CDER Office of Surveillance and Epidemiology: 2017 Update

Gerald J. Dal Pan, MD, MHS
Director
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

FDA/CMS Summit
December 5, 2017
Adverse Event Data
FDA Adverse Event Reporting System (FAERS)
Best Practices for Pharmacovigilance

FDAAA 2007 establishes requirement for 18-month/10,000 patient safety review.

“(D) preparing, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number;

Impact analysis show that these reviews have little value.

21st Century Cures Act 2016 removes this requirement

Assessment of the Impact of Scheduled Postmarketing Safety Summary Analyses on Regulatory Actions

S Sekinc1,2, EE Pinnow1, E Wu1, R Kurtzig1, M Hall1 and GJ Dal Pan1

(b) FAERS REVISION.—Section 505(r)(2)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(r)(2)(D)) is amended by striking ‘‘, by 18 months’’ and all that follows through the semicolon at the end of the sub-paragraph and inserting ‘‘and making publicly available on the Internet website established under paragraph (1) best practices for drug safety surveillance activities for drugs approved under this section or section 351 of the Public Health Service Act’’. 
Best Practices for Pharmacovigilance
Drug and Biologics Safety Surveillance Best Practice Statement
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration

The 21st Century Cures Act (the “Cures Act”), enacted on December 13, 2016, has the goal of advancing medical product innovation as well as ensuring patient access to safe and effective treatments as soon as possible. One of the provisions of the Cures Act includes a revision to a previous statutory requirement that generally required FDA to undertake routine safety analyses of drugs 18 months following approval or after 10,000 individuals have used the drug, whichever occurs later. See section 505(r)(2)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) before and after it was amended by the Cures Act. These assessments were largely redundant to our current surveillance practices at the Food and Drug Administration (FDA), were not an efficient use of FDA resources, and did not provide
Improved Access to Adverse Event Reports

For Immediate Release
September 28, 2017

The U.S. Food and Drug Administration today launched a new user-friendly search tool that improves access to data on adverse events associated with drug and biologic products through the FDA’s Adverse Event Reporting System (FAERS). The tool is designed to make it easier for consumers, providers, and researchers to access this information.

"Tools like the FDA Adverse Event Reporting System are critical to the FDA’s ability to help ensure the greatest level of transparency and help patients and providers make safe use of drug and biologic products after they are approved by the FDA," said FDA Commissioner Scott Gottlieb, M.D. "The FDA is committed to fully informing patients and providers of adverse events reported with medical products and this enhanced portal now provides patients, doctors and others with easier access to the data they are interested in."

The new dashboard enables users to search for and organize data by criteria such as drug/biological product, age of the patient, type of adverse event, year the adverse event occurred, or within a specific timeframe. In addition to making it easier for consumers to search for adverse events reported with drug or biologic products, the FDA hopes the increased transparency will spur the submission of more detailed and complete reports from consumers, health care professionals and others, by making it easier for people to see other reports that the FDA receives, and search the database for similar observations.
Sample Dashboard Search
Biotech stocks drop after FDA makes it easier for public to search for drug side effects

- Biotech stocks fell Friday, a day after the U.S. Food and Drug Administration made its database of side effects for medicines searchable.
- Sarepta Therapeutics, Ionis Pharmaceuticals, Biogen and Acadia Pharmaceuticals all traded lower after investors found reports on their drugs on the FDA’s Adverse Events Reporting System.
- It is not clear whether the adverse events were caused by the medicines themselves, or were incidental, an analyst said.

Sarepta’s Exondys 51, approved last year for certain patients with Duchenne muscular dystrophy, or DMD, had 11 reports of serious cases, including three deaths, according to FAERS.

Spinraza, a treatment from Biogen and Ionis for spinal muscular atrophy, or SMA, had 101 reports of serious cases, including 12 deaths.

And Acadia’s Nuplazid, for patients with Parkinson’s, had 1,343 serious case reports, including 483 deaths, FAERS reveals.
NLP and Machine Learning in FAERS
Can Social Media Generate Signals?

Digital Drug Safety Surveillance: Monitoring Pharmaceutical Products in Twitter

Clark C. Freifeld · John S. Brownstein · Christopher M. Menone · Wenjie Bao · Ross Filice · Taha Kass-Hout · Nabarun Dasgupta

- English-language Twitter posts mentioning 23 medical products
- Identified posts resembling adverse events (proto-AEs)
- Vernacular internet terms translated to MedDRA
- Terms aggregated by MedDRA SOC
- 4,401 proto-AEs identified
- High correlation with FAERS at SCO level

Author’s conclusion:

“Patients reporting AEs on Twitter showed a range of sophistication when describing their experience. Despite the public availability of these data, their appropriate role in pharmacovigilance has not been established. Additional work is needed to improve data acquisition and automation.”

