CDER Office of Surveillance and Epidemiology: 2018 Update

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

FDA/CMS Summit
December 11, 2018

Label Changes Study

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------**RECENT MAJOR CHANGES**----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------**INDICATIONS AND USAGE**----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------**DOSAGE AND ADMINISTRATION**----------
- [text]
- [text]

----------**DOSAGE FORMS AND STRENGTHS**----------
- [text]

----------**CONTRAINDICATIONS**----------
- [text]
- [text]

----------**WARNINGS AND PRECAUTIONS**----------
- [text]
- [text]

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------**DRUG INTERACTIONS**----------
- [text]
- [text]

----------**USE IN SPECIFIC POPULATIONS**----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Data Source - Issues

- Issue were identified by reviewing label and approval letter
- Issues were recorded as stated in the label text
- A second reviewer independently reviewed the abstracted individual safety issues
- Enumerated the number of issues incorporated into:
  - Each relevant section of the label
  - Issues per labeling update

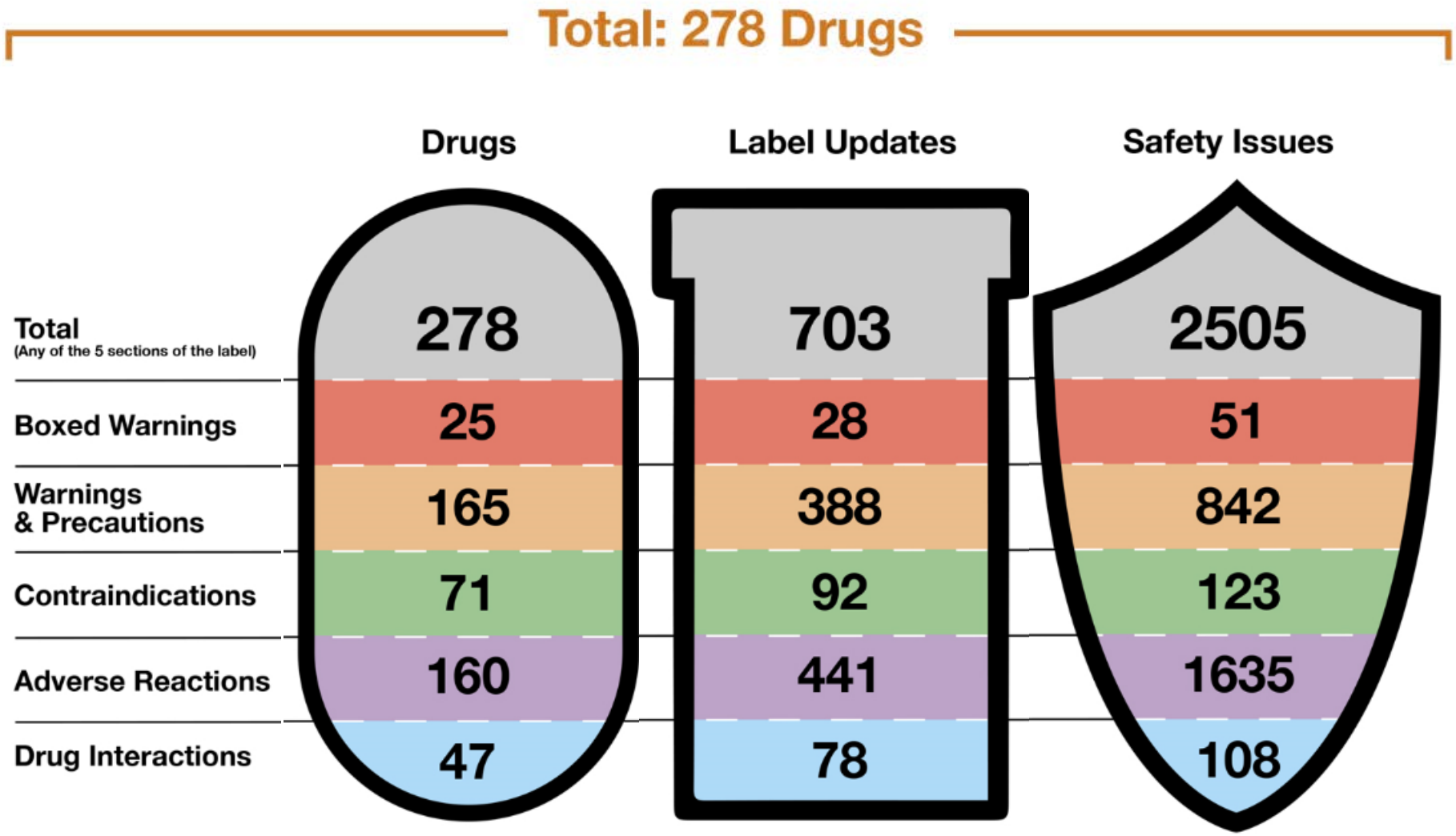
Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Results

