.fda.gov/safety/fdas-sentinel-initiative

Select Postmarketing Data Sources

- Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Scientific literature publications
- Postmarketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials
- Other surveillance tools
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel
  - National Electronic Injury Surveillance System -- Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)
  - National Poison Data System (NPDS)

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm.

REMS

- Designed to achieve specific goals to mitigate risks associated with use of a drug.
- FDA specifies the required elements of a REMS.
- Drug sponsors develop the REMS program based on required elements. FDA reviews and approves the REMS.
- Each REMS has specific safety measures that are targeted to the serious risk(s) associated with the drug or class of drugs.
- All REMS include elements, communication, and/or educational materials to communicate risk information to various stakeholders.

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Considerations in determining the need for a REMS

- Estimated size of the population likely to use the drug
- Seriousness of the disease or condition being treated
- Expected benefit of the drug
- Duration of treatment
- Seriousness of any known or potential adverse effects
- Drug is a new molecular entity

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Goal(s) of a REMS

- All REMS should include a statement of one or more goals
- If element(s) to assure safe use (ETASU), must include one or more goals to mitigate a serious risk listed in the labeling
- Assessments of approved REMS should measure whether the goals are being met

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Possible Components of a REMS

- A REMS can include
  - Medication Guide or Patient Package Insert
  - Communication Plan for Healthcare Providers (HCPs)*
  - Elements to Assure Safe Use (ETASU)
  - Implementation System

- Must include a timetable for submission of assessments of the REMS

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Examples of the Types of Risk REMS Requirements Aim to Mitigate

Risk Example	Possible REMS Action
Serious infection	Patient education on initial warning signs prior to prescribing
Severe allergic reaction	Healthcare professional must be certified prior to administer the product
Liver damage	Liver function monitoring while patient is taking the drug
Severe birth defects	Negative pregnancy test prior to dispensing each prescription

Source: Slides from Division of Risk Management on Risk Management in US available at link: https://www.fda.gov/media/94339/download

Possible Components of a REMS

A REMS can include one or more of the following:

- Medication Guide (MG) or Patient Package Insert
- Communication Plan (CP) for Healthcare Providers
- Elements to Assure Safe Use (ETASU)
- Implementation System

Source: Slides from CDER SBIA Webinar on REMS available at link: https://www.fda.gov/media/105565/download

Major Changes (PAS): Examples

- **Process Changes including but not limited to:**
  - Recovery procedures; change in a column; change in processing steps
- **Changes to Analytical Methods:**
  - Establish a new method, changes to specifications, eliminate a test, etc.
- **Changes to Excipients**
- **Changes to Reference Standards**
- **Significant manufacturing changes or addition of new manufacturing sites**
  - Scale up or Scale out of the manufacturing process
- **Facility changes that could introduce contaminations or cross-contaminations**

Moderate Changes (CBE-30): Examples

- Change in the site of compendial tests from one facility to another (e.g., Sterility/Endotoxin tests from an existing contract lab to a new contract lab; from the applicant to a new contract lab).
- Change in the structure of a legal entity that would require issuance of a new license(s), or change in name of the legal entity or location that would require reissuance of the license(s).

Minor Changes (CBE): Examples

Any previously agreed upon changes to the manufacturing process or testing as a part of the NDA/ANDA review

- Addition of release tests and/or specifications
- Addition of in-process tests
- Tightening of specifications for intermediates

FDA can, upon a review of the submission, change the submission category

- In the event of a recategorization of the application, the applicant will be notified.

Annual Report Reportable Changes: Examples

- Changes to the supplier of manufacturing reagents
  - Without changing the type of reagents or quality (Example: Buffers, nonanimal derived reagents)
- Minor changes to manufacturing equipment (replacement of centrifuges, laboratory equipment, biosafety safety hoods, etc.)
- Administrative changes (changes to the management/technical teams)
- The report shall also include all information related to each change made during the annual reporting period

Withdrawal of Approval

- FDC Act §505(e)
  - 5 Mandatory bases (“shall”)
  - 3 Discretionary bases (“may”)
- 21 C.F.R. §314.150(b)
  - Additional “regulatory” bases not in statute
- Formal process requires administrative hearing (substantial effort by FDA)
- Statutory basis for reinstating approval when “the facts so require”
  - FDC Act §505(f)

Source: Past FDLI Courses on topic. See slides at link:
https://www.alston.com/-/media/files/insights/events/2013/11/introduction-to-drug-law-and-regulation/files/view-event-presentation/fileattachment/fdli--post-approval-drug-issues_1-(3).pptx

Medicare – Basics

Eligibility

“Beneficiaries”:

- Part A – no premium payment if:
  - 65 years of age or older; paid Medicare taxes for at least 10 years; and receiving, or eligible to receive, retirement benefits from Social Security or the Railroad Retirement Board
  - Permanent kidney failure requiring dialysis or transplant (“ESRD”) – *regardless of age*
  - Entitled to Social Security or Railroad Retirement Board disability benefits for 24 months - *regardless of age*
  - Government employee, or spouse of government employee
- Part A – with premium payment if:
  - Did not pay Medicare taxes; age 65 or older; and a citizen or permanent resident of the United States,
- Part B –
  - Eligible for Part A and payment of monthly premium

Reference Sources: 42 C.F.R §§ 406.10, 406.20, 406.12, 406.13, 407.10, 407.17; and link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Program Administration

- Centers for Medicare and Medicaid Services (“CMS”) formerly known as “Health Care Financing Administration” (“HCFA”)
  - Operational control over Medicare Program
- CMS Central Office (Baltimore, Maryland)
- CMS Regional Offices
  - Boston (Region 1), New York (Region 2), Philadelphia (Region 3), Atlanta (Region 4), Chicago (Region 5), Dallas (Region 6), Kansas City (Region 7), Denver (Region 8), San Francisco (Region 9) and Seattle (Region 10).
- DHHS Office Of Inspector General (“OIG”)
- State agencies

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Program Administration

- Quality Improvement Organizations (“QIOs”)
- Medicare Administrative Contractors (“MACs”)
  - ❑ Private insurers under contract with CMS for:
    - ➢ provider/supplier enrollment
    - ➢ claims payment; and
    - ➢ Appeals
- Part C Insurance Plans
- Part D Prescription Drug Plans (“PDPs”)

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Regulations

- 42 C.F.R. § 406– Part A Eligibility
- 42 C.F.R. § 407—Part B Eligibility
- 42 C.F.R. § 412—Inpatient Hospital PPS
- 42 C.F.R. § 413—End Stage Renal Disease
- 42 C.F.R. § 416—Ambulatory Surgery Services
- 42 C.F.R. § 420—Program Integrity
- 42 C.F.R. § 424—Assignment/Reassignment
- 42 C.F.R. § 1000-1008—OIG Regulations

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics
Sources of Law and Policy

- Medicare Manuals
  - Repository of operating instructions, policies, and procedures to administer CMS programs.
  - Based on interpretations of statutes and regulations
  - Drafted for CMS agencies, contractors, and State survey agencies
  - Useful for many others as source of technical and professional information about the Medicare and Medicaid
- Paper Manuals
  - Original manual system (e.g., Medicare Carrier's Manual)
- Internet Only Manuals ("IOM")
  - CMS has moved most of the manuals into new IOM
  - IOM is organized by functional area (i.e., program integrity, eligibility, entitlement, claims processing, etc.).
  - Once all information is moved to the IOM the paper based manuals will be discontinued

Source for Manuals: http://www.cms.hhs.gov/manuals/; and link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare - Basics
Provider/Supplier Enrollment

CMS Forms 855

- Health Care Providers that will bill Medicare fiscal intermediaries* (CMS 855A)
- Health Care Providers that will bill Medicare carriers* (CMS 855B)
- Individual Health Care Practitioners (CMS 855I)
- Individual Reassignment of Benefits (CMS 855R)
- DMEPOS Suppliers that bill DMERCS (CMS 855S)

**All FIs and Carriers are being switched to MACs and DMACS*

Source links: http://www.cms.hhs.gov/providers/enrollment/forms/; and link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Medicare Lingo

“Provider vs. Supplier”

–“Provider” is a Part A term which includes:

- Hospital
- Skilled nursing facility (“SNF”)
- Comprehensive outpatient rehabilitation facility (“CORF”)
- Home health agency (“HHA”)
- Hospice
- Critical access hospital (“CAH”)
- Outpatient physical therapy or speech pathology services
- Community mental health center furnishing partial hospitalization services

Sources: 42 C.F.R. § 400.202; link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Medicare Lingo

“Provider vs. Supplier”

–“Supplier” is a Part B term which includes:

- Durable medical equipment prosthetic orthotic suppliers (“DMEPOS”)
- Ambulatory Surgery Center (“ASC”)
- Independent Diagnostic Testing Facility (“IDTF”)
- Physicians

Sources: 42 C.F.R. § 400.202; and link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Medicare Lingo

- Advanced Beneficiary Notice (“ABN”)
  - –Informs beneficiaries of items/services not covered by Medicare
  - –Applies to providers and suppliers
  - –Must be in writing
  - –Must be provided before items/services provided
  - –Must conform to certain requirements and inform beneficiary why coverage is not anticipated and extent of anticipated charge

