

CDER Office of Surveillance and Epidemiology: 2017 Update

Gerald J. Dal Pan, MD, MHS

Director

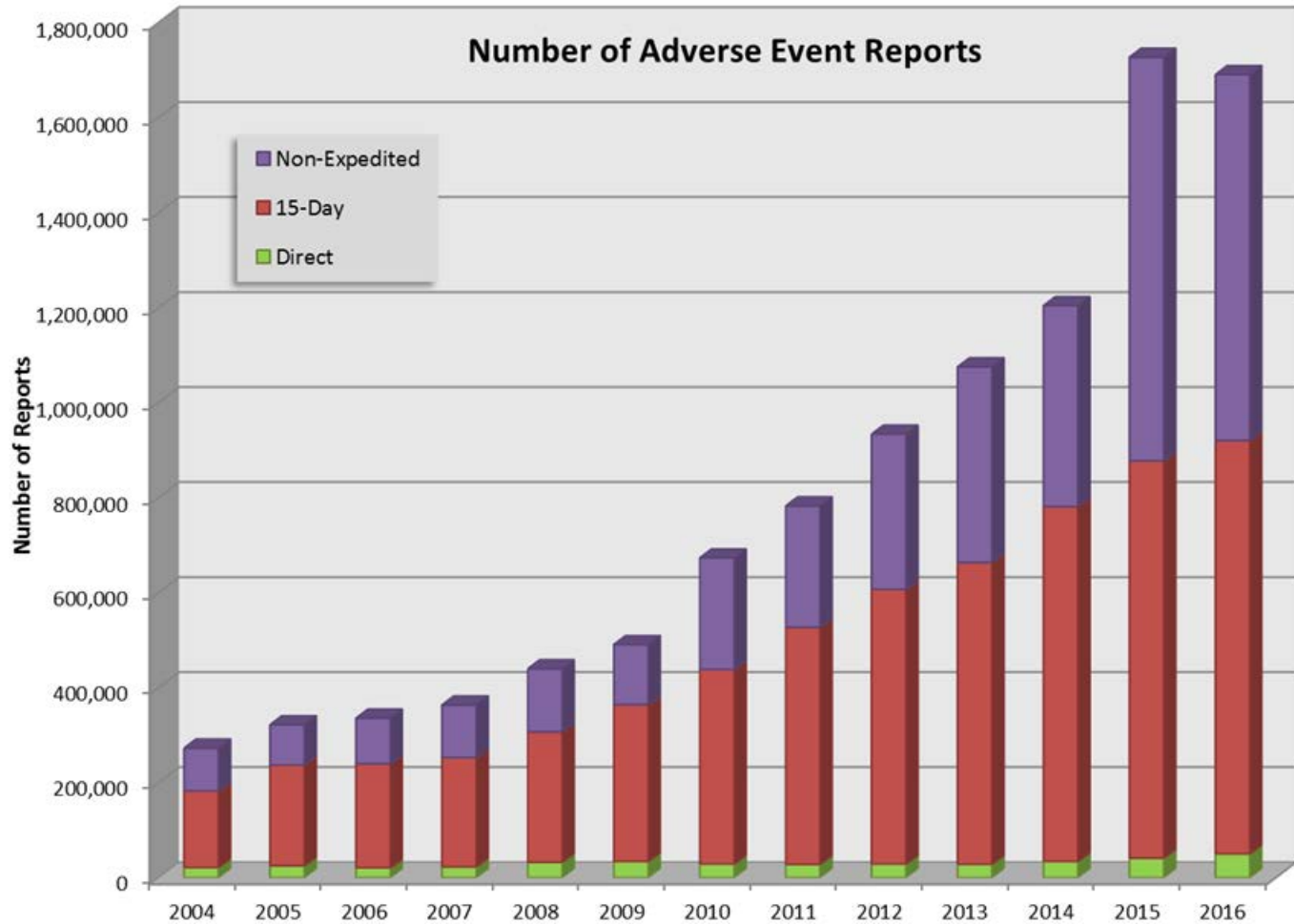
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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;



ARTICLES

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

S Sekine^{1,2}, EE Pinnow¹, E Wu¹, R Kurtzig¹, M Hall¹ and GJ Dal Pan¹



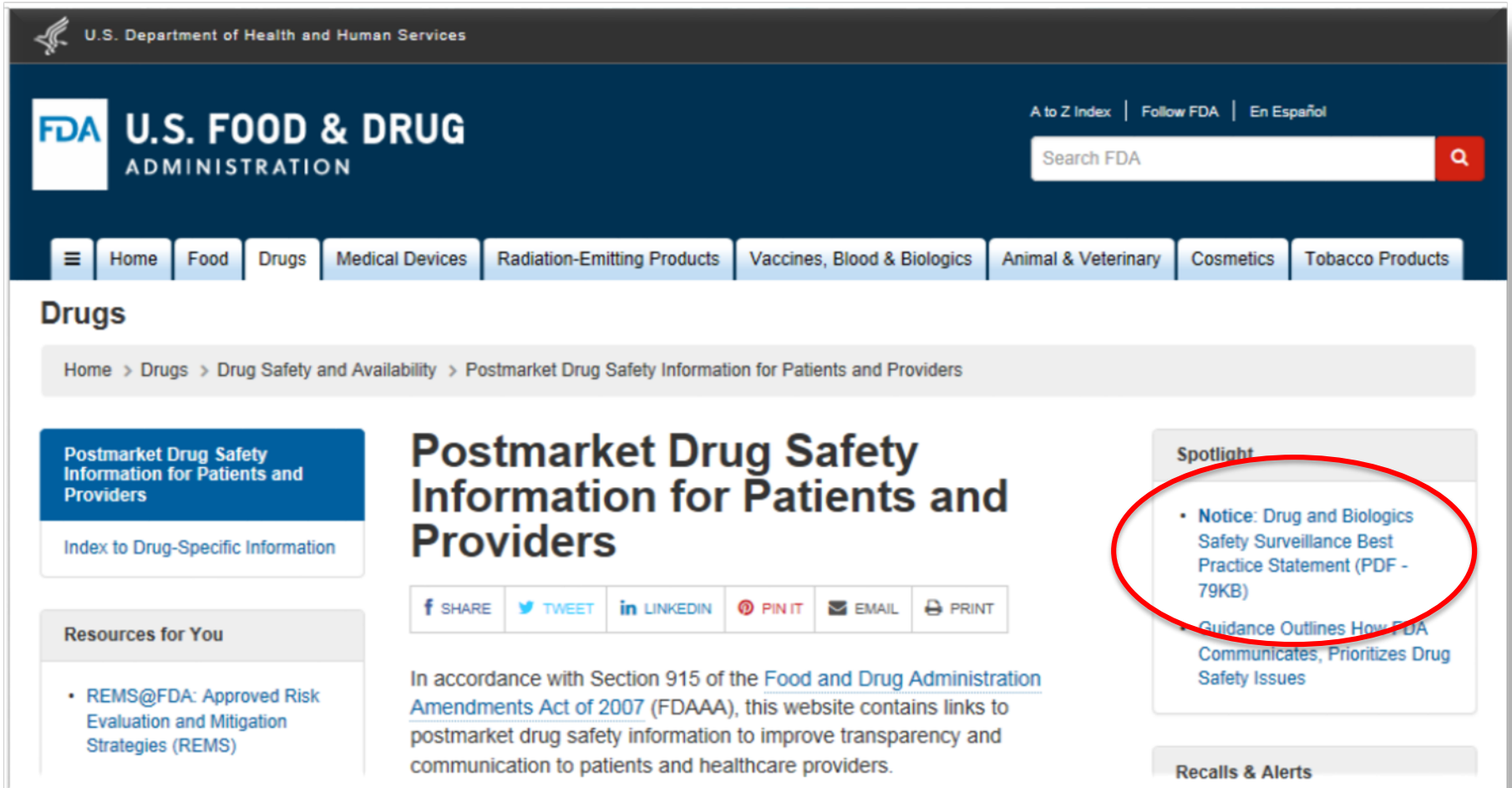
Impact analysis show that these reviews have little value.