Methods Development

Pharmacovigilance from social media: mining adverse drug reaction mentions using sequence labeling with word embedding cluster features

Azadeh Nikfarjam¹, Abeed Sarker¹, Karen O'Conor¹, Rachel Ginn¹, Graciela Gonzalez³

Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products: An Analysis of Recent FDA Safety Alerts

Carrie E. Pierce¹ · Khaled Bouri² · Carol Pamer² · Scott Proestel² · Harold W. Rodriguez¹ · Hoa Van Le¹ · Clark C. Freifeld¹,³ · John S. Brownstein¹ · Mark Walderhaug² · I. Ralph Edwards⁴ · Nabarun Dasgupta¹,³

BMJ Open Utility of social media and crowd-sourced data for pharmacovigilance: a scoping review protocol

Andrea C Tricco,¹,² Wasifa Zarin,¹ Erin Lillie,¹ Ba Pham,¹ Sharon E Straus¹,³

FDA Sentinel System

• 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

www.sentinelinitiative.org/
“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).”

FDAAA = FDA Amendments Act 2007
Active Risk Identification and Analysis

Summary Table (ST)
- Simple counts

Level 1 (L1)
- Complex descriptive analyses

Level 2 (L2)
- Inferential analyses

Modular Programs: Validated, re-usable analytic tools that facilitate rapid safety analyses to be run on high quality electronic healthcare data
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From all FDA Centers, by date of distribution to Data Partners
10th Annual Public Workshop

2018 Sentinel Initiative Annual Public Workshop

February 7, 2018 - 9:00 am
Hyatt Regency Bethesda
1 Bethesda Metro Center
Bethesda, MD 20814

Description
This annual workshop serves as a forum to bring together leading experts and interested stakeholders to discuss the ongoing development of the Sentinel Initiative. The Food and Drug Administration, which sponsors the Sentinel Initiative, leads efforts to establish the Sentinel Network.

Speakers
Dr. Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research

Sentinel and PDUFA

PDUFA V Commitments

• Public stakeholder meeting ✔
• Fund 4 – 6 activities ✔
• Interim Sentinel Assessment ✔
• Final Sentinel Assessment ✔

PDUFA VI Commitments

• Expand data sources and core capabilities
• Enhance communications with sponsors and public
• Evaluate additional ways to facilitate public and sponsor access to Sentinel
• Hold public stakeholder meeting
• Establish MAPPS and SOPPs for sponsor communication
• Integrate Sentinel into drug review
• Develop a comprehensive training program for review staff
• Report impact of Sentinel expansion and integration by FY2022
New Base Contract for Sentinel Coordinating Center

https://www.fbo.gov/index?s=opportunity&mode=form&id=ec59b8dbb36970e2912801aa2cfdd87d&tab=core&cview=0
Making Sentinel Available to Others

• IMEDS shares the same analytic center at Harvard Pilgrim Healthcare as Sentinel
• IMEDS has the same analytic tools and similar database available to FDA
• IMEDS is publicly accessible
• Currently active with multiple analyses ongoing

https://www.sentinelinitiative.org/sentinel/reagan-udall-foundation-and-imeds
Real-world Evidence

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P.,
Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H.,
Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D.,
Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D.,
Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.
Risk Evaluation and Mitigation Strategies
Format and Content of REMS Document

- Format and Content of a REMS Document
  - Revised draft guidance
- Includes a section for each participant
  - Who
  - What
  - When
  - With what
Use of a Drug Master File for Shared System REMS Submissions

- Draft guidance issued November 2017
- Intended to improve efficiency
REMS Document and Structured Product Labeling

- REMS into SPL format
  - Draft guidance
- Make REMS information available within existing healthcare systems and workflows
  - Easier sharing of information and incorporation in health information technology
REMS Website

Approved Risk Evaluation and Mitigation Strategies (REMS)

The table below provides links to currently approved individual and shared system REMS. Information on historical and released REMS is available in downloadable data files.