- Notice of Non-Coverage
  - –Specific to hospital inpatients
  - –Care is not covered because (i) it is not medically necessary, (ii) it is not delivered in the most appropriate setting, or (iii) is custodial

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare – Basics

Medicare Lingo

Assignment vs. Reassignment

- –Determination of who receives payment for items, services, or supplies furnished to beneficiaries
- –Assignment requires that payment for covered items, services, or supplies go to the provider/supplier and not the beneficiary
- –Reassignment permits provider/supplier to redirect payment to another person or entity
- –General rule is against reassignment, unless the criteria of an exception are met
- –Providers/suppliers accepting assignment may not charge beneficiaries more than the Medicare payment amount
- –Physicians rejecting assignment may charge up to 115% of the fee schedule amount (i.e., no more than 115% of 80% of the fee schedule amount).

Sources: 42 U.S.C.A. § 1395u(b)(3)(B); 42 U.S.C.A.§§ 1395w-4(g)(2)(C); 42 C.F.R. §424; Medicare Carriers Manual §§ 3045.1, 3060; link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Primary Types of Medicare Advantage Plans

Private Fee for Service (PFFS) Plans

- Pays providers on a fee-for-service basis through contracts or “deeming” that providers accept fees and terms
- From 2011, individual PFFS plans in a service area with two or more network MA plans must have a contracted provider network

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Medicare – Basics

Medicare Lingo

- Shared Federal-State Program Since 1965
  1. CM[M]S
  2. Single State Agency
- Federal Rule Compliance Required for Federal Financial Participation (FFP) or will be withheld
- States Not Required to Participate
  - Arizona last state to join in 1982
  - Currently 54 Medicaid Programs: 50 States, District of Columbia, Puerto Rico, USVI, Guam & American Samoa
- Significant Variety in the Programs
  - Eligibility
  - Services Covered,
  - Administration (e.g. reimbursement rules)

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicaid Eligibility

- Mandatory Categorically Needy With Various Income Guidelines
  - Pregnant Women
  - Infants up to Age 1
  - Children Age 1-5
  - Children ages 6 to 19
  - Parents at state's 1996 AFDC levels (likely less than 50% FP Guidelines)
  - Elderly and Disabled persons receiving SSI
- Optional Categorically Needy: higher income, resources
- Optional Medically Needy
  - Varies: parents of covered children, disabled, blind, aged individuals
- Legal Immigrants – five year waiting period
- Medicaid Expansion Population – Non-Custodial Adults

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Primary Types of Medicare Advantage Plans

Coordinated Care Plans

- **Health Maintenance Organization (HMO)** – care through contracted network of providers
- **Preferred Provider Organization (PPO)** – contracted network plus out-of-network benefits
- **Special Needs Plan (SNP)** – for individuals with special needs such as nursing home residents, people with chronic or disabling conditions, or Medicaid eligibles

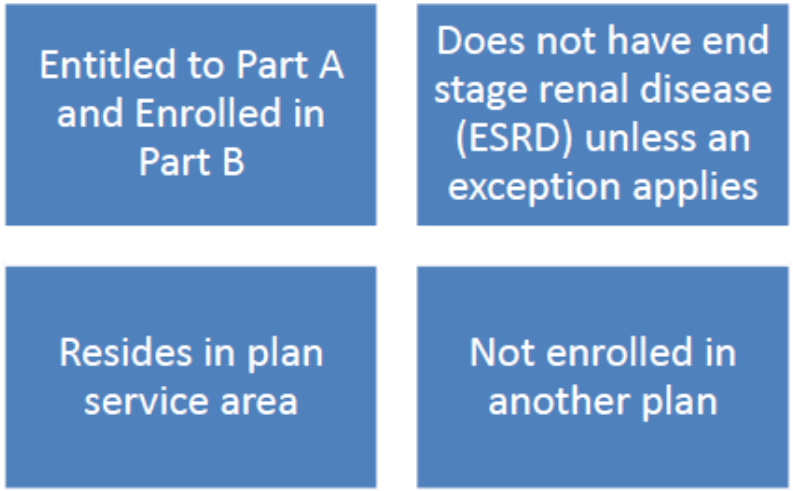
Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Medicare Advantage Plan Benefits

- Must cover all services covered under Original Medicare
- Can design own benefit structure with co-payments, coinsurance, deductibles or no deductibles
- May offer supplemental benefits
- Follow National and Local Medicare Coverage Determinations and Coverage Guidelines
- May employ utilization management
- Generally must have quality improvement and chronic care management programs
- Mandated out-of-pocket maximum for year