21st Century Cures Act 2016 removes this requirement



(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 subparagraph 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



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Tobacco Products

Drugs

Home > Drugs > Drug Safety and Availability > Postmarket Drug Safety Information for Patients and Providers

Postmarket Drug Safety Information for Patients and Providers

Index to Drug-Specific Information

Resources for You

- REMS@FDA: Approved Risk Evaluation and Mitigation Strategies (REMS)

Spotlight

- Notice: Drug and Biologics Safety Surveillance Best Practice Statement (PDF - 79KB)
- Guidance Outlines How FDA Communicates, Prioritizes Drug Safety Issues

Recalls & Alerts

Postmarket Drug Safety Information for Patients and Providers

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

In accordance with Section 915 of the [Food and Drug Administration Amendments Act of 2007 \(FDAAA\)](#), this website contains links to postmarket drug safety information to improve transparency and communication to patients and healthcare providers.

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



The screenshot shows the FDA website's news release page. At the top, there is a navigation bar with the FDA logo, the text 'U.S. FOOD & DRUG ADMINISTRATION', and a search bar. Below the navigation bar are several menu items: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The main content area is titled 'News & Events' and features a breadcrumb trail: Home > News & Events > Newsroom > Press Announcements. The news release is dated September 28, 2017, and is categorized as 'For Immediate Release'. The headline is 'FDA improves access to reports of adverse drug reactions', with a sub-headline: 'New online tool makes it easier for users to search the FDA Adverse Event Reporting System'. The release text states that the FDA has launched a new user-friendly search tool to improve 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. A quote from FDA Commissioner Scott Gottlieb, M.D., emphasizes the importance of transparency and the FDA's commitment to fully informing patients and providers of adverse events reported with medical products. The release concludes by stating that 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. On the right side of the page, there are sections for 'Inquiries' (Media contact: Lauren Smith Dyer, 301-348-1888; Consumers contact: 888-INFO-FDA) and 'Follow FDA' (social media links for @US_FDA, Follow FDA, and @FDAmedia).

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA improves access to reports of adverse drug reactions

New online tool makes it easier for users to search the FDA Adverse Event Reporting System

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release September 28, 2017

Release

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.

Inquiries

Media

Lauren Smith Dyer
301-348-1888

Consumers

888-INFO-FDA

Follow FDA

Follow @US_FDA
Follow FDA
Follow @FDAmedia

Sample Dashboard Search

FDA Adverse Events Reporting System (FAERS) Public Dashboard

Search Term: EXONDYS 51

Total Cases: 11

Severe Cases (Including Death): 11

Death Cases: 0

Resolved Year or Outcome: 2017

Reaction Group and Reaction

Outcome counts by Resolved Year and Outcome

Number of Cases

Legend: Die, Hospitalized, Other Outcomes

Total Cases

- General Disorders And Administration Site Conditions: 6
- Respiratory, Thoracic And Mediastinal Disorders: 6
- Infections And Infestations: 4
- Cardiac Disorders: 3
- Injury, Poisoning And Procedure Complications: 3
- Neurological Disorders: 2
- Hyperkalemia: 1
- Flushing: 1

Source of August 11, 2017

This page displays the number of cases identified for the product of interest by "Reaction Group", "Reaction", patient age and sex, and report outcome. A case may describe one or more "Reaction Group", "Reaction", or outcome. "Reaction Groups" are based on a classification of the side effect (also known as "Reaction" or adverse event or adverse drug reaction), using the MedDRA dictionary of adverse event terms. For example, "Cardiac Disorders" is one of the "Reaction Groups" defined by the MedDRA dictionary as a grouping of several related "Reactions" such as "Cardiac Arrest" and "Cyanosis." "Reaction" corresponds to the suspected reaction reported by the reporter. The "Reaction" is based on the MedDRA dictionary ("Preferred Term (PT)", including one or more of those outcomes or suspected reactions in a report does not necessarily mean that the suspect product of interest was the cause of the reported outcome or reaction. A case may have one or more reported outcomes.

FDA Adverse Events Reporting System (FAERS) Public Dashboard

Search Term: SPINRAZA

Total Cases: 383

Severe Cases (Including Death): 181

Death Cases: 12

Case Count by Reaction

Category	Number of Cases	Percentage
Headache	81	21.15%
Nausea	38	9.92%
Post Lumbar Puncture Syndrome	23	5.98%
Back Pain	18	4.70%
Fatigue	15	3.92%
Constipation	12	3.13%
Nasals	11	2.87%
Head	11	2.87%
Upper Respiratory Tract Infection	9	2.35%
Pneumonia	8	2.09%
Drug Ineffective	7	1.83%

Case Count by Reaction

Legend: Headache, Nausea, Post Lumbar Puncture Syndrome, Back Pain, Fatigue, Constipation, Nasals, Head, Upper Respiratory Tract Infection, Pneumonia, Drug Ineffective, Pulverized Protein

Total: 383 / 100.00%

Source of August 11, 2017

This page displays the number of cases identified for the product of interest by "Reaction", "Reaction" is the suspected side effect (also known as adverse event or adverse drug reaction) reported by the reporter and is based on the MedDRA dictionary ("Preferred Term (PT)", A "Reaction" is a unique medical concept for a symptom, sign, disease, diagnosis, the toxicologic indication, investigator, surgical or medical procedure, etc. A case may contain more than one "Reaction".