- 278 NMEs approved between October 1, 2002 and December 31, 2014.
- 1 safety withdrawal
- 195 (70.1%) with ≥ 1 safety outcome
- 83 (29.9%) no safety related label change or withdrawal

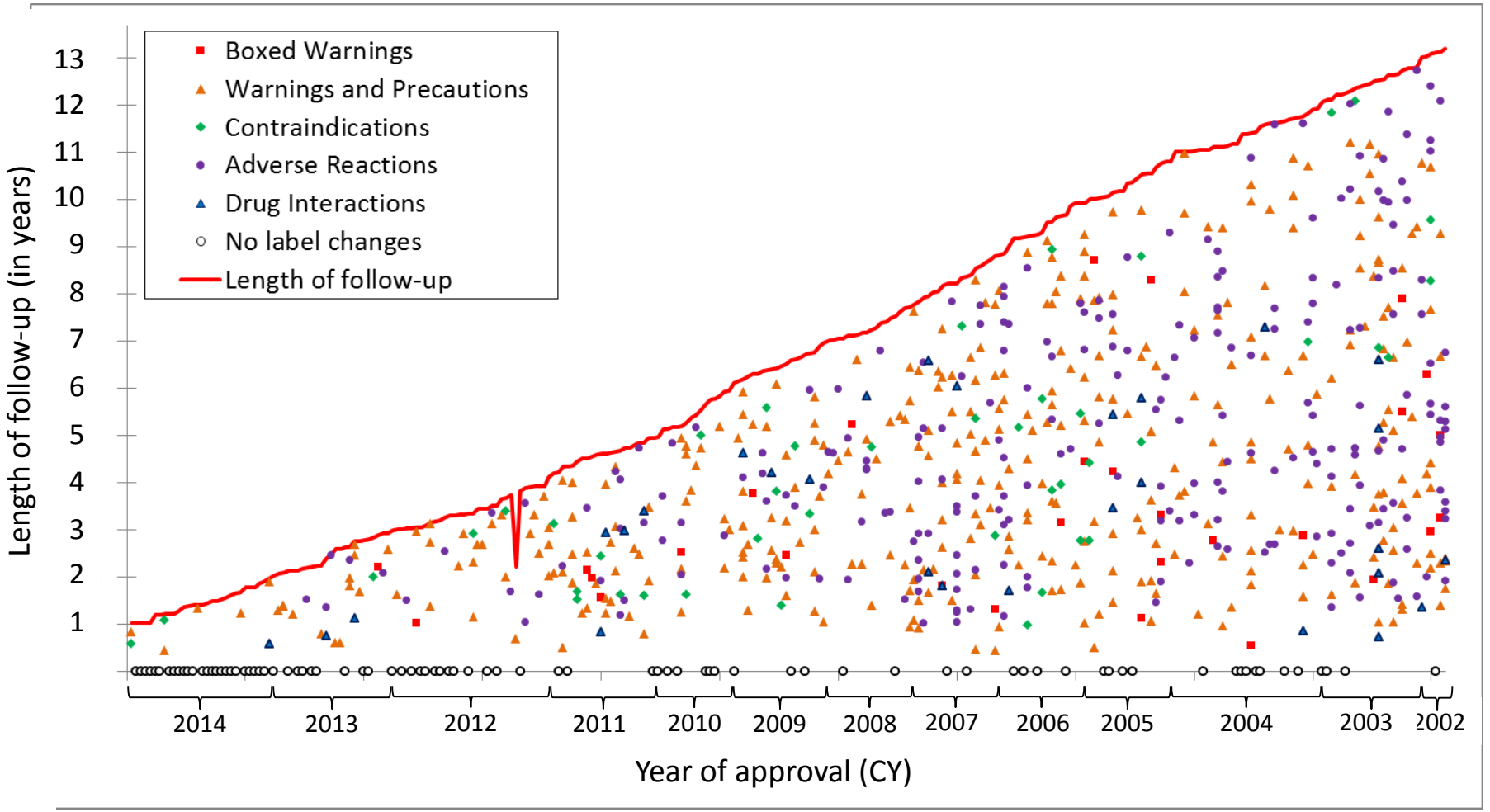
Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Results