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Eligibility for Medicare Advantage



Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Primary MA Election Periods

Initial Election Period (IEP)	• 7 month period beginning 3 months before eligible for Parts A and B and ending 3 months after month of eligibility
Annual Election Period (AEP)	• Fall Open Enrollment • October 15 through December 7
Special Election Periods (SEPs)	• Based on numerous special circumstances such as change in residence or plan termination • Ongoing SEP for Medicaid eligible and institutionalized • Ongoing SEP to enroll in 5-Star plans

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Provider Network

- MA plans must maintain a network that meets care access requirements
- Need written provider agreements that contain provisions required by regulations
- Regulated credentialing process – initial and recredentialing at least every three years
- “Non-interference clause” – government is not involved in rate negotiations or disputes between plan sponsors and providers

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Providers and Marketing

- Providers may not
  - attempt to induce or steer beneficiaries to a particular plan or plans
  - accept enrollment forms
  - accept compensation directly or indirectly from plan for enrollment activities

- Providers may
  - provide names of plans with which they contract
  - distribute plan marketing materials (not in an exam room setting and not including enrollment applications) for a subset of contracted plans if option available to all contracted plans
  - refer patients to medicare.gov plan comparison tool and print information

- Other CMS requirements abound

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Resources: Medicare, Medicaid, and Reimbursement Topics

MA

- Title XVIII of the Social Security Act, Part C, §1851, et. seq., 42 U.S.C. § 1395w- 21, et seq.
- 42 C.F.R. Part 422
- CMS Medicare Managed Care Manual
- Additional CMS guidance, including HPMS memos sent to plan sponsors

Part D

- Title XVIII of the Social Security Act, Part D, § 1860D- 1, et seq., 42 U.S.C. § 1395w101, et. seq.
- 42 C.F.R. Part 423
- CMS Medicare Prescription Drug Benefit Manual
- Additional CMS guidance, including HPMS memos sent to plan sponsors

Source link: https://www.healthlawyers.org/events/programs/materials/documents/mm14/a_alexander_evans_lippincott_slides.pdf

Definitions (Section 581 of the FD&C Act)

- Dispenser
- Distribute
- Illegitimate product
- Manufacturer
- Package
- Product
- Product identifier
- Quarantine
- Repackager
- Return
- Standardized numerical identifier
- Suspect product
- Trading partner
- Transaction
- Transaction history
- Transaction information
- Transaction statement
- Wholesale Distributor
- Among others…

Source: See DSCSA resources slide in back-up

Scope of the law*

Product

- What's covered:
  - Prescription drug in finished dosage form for administration to a patient without further manufacturing (such as capsules, tablets, lyophilized products before reconstitution)
- What's not covered:
  - Blood or blood components intended for transfusion
  - Radioactive drugs or biologics
  - Imaging drugs
  - Certain IV products
  - Medical gas
  - Homeopathic drugs
  - Lawfully compounded drugs

Transaction

- Transfer of product where a change of ownership occurs
- Exemptions
  - Intracompany distributions
  - Distribution among hospitals under common control
  - Public health emergencies
  - Dispensed pursuant to a prescription
  - Product sample distribution
  - Blood and blood components for transfusion
  - Minimal quantities by a licensed pharmacy to a licensed practitioner
  - Certain activities by charitable organizations
  - Distributions pursuant to a merger or sale
  - Certain combination products
  - Certain medical kits
  - Certain IV products
  - Medical gas distribution
  - Approved animal drugs

**Refer to definitions in Section 581(13) for product and 581(24) for transaction for specific information regarding exclusions or exemptions.*

Source: See DSCSA resources slide in back-up

Product tracing

- Beginning 7/1/2015, dispensers in the drug supply chain must exchange information about a drug and who handled it each time it is sold in the U.S. market.

- Manufacturers, repackagers and wholesale distributors – began 1/1/2015

- For each transaction, “product tracing information” should be exchanged. Product tracing information consists of:
  - Transaction *information (TI)* *(which include lot number of product (except for certain wholesale drug distributor transactions))*
  - Transaction *history (TH)*
  - Transaction *statement (TS)*

Source: See DSCSA resources slide in back-up

Definitions: Transaction Information, Transaction History, and Transaction Statement

Transaction Information (TI):

- Proprietary or established name or names of the product;
- Strength and dosage form of the product;
- National Drug Code number of the product;
- Container size;
- Number of containers;
- Lot number of the product;
- Date of the transaction;
- Date of the shipment, if more than 24 hours after the date of the transaction; and
- Business name and address of the person from whom and to whom ownership is being transferred.