FDA Adverse Events Reporting System (FAERS) Public Dashboard

Search Term: NUPLAZID

Total Cases: 4,488

Severe Cases (Including Death): 1,340

Death Cases: 493

Listing of Cases

Case ID	Suspect Product Name	Suspect Product Active Ingredients	Reason for Use	Reactions	Severity	Outcomes	Sex	Event Date	Received Date	Case Priority	Patient Age	Patient Weight	Sender	Rep. Type	Country
1382586	NUPLAZID	Paroxetine Tartrate	Depression/Medication/Ph... Disease/Depression	Renal Disorder/Aggravat...	Severe	Hospitalized	Male	-	31-AUG-2017	Expedited	Not Specified	Not Specified	Acacia Pharmaceutical...	Consumer	US
1388766	NUPLAZID	Paroxetine Tartrate	Antipsychotic Therapy/Depressive With... Leaky	GI Disturbance/Diar... Stool/Perianth...	Severe	Other Outcomes	Female	JUL-2017	31-AUG-2017	Expedited	77 YR	68.27 KG	Acacia Pharmaceutical...	Consumer	Aggrav. Tram... DI/Carbidoip...
1388780	NUPLAZID	Paroxetine Tartrate	Paroxetine S... Disease/Product Used For... Unknown Indication	Anxiety/Anxiety	Severe	Hospitalized	Male	25-JUL-2017	31-AUG-2017	Expedited	72 YR	Not Specified	Acacia Pharmaceutical...	Consumer	Greenet, Rep...
1382964	NUPLAZID	Paroxetine Tartrate	Depression/Medication/Ph... Disease/Product Used For... Unknown Indication	Hallucination/Pho... Tact/Infection/Drug... Infectious/Dement...	Severe	Hospitalized	Female	2017	31-AUG-2017	Expedited	82 YR	Not Specified	Acacia Pharmaceutical...	Consumer	Lansdowne, St...
1391936	NUPLAZID	Paroxetine Tartrate	Paroxetine S... Disease	Death	Severe	Die	Male	-	30-AUG-2017	Expedited	Not Specified	Not Specified	Acacia Pharmaceutical...	Consumer	US
1391937	NUPLAZID	Paroxetine Tartrate	Depression/Medication/Ph... Disease/Depression/Ph... Schedule Of Drug... Administration/Co...	Inappropriate	Severe	Hospitalized	Male	15-AUG-2017	30-AUG-2017	Expedited	61 YR	Not Specified	Acacia Pharmaceutical...	Consumer	Zichroms
1391938	NUPLAZID	Paroxetine Tartrate	Depression/Medication/Ph... Disease/Depression	Feeling	Severe	Hospitalized	Female	13-AUG-2017	30-AUG-2017	Expedited	88 YR	Not Specified	Acacia Pharmaceutical...	Consumer	US
1391934	NUPLAZID	Paroxetine Tartrate	Paroxetine S... Disease	Non-specific Reaction	Severe	Hospitalized	Female	-	30-AUG-2017	Expedited	Not Specified	Not Specified	Acacia Pharmaceutical...	Consumer	US

Source of August 11, 2017

Media Article





HOME U.S. NEWS MARKETS INVESTING TECH MAKE IT VIDEO SHOWS MORE 

BIOTECH AND PHARMACEUTICALS

HEALTH CARE | HOSPITALS | PHARMA | HEALTH INSURANCE | MODERN MEDICINE

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 493 deaths, FAERS reveals.

NLP and Machine Learning in FAERS

Research and Applications

Development of an automated assessment tool for MedWatch reports in the FDA adverse event reporting system

Lichy Han,¹ Robert Ball,² Carol A Pamer,² Russ B Altman,^{3,4} and Scott Proestel²

¹Biomedical Informatics Training Program, Stanford University, Stanford, CA, USA, ²Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA, ³Department of Genetics, Stanford University and ⁴Department of Bioengineering, Stanford University

Corresponding Author: Scott Proestel, Division of Epidemiology, Office of Biostatistics and Epidemiology, FDA Center for Biologics Evaluation and Research, White Oak Building 71, Room 1260, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA. Phone: (240) 402-0396. E-mail: Scott.Proestel@fda.hhs.gov

Received 1 September 2016; Revised 30 January 2017; Accepted 24 February 2017

ABSTRACT

Objective: As the US Food and Drug Administration (FDA) receives over a million adverse event reports associated with medication use every year, a system is needed to aid FDA safety evaluators in identifying reports most likely to demonstrate causal relationships to the suspect medications. We combined text mining with machine learning to construct and evaluate such a system to identify medication-related adverse event reports.

Methods: FDA safety evaluators assessed 328 reports for medication-related causality. We engineered features from these reports and constructed random forest, L1 regularized logistic regression, and support vector machine models. We evaluated model accuracy and further assessed utility by generating report rankings that represented a prioritized report review process.

Results: Our random forest model showed the best performance in report ranking and accuracy, with an area under the receiver operating characteristic curve of 0.66. The generated report ordering assigns reports with a higher probability of medication-related causality a higher rank and is significantly correlated to a perfect report ordering, with a Kendall's tau of 0.24 ($P = .002$).

Conclusion: Our models produced prioritized report orderings that enable FDA safety evaluators to focus on reports that are more likely to contain valuable medication-related adverse event information. Applying our models to all FDA adverse event reports has the potential to streamline the manual review process and greatly reduce reviewer workload.

