Compounding Quality Center of Excellence Annual Conference
COMPOUNDING INCIDENT MANAGEMENT
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OBJECTIVES

- Describe the types of adverse event reporting.
- Explain adverse event reporting requirements for outsourcing facilities.
- Highlight data related to the reporting of incidents to FDA's Compounding Incidents Program.
- Describe the surveillance activities of the Compounding Incidents Branch.
- Understand the overall process of investigating compounding incidents.
- Explain the intention of compounding risk alerts and provide examples.
- Discuss examples of compounding incidents investigated by the FDA.

WHAT IS AN INCIDENT?

Types of Reports:

- Adverse Drug Experience
  - 21 CFR 310.305
- Complaints; Examples include:
  - ✓ Product quality issues
  - ✓ Insanitary conditions
  - ✓ Failure of an outsourcing facility to comply with CGMP requirements
  - ✓ False/misleading claims
  - ✓ Office stock from pharmacies compounding under 503A
  - ✓ Copies

Adverse Event Reporting (503A)

- Voluntary reporting
  - 503A facilities generally do not submit reports of adverse events to FDA
  - State-licensed pharmacies, healthcare professionals and consumers
  - MedWatch reports

Adverse Event Reporting (503B)

- Mandatory reporting
  - Section 503B(b)(5) of the FD&C Act requires outsourcing facilities to report adverse events in accordance with content and format requirements established through guidance or regulation under 21 CFR 310.305 (or any successor regulations)
  - 21 CFR § 310.305 "Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications."
  - Outsourcing facilities are required to report:
    - Serious **AND** unexpected adverse events
      - Within **15 calendar days** of receipt
    - Follow-up reports
      - Within **15 calendar days** of receipt of new information or as requested by FDA

Outsourcing Facility Mandatory Adverse Event Reporting

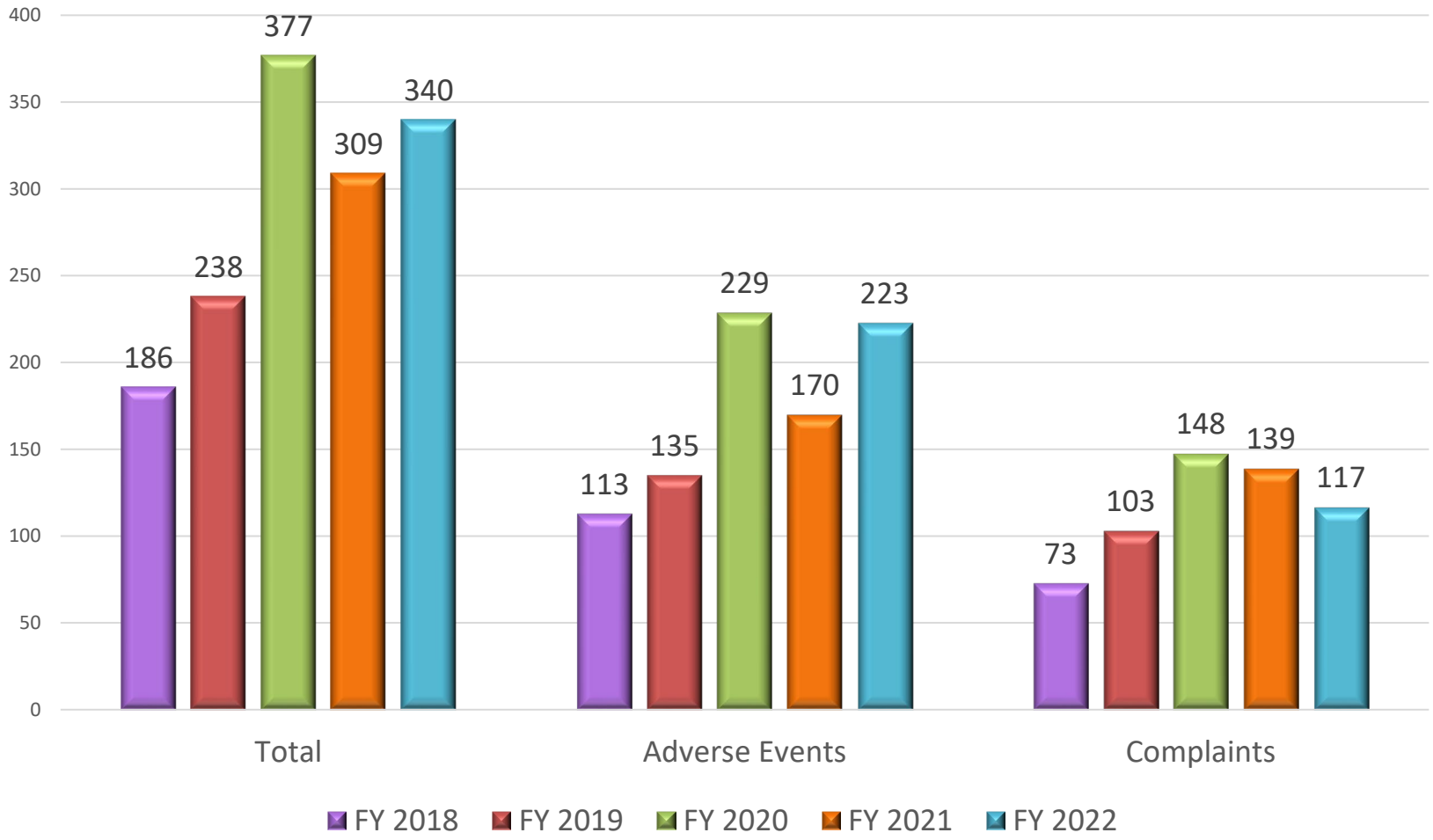
- **Serious adverse drug experience** (as defined in 21 CFR 310.305(b)) is an adverse drug experience where the patient outcome is:
  - Death,
  - Life-threatening adverse drug experience,
  - Inpatient hospitalization or prolongation of existing hospitalization,
  - Persistent or significant disability/incapacity, or
  - Congenital anomaly/birth defect.
  - Medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when they may jeopardize the patient and may require medical or surgical intervention to prevent one of the listed outcomes
- **Unexpected adverse events**
  - Any adverse drug experience that is not listed in the current labeling for *the drug product.*
- FDA strongly recommends that outsourcing facilities **report all serious adverse drug experiences** associated with their compounded prescription drug products.

