Postmarketing Safety and Risk Management
Positron Emission Tomography Workshop
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Objectives

• Discuss the lifecycle approach to tracking and acting on safety data
• Review how to report adverse events to FDA
• Explain how the agency uses adverse event report information to monitor the safety of marketed products
• Introduce FDA Adverse Event Reporting System (FAERS)
• Delve into reporting trends for positron emission tomography (PET) drugs
• Provide examples of PET drug adverse events and risk mitigation including safety labeling changes, and other communications
Lifecycle Approach to Product Safety Monitoring

Lifecycle Approach to Safety Assessment

Preclinical
Safety & Biological Activity

Phase 1
Safety & Dosage

Phase 2
Safety & Efficacy

Phase 3
Safety & Efficacy

Benefit-Risk Assessment

Yes
No

Safety Monitoring

Strategies and Actions to Minimize Risk

IND – investigational new drug; NDA – new drug application

www.fda.gov
The Void That Pharmacovigilance Fills

Limitations of Clinical Trials
- While completion of phase 1, 2, and 3 trials are the standard for generating evidence to evaluate efficacy and safety, not all potential safety outcomes will be known at the time of approval.
- Because trials are limited in size, duration, and may not always reflect real world use of the drug, it is not uncommon for safety events to emerge after a drug is approved.
- FDA relies on a robust postmarketing surveillance program to detect and evaluate new safety signals. These signals come from a variety of sources.

Postmarketing Adverse Events & FAERS Submission

Under 21 CFR 314.80 individual case safety reports must be submitted to FDA for:
- Expedited reports: Both serious* and unexpected† adverse events from all sources (domestic and foreign).
- Non-expedited 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

*Serious adverse events are those that result 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
†Unexpected: not listed in product’s current labeling
‡Expected: listed in product’s current labeling

FAERS - FDA Adverse Event Reporting System
CFR - Code of Federal Regulations
How to Directly Report Adverse Events to FDA

• How to report:
  – Online (www.fda.gov/medwatch)
  – Download the form
    • Mail
    • Fax 1–800–332–0178
• For questions about the form:
  – 1–800–332–1088

How Does FDA Use FAERS Reports?

• Pharmacovigilance staff review FAERS reports and medical literature reporting a safety concern with a drug
• We consult the prescribing information of the drug to determine if the adverse event reported is already known or is new information
• If a new safety signal is identified, we work with DIRM to open a newly identified safety signal (NISS) and may ask the company to assess the issue too
  • NISS are posted to a public FDA website
• If we determine that a new safety concern should be labeled or communicated to the public, then we work to make that happen
Number of Adverse Event Reports in FAERS for All Products Compared to PET Drugs (N=562) by Year

1/1/2002 – 12/31/2022

- Slides adapted from FAERS Public Dashboard displaying all report types (direct, expedited and periodic) received by the FDA for drugs and therapeutic biologic products.
- FAERS database contains 25,998,916 ICSRs from 1/1/1968 to 12/31/2022
- A case-level analysis was not performed on all reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, healthcare provider), miscoded reports, or unrelated reports.

C - carbon; Cu - copper; F - fluorine; FAERS - FDA Adverse Event Reporting System; Ga - gallium; ICSR - Individual Case Safety Report; N - nitrogen; PET - Positron emission tomography; Rb – rubidium; SrLC – safety-related labeling change

Other Public Communications for PET Radiopharmaceutical Drug Safety-Related Labeling Changes (SrLC)

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Event</th>
<th>SrLC Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubidium Chloride Rb-82</td>
<td>High level radiation exposure with incorrect eluent; quality control testing procedure</td>
<td>04/26/2019</td>
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<tr>
<td>Rubidium Chloride Rb-82</td>
<td>Patient Counseling Information - pregnancy, lactation, post study voiding</td>
<td>10/15/2020</td>
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<tr>
<td>Fluciclovine F-18</td>
<td>Patient Counseling Information – voiding</td>
<td>05/21/2021</td>
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<tr>
<td>Gallium Dotatate Ga-68</td>
<td>Radiation exposures – infants, pregnancy; drug-drug interaction of false negative image with glucocorticoid</td>
<td>06/22/2021</td>
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<tr>
<td>Copper Cu-64 Dotatate</td>
<td>Hypersensitivity reactions</td>
<td>12/22/2021</td>
</tr>
<tr>
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</tbody>
</table>


NDA – new drug application; BLA - biologics license application
An Example of FDA's Risk Mitigation Response
Excess Radiation Exposure
Secondary to Incorrect Eluent Use with Rubidium Chloride Rb-82 Generators

Rubidium Chloride Rb-82 Generators
Incorrect Eluent and Excess Radiation Exposure

**Background**
- Rubidium chloride Rb-82 generator systems produce the Rb-82 chloride tracer on-demand from the parent radioisotope strontium-82 (Sr-82) and are used for PET myocardial perfusion imaging
- Use only additive free 0.9% sodium chloride injection USP to elute the generator

**Event**
- FDA received FAERS reports of events resulting in excess radiation exposure following use of incorrect eluent, including calcium-containing solutions such as Lactated Ringer’s, with the generators that produce rubidium chloride Rb-82
- When calcium is present in a solution, the calcium cation (Ca$^{+2}$) will displace more strontium ion (Sr$^{+2}$) than desired. As a result, the eluate will contain a higher fraction of Sr-82 and Sr-85. This eluate is infused into the patient with higher radioactive exposure from extended half-life of Sr-82 (~25 days) compared to Rb-82 (75 seconds)
  - Long-term health effects are unknown
    - Strontium isotopes can deposit high levels of radioactivity in organs including the bone, potentially leading to suppressed bone marrow function, suppression of the immune system, and increased risk of radiation-induced cancers


Rubidium Chloride Rb-82 Generator and Infusion System (Yoshinaga et al.)

Risk Mitigation Measures and Response
Rubidium Chloride Rb-82 Generators
Incorrect Eluent and Excess Radiation Exposure

- Safety Labeling Changes to rubidium chloride Rb-82 labels reflecting high level radiation exposure with use of incorrect eluent
- Communication to the public and healthcare providers
  - Urged patients who need these imaging scans to continue to get them and to talk to their healthcare providers regarding any concerns about use of these systems
  - Dear Healthcare Provider Letters directed to imaging centers and clinicians
- Additional risk mitigation measures
  - Saline Confirmation Label and Saline Tag applied to the additive free 0.9% sodium chloride injection USP
FDA: Drug Safety Information for the Public

**FAERS Public Dashboard**
An interactive web-based tool that allows for the querying of FAERS data

**Potential Signals**
FDA shares early safety signals or potential signals identified through FAERS

**Communications**
U.S. Prescribing Information, Drug Safety Communications, and other communication tools

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Overall Summary

• FDA continues to monitor all products, including PET drugs, throughout the lifecycle utilizing pharmacovigilance data sources, multidisciplinary teams and a risk-based approach to surveillance

• Voluntary reporting of adverse events associated with drug products, including PET drugs, by healthcare professionals and patients, is an important activity to support the safe use of FDA-approved drugs

• We encourage continued reporting of drug related adverse events through MedWatch: the FDA Safety Information and Adverse Event Reporting Program (https://www.fda.gov/Safety/MedWatch/default.htm)