Key words: drug-related side effects and adverse reactions, supervised machine learning

BACKGROUND AND SIGNIFICANCE

The US Food and Drug Administration (FDA) receives more than 4000 medication safety reports every day, and the number of reports received each year has been increasing exponentially over the last decade. These reports are stored in a database known as the FDA Adverse Event Reporting System (FAERS), which has collected over 11 million reports since its inception in 1969.¹ In the United States,

reporting these adverse events, medication errors, and product quality issues by health care professionals and consumers via the MedWatch program is voluntary, but it is mandatory for drug manufacturers.² The FDA uses these reports to detect safety issues that may not have been identified during pre-market clinical trials used as the basis for medication approval. Among the reasons for not detecting safety issues during pre-market evaluation are that the

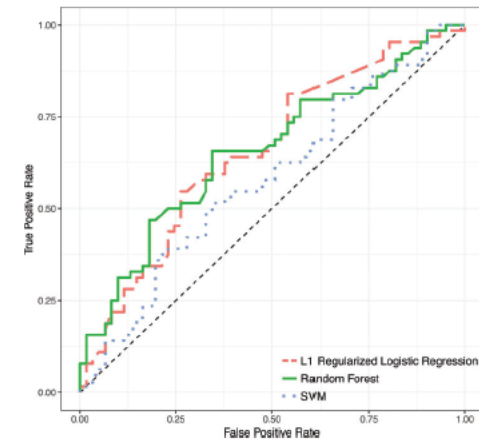


Figure 2. ROC curves for all classification models.

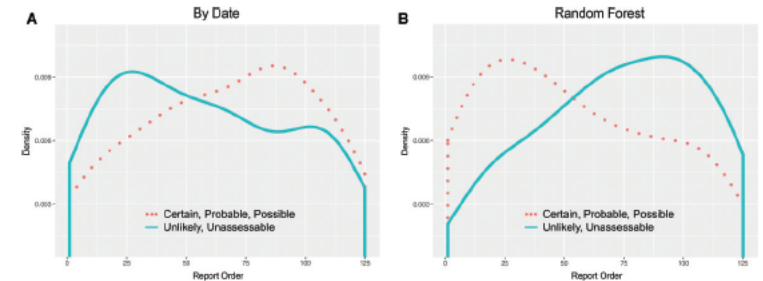


Figure 3. Comparison of report orderings in the held-out test set by (A) date and (B) random forest with assessments of Certain, Probable, or Possible vs assessments of Unlikely or Unassessable.

reporting systems, including the FDA Adverse Event Reporting System. Over the last decade, the number of adverse event reports has increased exponentially, resulting in a substantial workload for reviewers. Delays in detecting drug adverse events can have costly and detrimental effects on public health, and thus a system to identify reports most likely to contain information demonstrating causal drug events would be highly beneficial. Researchers have investigated such approaches using the US Vaccine Adverse Event Reporting System, in which extracted text features^{16,17} were used with multiple classification algorithms to create an effective report classification model.¹⁸⁻²⁰

The success of text classification in the Vaccine Adverse Event Reporting System and previous computational discoveries of new medication-related adverse events in FAERS²¹⁻²⁷ have generated significant interest in developing a classification system for FAERS. To accomplish this, we built models to classify and rank adverse event reports based on the likelihood of medication-related causality. In addition, we showed the potential utility of our models to assist manual adjudicators by shifting reports with a higher probability of medication-related causality to a higher priority in rank order.

For the first phase of this study, we chose to focus on reports with assessments of *Certain* to *Unassessable*, as they constituted

Can Social Media Generate Signals?



Drug Saf (2014) 37:343–350
DOI 10.1007/s40264-014-0155-x

ORIGINAL RESEARCH ARTICLE

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

RECEIVED 29 July 2014
REVISED 2 December 2014
ACCEPTED 4 December 2014
PUBLISHED ONLINE FIRST 9 March 2015



Azadeh Nikfarjam¹, Abeer Sarker¹, Karen O'Connor¹, Rachel Ginn¹, Graciela Gonzalez¹

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. Freifeld^{1,3} · John S. Brownstein¹ ·
Mark Walderhaug² · I. Ralph Edwards⁴ · Nabarun Dasgupta¹ 

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

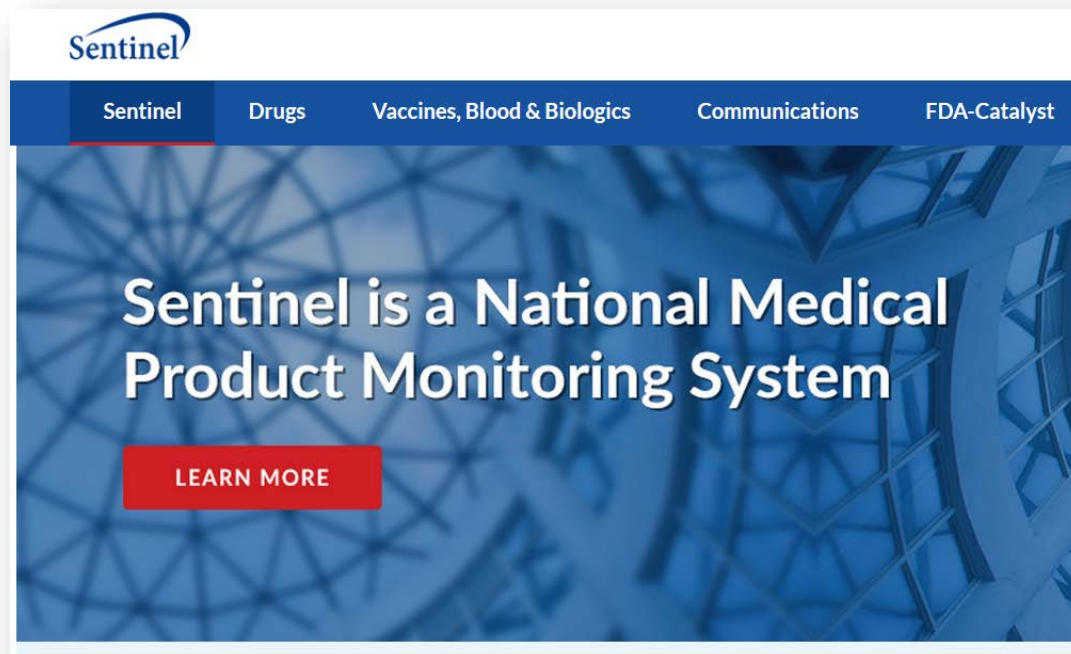
Andrea C Tricco,^{1,2} Wasifa Zarin,¹ Erin Lillie,¹ Ba Pham,¹ Sharon E Straus^{1,3}