Transaction History (TH): A statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.

Transaction Statement (TS): A statement, in paper or electronic form, that the entity transferring ownership in a transaction—

- Is authorized as required under DSCSA;
- Received the product from a person that is authorized as required under DSCSA;
- Received transaction information and a transaction statement from the prior owner of the product, as required under the law;
- Did not knowingly ship a suspect or illegitimate product;
- Had systems and processes in place to comply with verification requirements under the law;
- Did not knowingly provide false transaction information; and
- Did not knowingly alter the transaction history.

Source: See DSCSA resources slide in back-up

FDA established standards

Guidance: DSCSA Standards for the Interoperable Exchange of Information…How to Exchange Product Tracing information

- Can use or build on current systems and processes to comply with the product tracing requirements
- Can use current paper-based or electronic-based methods as long as the selected method(s) allow product tracing information to be exchanged in a manner that complies with the applicable requirements.
- Examples of methods that could be used include, but are not limited to:
  - paper or electronic versions of invoices;
  - paper versions of packing slips;
  - Electronic Data Interchange (EDI) standards, such as the Advance Ship Notice (ASN),
  - EPCIS (Electronic Product Code Information Services)
- Email or web-based platforms are acceptable for transmitting or providing access to the product tracing information, as long as the information that is captured, maintained, and provided is in compliance with the law.

Source: See DSCSA resources slide in back-up

Authorized trading partners are:

- Manufacturers and repackagers with valid registration with FDA
- Wholesale distributors with valid State or Federal license and compliance with reporting requirements; considered authorized before federal licensing regulations effective if possesses valid license under State law
- Third-party logistic providers with valid State or Federal license and compliance with reporting requirements; considered authorized before federal licensing regulations effective, unless FDA makes certain findings and gives notice
- Dispensers with valid State license

Beginning 1/1/2015 - trading partners must be “authorized”

Source: See DSCSA resources slide in back-up

Requests for information

When responding to requests for information from FDA or other appropriate Federal or State official in the event of a recall or for the purpose of investigating a suspect or illegitimate product

- Manufacturers, Wholesale Distributors, Repackagers:

  Shall provide applicable TI, TH, and TS, not later than 1 business day, not to exceed 48 hours after receiving request

- Dispensers:

  Shall provide applicable TI, TH, TS not later than 2 business days (or another reasonable time as determined by FDA) after receiving request; shall not include lot, initial transaction date or initial shipment date unless such information was provided; may respond in paper or electronic format; certain limitations to information requests apply until November 27, 2017.

Source: See DSCSA resources slide in back-up

DSCSA pilot project(s)

- FDA shall establish 1 or more pilot projects
- Coordinate with manufacturers, repackagers, wholesale distributors and dispensers
- Explore and evaluate methods to enhance the safety and security of the pharmaceutical distribution supply chain
- Design: utilization of product identifiers for product tracing and verification, improve technical capabilities needed to utilize product identifiers, identify system attributes that are necessary, other

Source: See DSCSA resources slide in back-up

Definitions: Suspect and illegitimate product

- Suspect Product - reason to believe that product potentially:
  - counterfeit, diverted, stolen
  - subject of fraudulent transaction
  - intentionally adulterated or appears otherwise unfit for distribution such that would result in serious adverse health consequences or death to humans

- Illegitimate Product - credible evidence that the product actually is any of the above

Source: See DSCSA resources slide in back-up

How to handle suspect or illegitimate product

Guidance: Identification of Suspect Product and Notification

- Describes scenarios that increase risk of suspect product for entering supply chain
- Recommendations on how to identify and make determination of suspect product
- Sets forth process to notify FDA and consult with FDA to termination notifications about illegitimate product

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf

  - Proposes draft form FDA 3911: Drug Notification
  - Public docket comments are under review

Source: See DSCSA resources slide in back-up

DSCSA Stakeholders Involved

- Dispenser
- Manufacturer
- Repackager
- Third-party logistics provider
- Wholesale distributor
- FDA
- State officials
- International regulatory counterparts
- Others

Source: See DSCSA resources slide in back-up

DSCSA Resources

- **FDA DSCSA web page:**
  http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm

  - Overview
  - Implementation Plan
  - Links to FDA webinars
  - Regulatory Documents (Guidances, FR notices…)

- **Questions about the DSCSA can be sent to:**
  drugtrackandtrace@fda.hhs.gov

- **Questions about Wholesale Distributor or 3PL requirements can be sent to:**
  wdd3plrequirements@fda.hhs.gov