Outsourcing Facilities: How to Report Adverse Events

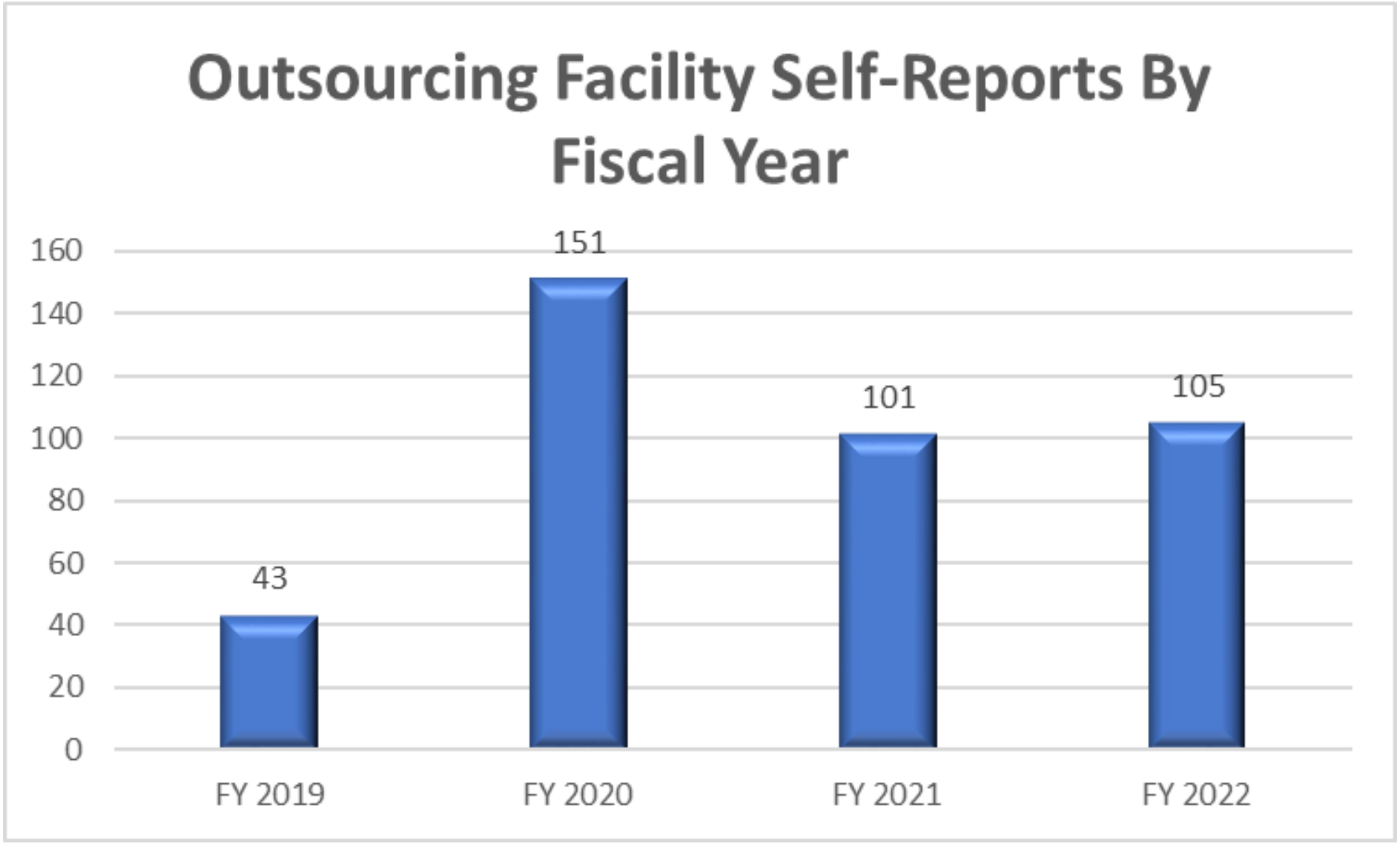
- Adverse event reports must be submitted to FDA electronically:
  1. Safety Reporting Portal (SRP)
     - Requires a free account, which takes 7-10 business days to set up
     - Firm can email FAERSESUB@fda.hhs.gov to advise FDA of their intent to begin submitting via the SRP
  2. Electronic Submissions Gateway (ESG)
     - Database-to-Database Transmission ("E2B")