Sentinel

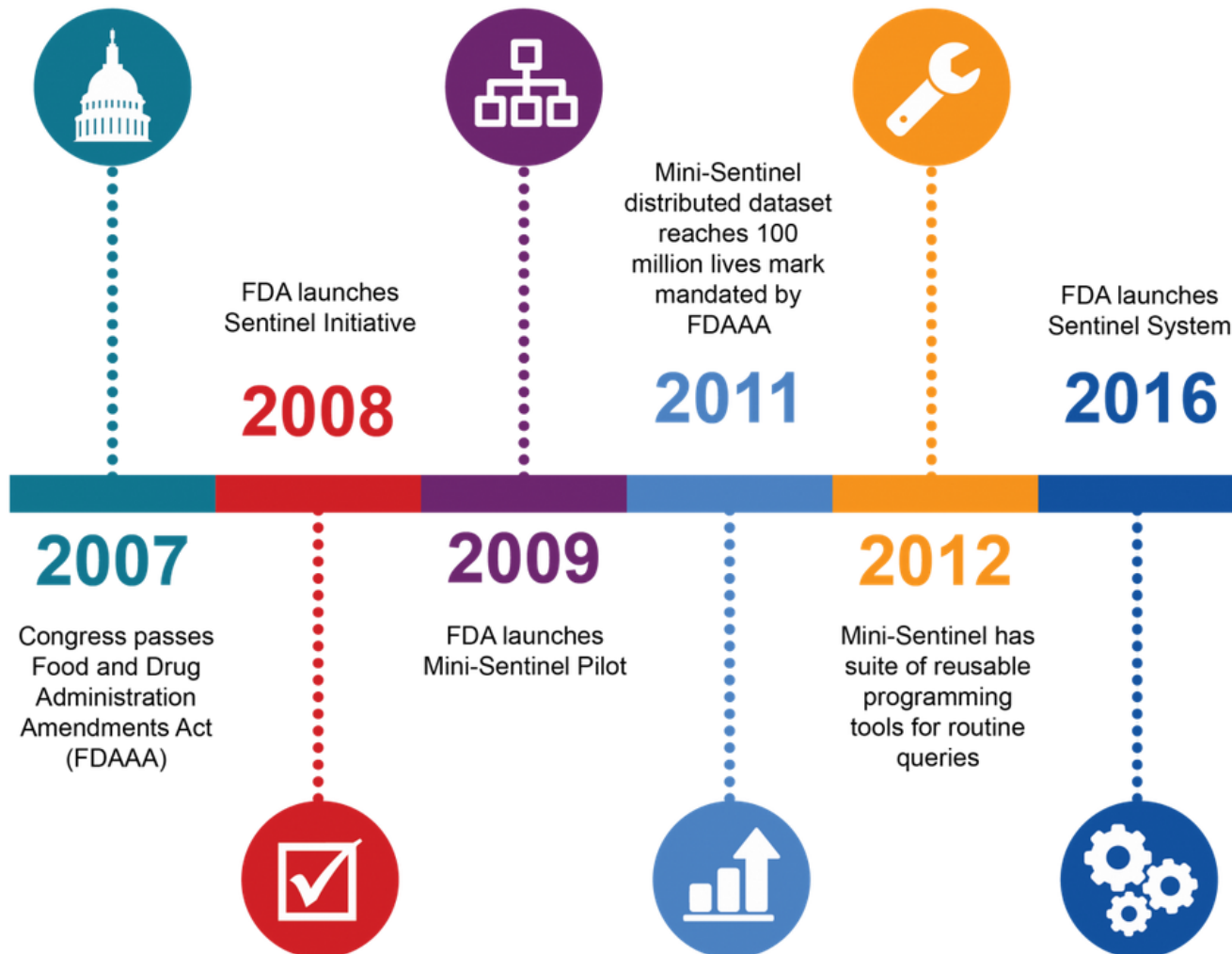
FDA Sentinel System

- 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/



Timeline



Requirement to Consider Sufficiency of ARIA before PMR

Section 905

Mandates creation of ARIA

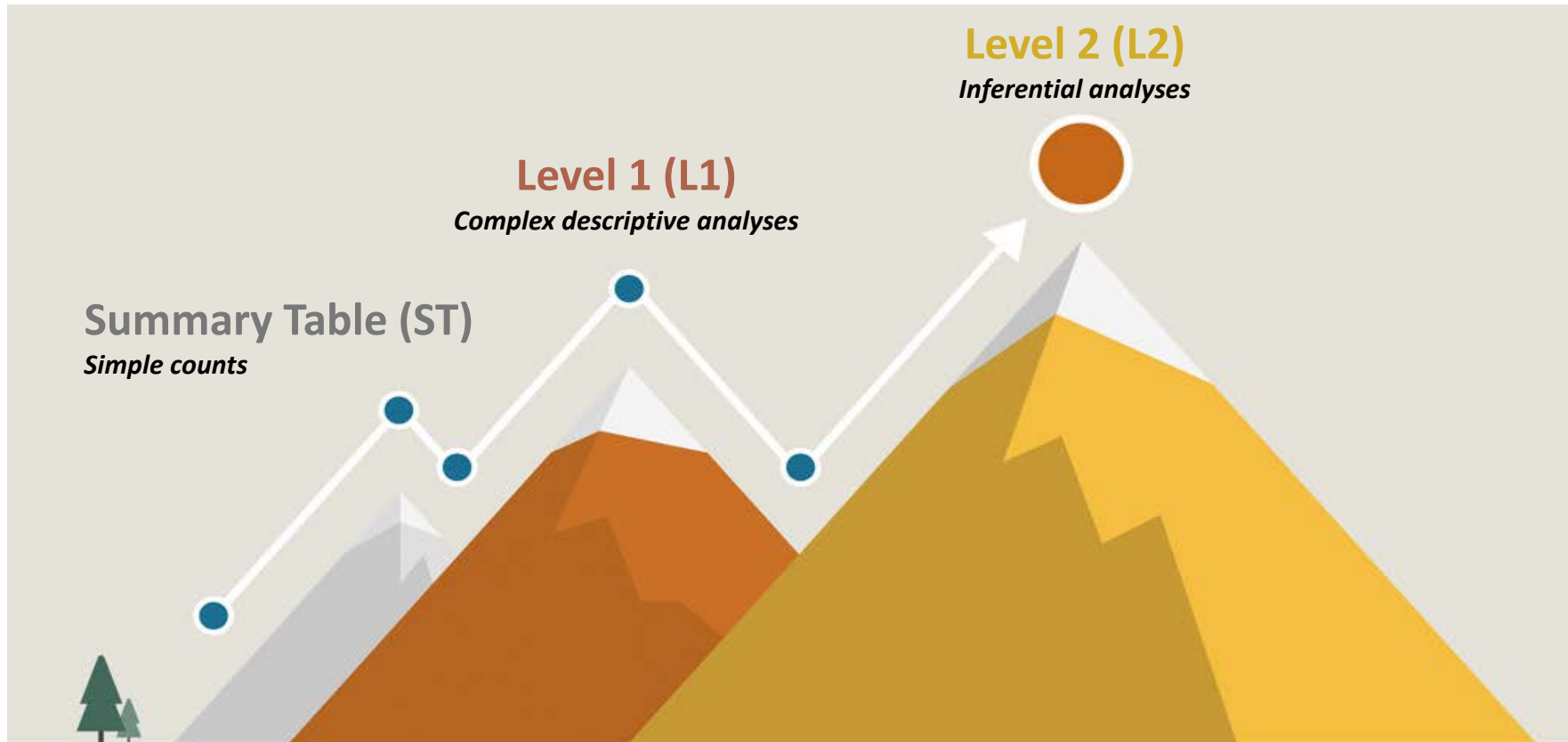


Section 901

New FDAAA PMR authority

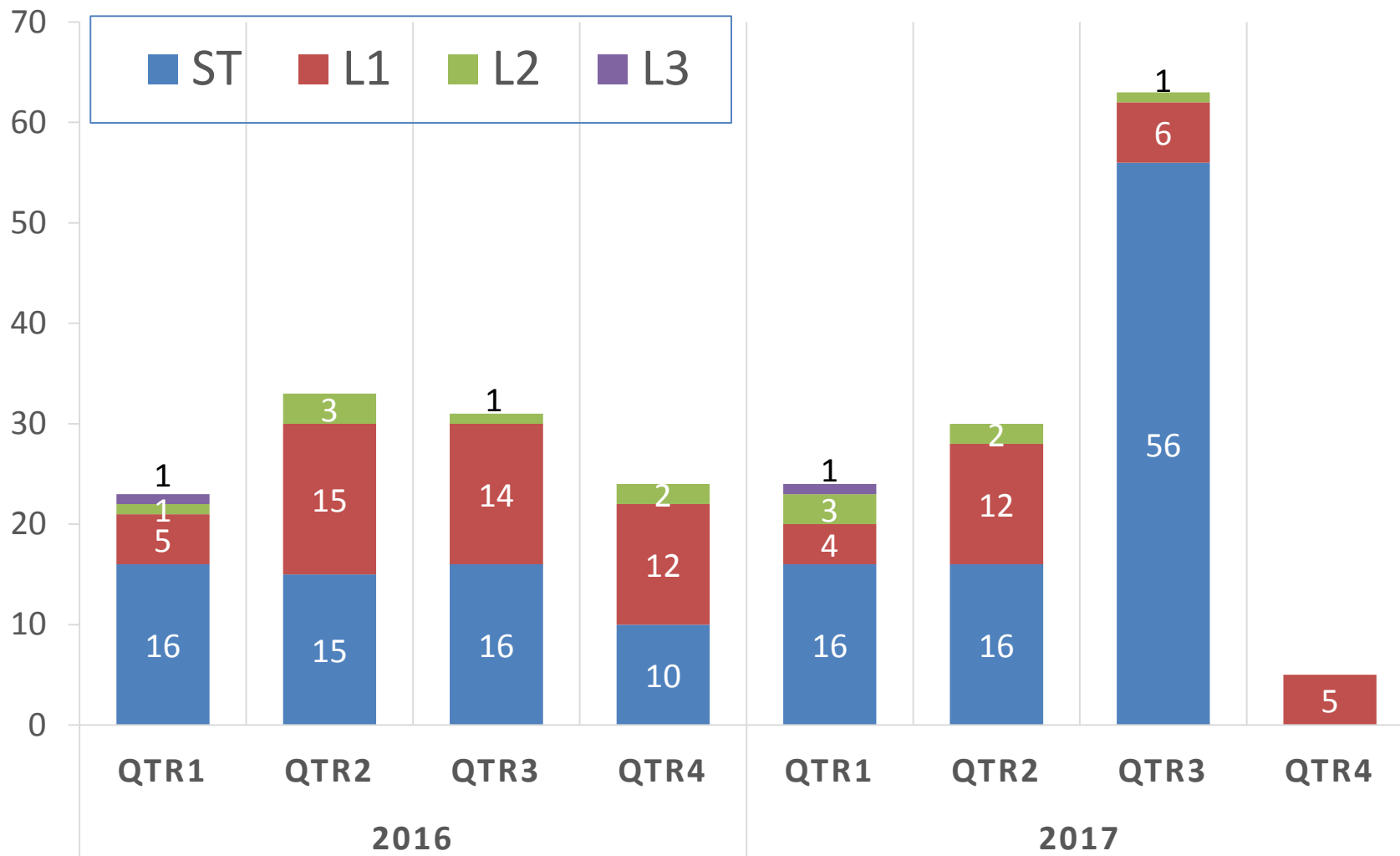
“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the **active postmarket risk identification and analysis system** as available under subsection (k)(3) will not be **sufficient**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

Active Risk Identification and Analysis



Modular Programs: Validated, re-usable analytic tools that facilitate rapid safety analyses to be run on high quality electronic healthcare data

Sentinel ARIA Analyses (N=233)



From all FDA Centers, by date of distribution to Data Partners



10th Annual Public Workshop

The screenshot shows the website for the 2018 Sentinel Initiative Annual Public Workshop. At the top left is the Duke University logo and the Margolis Center for Health Policy name. A search bar is on the top right. A navigation menu includes Home, About, Our Work, People, News, Events, and Support Our Work. The main heading is '2018 Sentinel Initiative Annual Public Workshop' with a date of 'February 7, 2018 - 9:00 am' and a 'Register now' button. The location is 'Hyatt Regency Bethesda, 1 Bethesda Metro Center, Bethesda, MD 20814'. A 'Description' section begins with '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 (FDA) is sponsoring the 2018 Sentinel Initiative Annual Public Workshop.' A 'Speakers' section lists 'Dr. Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research'.