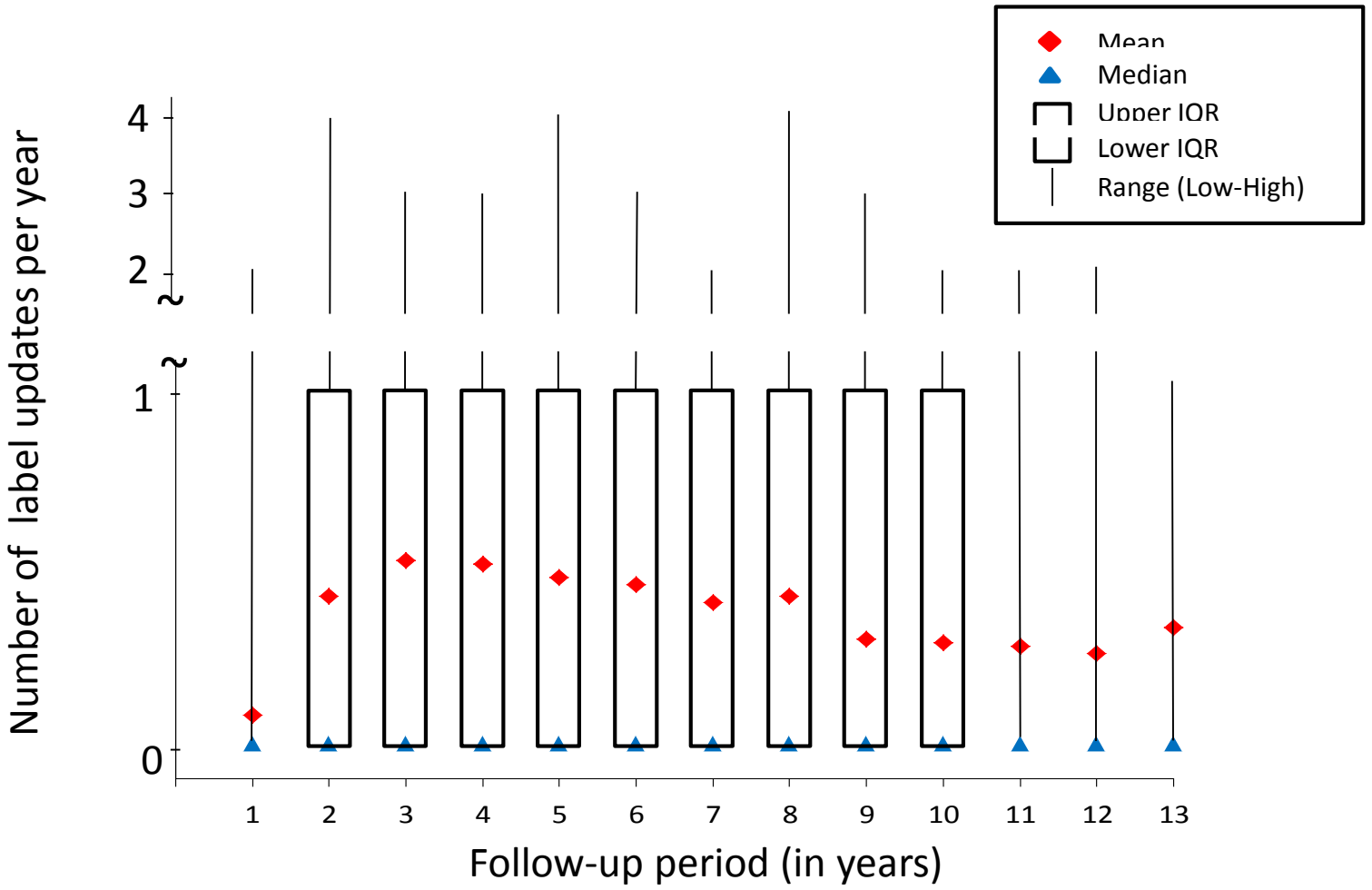
Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Hierarchical presentation of time to drug label updates for NMEs by section of the label updated as of December 31, 2015