Adverse Events By Year

TOTAL INCIDENTS BY FISCAL YEAR



Outsourcing Facility Reports By Year



SURVEILLANCE AND CASE PROCESS

CASE PROCESS

Receipt

Triage

Assignment

Research/Review/Follow-Up

Presentation

Action

RECEIPT-REPORT SOURCE

- Sources of Information
  - MedWatch (FAERS DAILY REPORT)
  - Outsourcing Facility Self-Reports
  - Internally within FDA
    - Office of Regulatory Affairs (ORA)
    - Division of Drug Information
  - State regulatory agencies
  - Center for Disease Control and Prevention
  - Professional Organizations
  - Direct email to OCQC

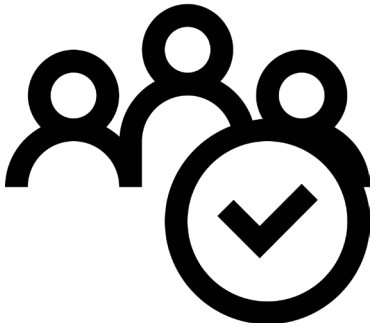
RECEIPT-REPORTER

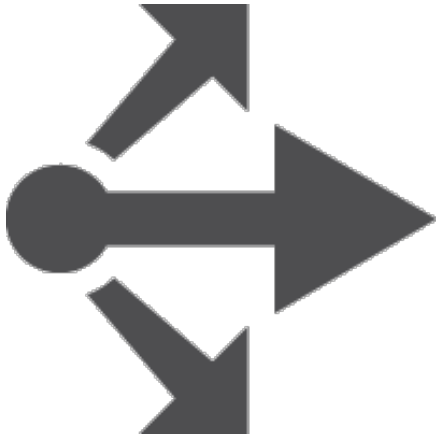
- Consumer
- Healthcare Provider
- Firm Employee or Whistleblower
- State
- Different Firm
- Firm Self-Report
- Other

TRIAGE & ASSIGNMENT

- Log case
- Assign to Incident Consumer Safety Officer (CSO)
- CSO begins research and investigation

Note: We log our cases and the incident is assigned to a Consumer Safety Officer in OCQC Branch 4, who researches and investigates the incident





RESEARCH/REVIEW/FOLLOW-UP

- Research
  - –Firm
- Review
- Follow-Up
  - –Contact reporter to obtain missing or additional information
- Coordinate/Consult
  - –Within OCQC, Other Offices, Centers, Agencies

PRESENTATION

- Weekly Incident Coordination Group (ICG) Meetings
  - Multi-office collaboration of stakeholders in the agency with expertise in various areas such as manufacturing and pharmaceutical quality, drug information, and pharmacovigilance

ACTION

- Example Actions
  - For-Cause Inspection
  - Sample Collection
  - Internal consults with other offices
  - Transfer to other FDA centers and/or offices
  - Referral/Notification to/correspondence with other government agencies or state regulatory authorities
  - Public communication (e.g., CRAs)
  - Drafting of new policies and/or guidances
- Incorporate into Risk Model