<https://healthpolicy.duke.edu/events/2018-sentinel-initiative-annual-public-workshop>

Sentinel and PDUFA

PDUFA V Commitments

- Public stakeholder meeting
- Fund 4 – 6 activities
- Interim Sentinel Assessment
- [Final Sentinel Assessment](#)



PDUFA VI Commitments

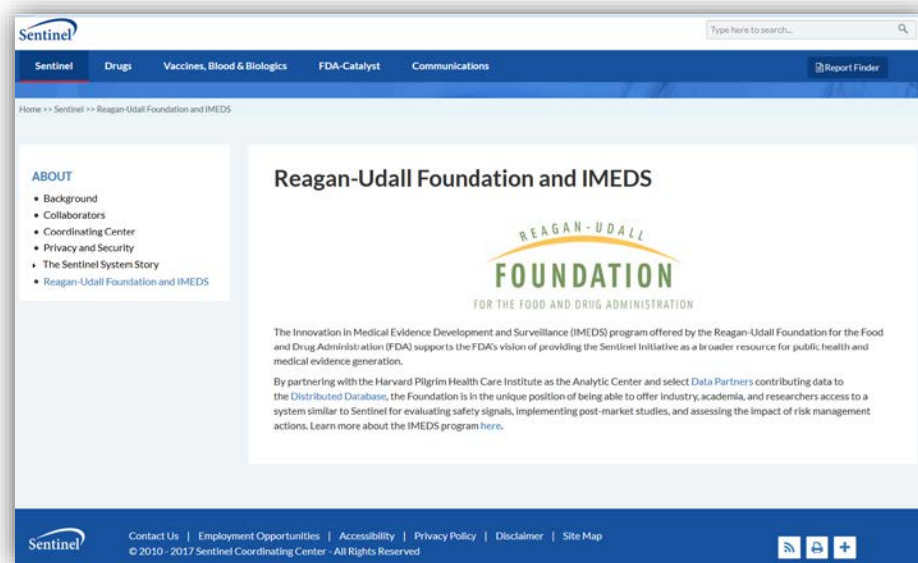
- Expand data sources and core capabilities
- Enhance communications with sponsors and public
- Evaluate additional ways to facilitate public and sponsor access to Sentinel
- Hold public stakeholder meeting
- Establish MAPPS and SOPPs for sponsor communication
- Integrate Sentinel into drug review
-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

New Base Contract for Sentinel Coordinating Center



The screenshot displays the FedBizOpps.gov website interface. At the top, there is a navigation bar with links for Home, Getting Started, General Info, Opportunities (highlighted), Agencies, and Privacy. Below the navigation bar, the page title is "Sentinel Initiative Request for Information" with a sub-header "Sentinel Initiative Request for Information". The page includes the FDA logo and the following details: Solicitation Number: FDA-RFI-18-0001, Agency: Department of Health and Human Services, Office: Food and Drug Administration, and Location: Office of Acquisitions and Grants Services - Rockville. There are buttons for "Return To Opportunities List", "Watch This Opportunity", and "Add Me To Interested Vendors". The page also features a "Notice Details" tab, a "Packages" tab, and an "Interested Vendors List" tab. A "Print" button and a "Link" button are visible. The main content area shows the "Original Synopsis" with a date of Dec 01, 2017, 12:46 pm. The synopsis includes the solicitation number (FDA-RFI-18-0001) and the notice type (Special Notice). A note states: "Please consult the list of [document viewers](#) if you cannot open a file." The page also features a "Sentinel Initiative Request for Information FY19" section. On the right side, there is an "ALL FILES" section with a link to "Sentinel Initiative Request for Information FY19" and a "GENERAL INFORMATION" section with details on the notice type, posted date (December 1, 2017), and response date (Mar 01, 2018 11:59 pm Eastern).

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

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

Format and Content of a REMS Document Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gita Toyserkani at 301-796-1783, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2017
Drug Safety
Revision 1

Use of a Drug Master File for Shared System REMS Submissions



- Draft guidance issued November 2017
- Intended to improve efficiency

**Use of a Drug Master File for
Shared System REMS Submissions**

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2017
Procedural

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

Providing Regulatory Submissions in Electronic Format — Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 180 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Adam Kroetsch, 301-796-3842, Aaron Sherman, 240-402-0493, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2017
Electronic Submissions

REMS Website

U.S. Department of Health and Human Services

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Approved Risk Evaluation and Mitigation Strategies (REMS)

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The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

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) Excel CSV Print

Name	REMS Approved	Last Updated	MedGuide (MG)*	Comm. Plan (CP)	ETASU	Imp. System (IS)
Adasuve (loxapine), aerosol, powder NDA #022549	12/21/2012	10/10/2017			ETASU	IS
Addyi (flibanserin), tablet NDA #022526	08/18/2015	06/16/2017			ETASU	IS
Adempas (riociguat), tablet, film coated NDA #204819	10/08/2013	01/17/2017	MG		ETASU	IS
Afrezza (insulin human), powder, metered NDA #022472	06/27/2014	04/01/2016		CP		
Alosetron Shared System REMS	11/22/2016	11/22/2016			ETASU	
AndroGel 1% (testosterone), gel NDA #021015	09/18/2009	05/11/2015	MG			
AndroGel 1.62% (testosterone), gel NDA #022309	04/29/2011	05/11/2015	MG			
Aveed (testosterone undecanoate), injection NDA #022219	03/05/2014	12/09/2016			ETASU	IS

Stakeholder Sections



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Clozapine

Shared System REMS

REMS last update: 09/15/2015

Products | Goals | Summary | REMS Materials | Update history

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). The 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](#) | [繁體中文](#) | [Tiếng Việt](#) | [한국어](#) | [Tagalog](#) | [Русский](#) | [العربية](#) | [Kreyòl Ayisyen](#) | [Français](#) | [Polski](#) | [Português](#) | [Italiano](#) | [Deutsch](#) | [日本語](#) | [العربية](#) | [English](#)

Stakeholder Sections

Clozapine

Shared System REMS

REMS last update: 09/15/2015

Products Goals Summary **REMS Materials** Update history

What do participants need to know?