Filter by Keyword (e.g. REMS name, active ingredient, element)

<table>
<thead>
<tr>
<th>Name</th>
<th>REMS Approved</th>
<th>Last Updated</th>
<th>MedGuide (MG)</th>
<th>Comm. Plan (CP)</th>
<th>ETA SU</th>
<th>Imp. Sys (IS)</th>
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Stakeholder Sections

Approved Risk Evaluation and Mitigation Strategies (REMS)

Clozapine
Shared System REMS
REMS last update: 09/10/2013

What do participants need to know?

Below is a general overview of the REMS for all REMS participants (e.g., patients, pharmacies, and healthcare providers). See the application holder(s) REMS Website or the approved REMS materials for more information.

View application holder(s) REMS Website

- Healthcare Providers who prescribe clozapine products must
- Patients who are prescribed clozapine shared system products
- Outpatient pharmacies that support electronic telecommunication verification and that dispense clozapine shared system products must
- Outpatient pharmacies that do NOT support electronic telecommunication verification and that dispense clozapine shared system products must
- Inpatient pharmacies that dispense clozapine shared system products must
- Wholesalers that distribute clozapine shared system products must

View additional drug-specific postmarket safety information from the FDA

Disclaimer: This webpage provides general information about REMS programs to various REMS participants (e.g., patients, pharmacies, and healthcare providers). This summary information provided herein is not comprehensive and may not include all of the information relevant to REMS participants. This webpage does not constitute a replacement, modification, or revision of the approved REMS document, including any appended REMS materials. Refer to the approved REMS document for complete information on the REMS requirements for each approved application.

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 中文 | 한국어 | Tagalog | العربية | Kreyòl Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 | العربية | English
Stakeholder Sections

What do participants need to know?
Below is a general overview of the REMS for all REMS participants (e.g., patients, pharmacies, and healthcare providers). See the application holder(s) REMS Website or the approved REMS materials for more information.

View application holder(s) REMS Website #

To be able to prescribe

- Review the drug’s prescribing information.
- Complete the Knowledge Assessment for Healthcare Providers and submit the successfully completed knowledge assessment to the application holder. | Knowledge Assessment for Healthcare Providers |
- Enroll in the REMS by completing and submitting the Prescriber Enrollment Form | Prescriber Enrollment Form |

Before the first prescription

- Counsel the patient on the risks associated with clozapine including severe neutropenia and the REMS program requirements using What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers | What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers |
- Unless clinical judgment indicates that the patient’s adherence to the treatment regimen will be negatively impacted, provide the patient with What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers | What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers |
- Assess the patient’s absolute neutrophil count (ANC). Document and submit the results to the REMS program via the online system, by fax, or calling the contact center.
- Enroll the patient by completing and submitting the Patient Enrollment Form. Retain a completed copy in the patient’s record | Patient Enrollment Form |

At specified intervals, according to the Prescribing Information for a clozapine product, during treatment

- Assess the patient’s ANC. Document and submit the results to the REMS program via the online system, by fax, or calling the contact center.
- For patients with an ANC that falls below the acceptable range described in the Prescribing Information: assess the patient’s benefits of continuing treatment with the risks of developing severe neutropenia.
- For patients whose continuing treatment benefit exceeds the risk of developing severe neutropenia: document and submit the authorization to continue treatment to the REMS program.

- Patients who are prescribed clozapine shared system products
- Outpatient pharmacies that support electronic telecommunication verification and that dispense clozapine shared system products must
- Outpatient pharmacies that do NOT support electronic telecommunication verification and that dispense clozapine shared system products must
- Inpatient pharmacies that dispense clozapine shared system products must
- Wholesalers that distribute clozapine shared system products must

View additional drug-specific postmarket safety information from the FDA
Framework for Benefit-Risk Counseling to Patients About Drug with a REMS

• Part of REMS Integration Initiative
• Four Es:
  – Evaluate
  – Educate
  – Engage
  – Ensure
Prescription Opioid Abuse
Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015

Any Opioid

Heroin

Natural & Semi-Synthetic Opioids

Other Synthetic Opioids (e.g., fentanyl, tramadol)

Methadone

Opioids

• A busy year!

• Six of seven Drug Safety and Risk Management Advisory Committee meetings 2017 concerned opioids

• Three public meetings:
  – Packaging, Storage, and Disposal Options To Enhance Opioid Safety--Exploring the Path Forward, December 11-12, 2017
  – Training for Opioid Analgesic Prescribers, May 9-10, 2017
Opana ER

FDA requests removal of Opana ER for risks related to abuse

For Immediate Release

June 8, 2017