COMPOUNDING RISK ALERTS

- Alerts healthcare professionals, compounders and patients of adverse events, drug quality issues, or other issues related to compounded drugs that pose a risk to public health.
- First compounding risk alert posted in August 2017.
- FDA has posted 11 compounding risk alerts to date.
- https://www.fda.gov/drugs/human-drug-compounding/compounding-risk-alerts

Compounding Risk Alert Homepage

Compounding Risk Alerts

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Many serious patient illnesses and deaths linked to poor quality compounded drugs have occurred since the 2012 fungal meningitis outbreak. In response, FDA has established an Incidents Program to identify and prevent outbreaks through surveillance of adverse events and product quality incidents. This effort has led to many actions by FDA including the issuance of compounding risk alerts to inform health care professionals, compounders and consumers about risks associated with compounded drugs, including information on adverse events, outbreaks or product quality. These are intended to alert stakeholders of the risks so that practitioners can more effectively protect patients from unsafe, ineffective and poor-quality compounded medicines.

Please contact compounding@fda.hhs.gov if you have any questions regarding the information provided in a compounding risk alert below:

- FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray (February 16, 2022)
- FDA highlights concerns with compounding of drug products by medical offices and clinics under insanitary conditions (October 25, 2021)
- FDA alerts health care professionals and compounders of potential risks associated with the compounding of remdesivir drug products (February 4, 2021)
- FDA alerts health care professionals of risks associated with intraocular use of compounded moxifloxacin (August 12, 2020)
- FDA highlights concerns with using dietary ingredient glutathione to compound sterile injectables (June 7, 2019)
- Differences in strength expression on product labels of compounders and conventional manufacturers may lead to dosing errors (September 24, 2018)
- FDA alerts health care professionals of significant safety risks associated with cesium chloride (July 23, 2018)

Compounding Incidents Webpage

- https://www.fda.gov/drugs/human-drug-compounding/mitigating-risks-compounded-drugs-through-surveillance

Mitigating Risks of Compounded Drugs Through Surveillance

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Mitigating Risks of Compounded Drugs Through Surveillance

FDA's Compounding Incidents Program aims to help protect the public against poor quality compounded drugs through surveillance and review of complaints, which include adverse event and product quality reports. As the Incidents Program identifies risks related to compounded drugs, it takes action to mitigate these risks. The program also communicates to raise stakeholder and public awareness about risks related to human drug compounding.

- An adverse drug experience is defined as any adverse event associated with the use of a drug in humans, whether or not the event is considered drug-related, including those occurring:
  - in the course of the use of a drug product in professional practice
  - from drug overdose whether accidental or intentional
  - from drug abuse or drug withdrawal
  - any failure of expected pharmacological action
- Other complaints cover a wide range of issues beyond adverse events. Examples include:
  - product quality issues (such as sub- or super-potency, contamination, particulate matter, or pH issues)
  - insanitary conditions within a facility

CASE EXAMPLES

U.S. FOOD & DRUG ADMINISTRATION

CASE EXAMPLE #1

- A 50 y/o female patient who was hospitalized for suspected septic shock with multi-organ failure after receiving IV vitamin infusions
- FDA collaborated with state regulators
- A 5-Item FDA 483 was issued, including:
  - Lack of a certified ISO 5 classified area
  - Peeling paint, stained work surfaces, visibly dirty equipment, and dusty air vents
  - Carpeting in the IV storage and mixing room
  - Standing water in a refrigerator used to store sterile vials
  - Use of expired APIs
- Warning Letter was issued to the firm

CASE EXAMPLE #2

- FDA received multiple serious adverse events (SAEs) reports associated with one lot of Finasteride Plus
  - This specific lot contain undeclared minoxidil
  - Over 33 reports
- FDA collaborated with state regulators
- A 7-item FDA Form 483 was issued to the firm
- Warning Letter was issued to the firm
- The firm recalled the Finasteride Plus product

CASE EXAMPLE #3
GLUTATHIONE INJECTION

- Received reports that multiple patients experienced adverse events , including nausea, vomiting, lightheadedness, body aches, low blood pressure and difficulty breathing, after receiving intravenous injections containing L-glutathione 200mg/mL compounded by two different compounding pharmacies.
- L-glutathione powder repackaged by Letco Medical and used by both pharmacies was a dietary ingredient not intended for use in sterile drugs.
- FDA's analysis revealed excessive bacterial endotoxins levels.
- Compounding Risk Alert was posted on June 7, 2019.
- Ingredients not intended for use in compounding sterile injectable drugs can be harmful when administered to patients.

Questions?


FDA
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ADMINISTRATION