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Healthcare Providers who prescribe clozapine products must

To be able to prescribe

- Review the drug's prescribing information.
- Review Clozapine and Risk of Neutropenia: A Guide for Healthcare Providers. | [Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers](#) |
- 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

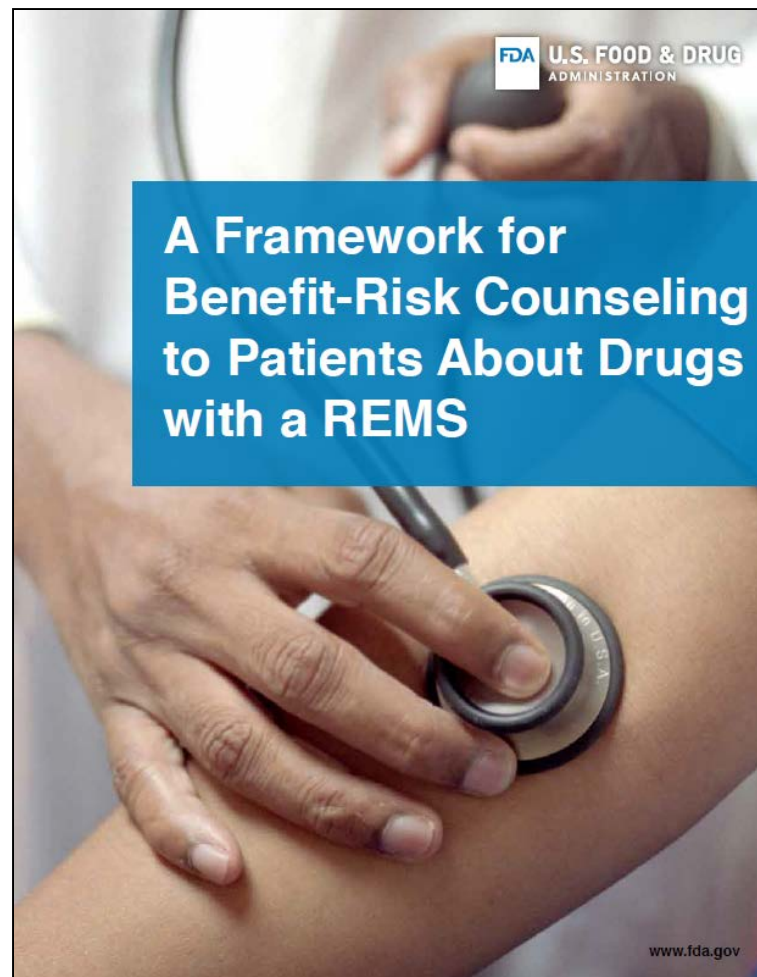
+ Wholesalers that distribute clozapine shared system products must

[View additional drug-specific postmarket safety information from the FDA](#)

Framework for Benefit-Risk Counseling to Patients About Drug with a REMS

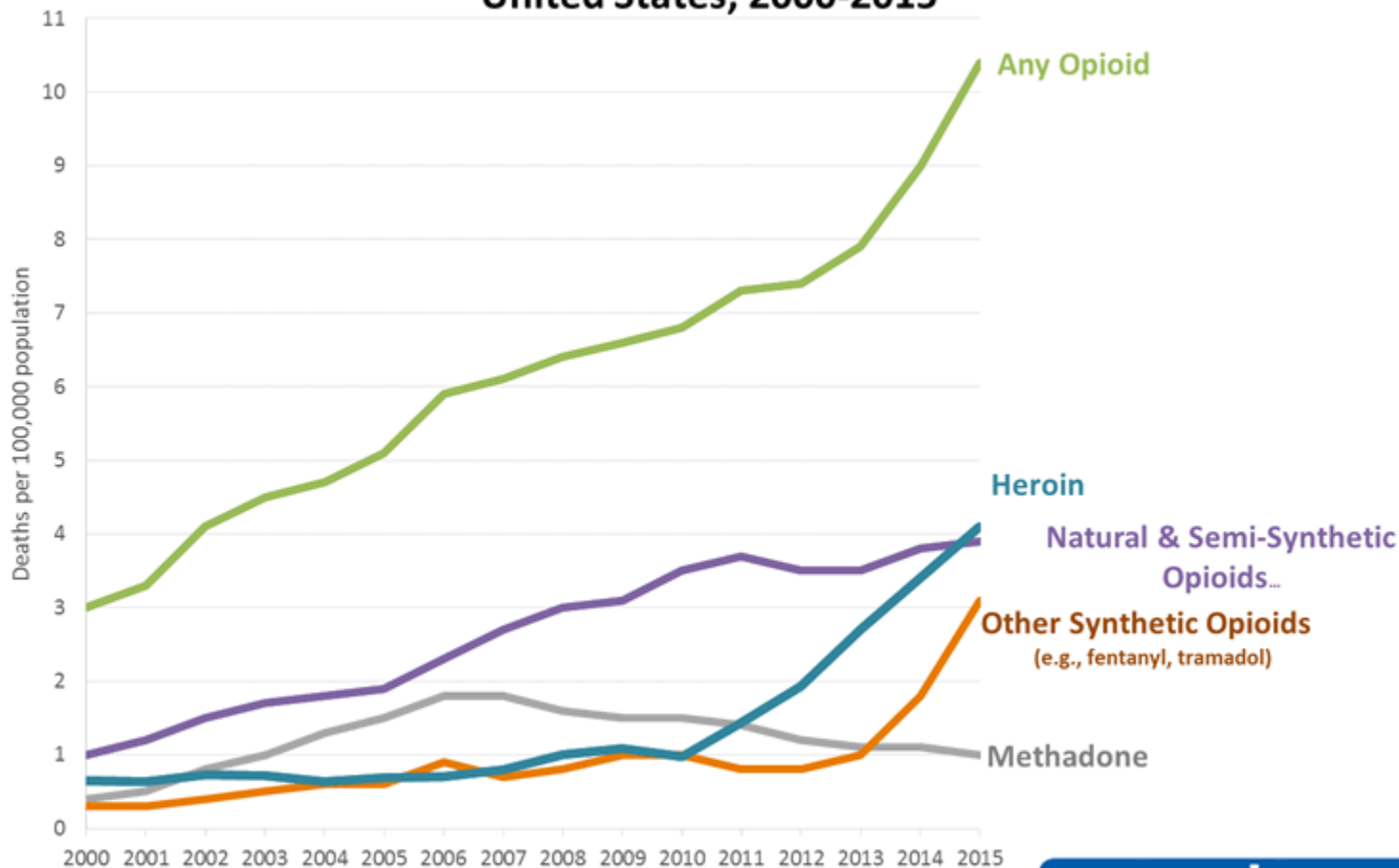


- Part of REMS Integration Initiative
- Four Es:
 - Evaluate
 - Educate
 - Engage
 - Ensure



Prescription Opioid Abuse

Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

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Your Source for Credible Health Information

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
 - Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities, July 10, 2017
 - Training for Opioid Analgesic Prescribers, May 9-10, 2017



Opana ER

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FDA News Release

FDA requests removal of Opana ER for risks related to abuse

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