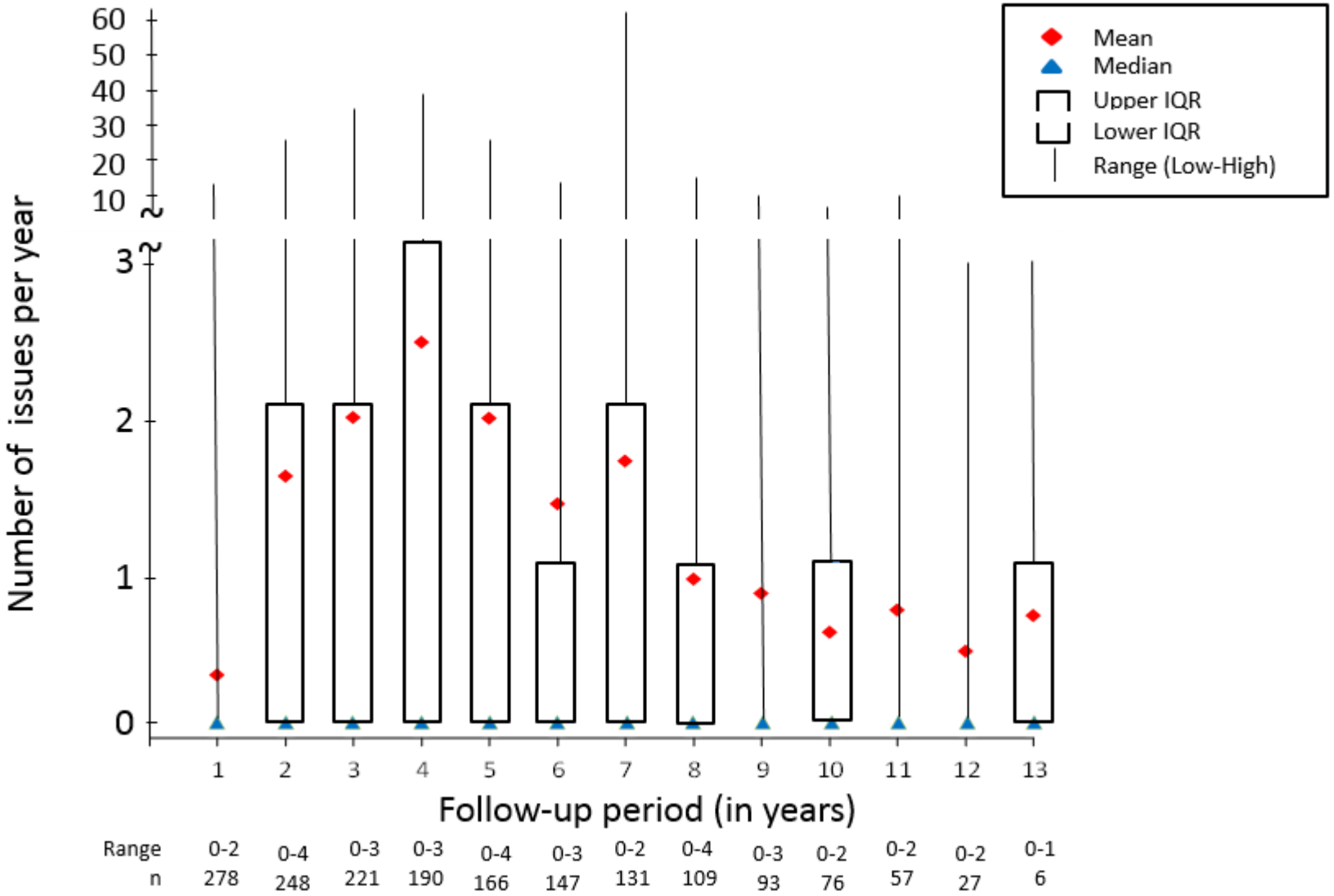
Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Average number of label updates per year of follow-up



Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

Average number of issues per year of follow-up

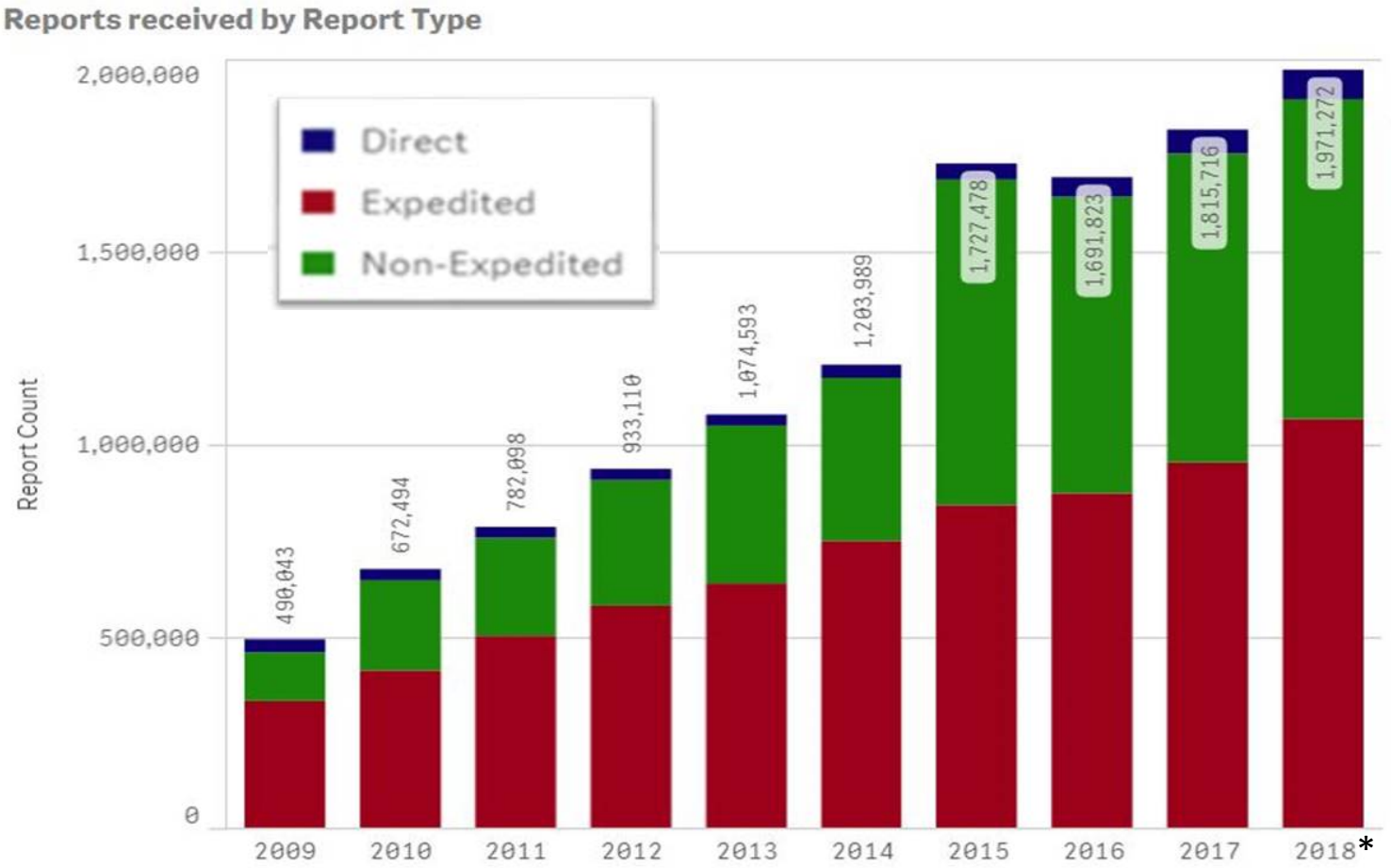


Source: Pinnow et al. *Clin Pharmacol Ther* 2017 Dec 20 doi: 10.1002/cpt.994 [Epub ahead of print]

U.S. FOOD & DRUG ADMINISTRATION

Adverse Event Data

FDA Adverse Event Reporting System (FAERS)



*2018 data through 20 November 2018

U.S. FOOD & DRUG ADMINISTRATION

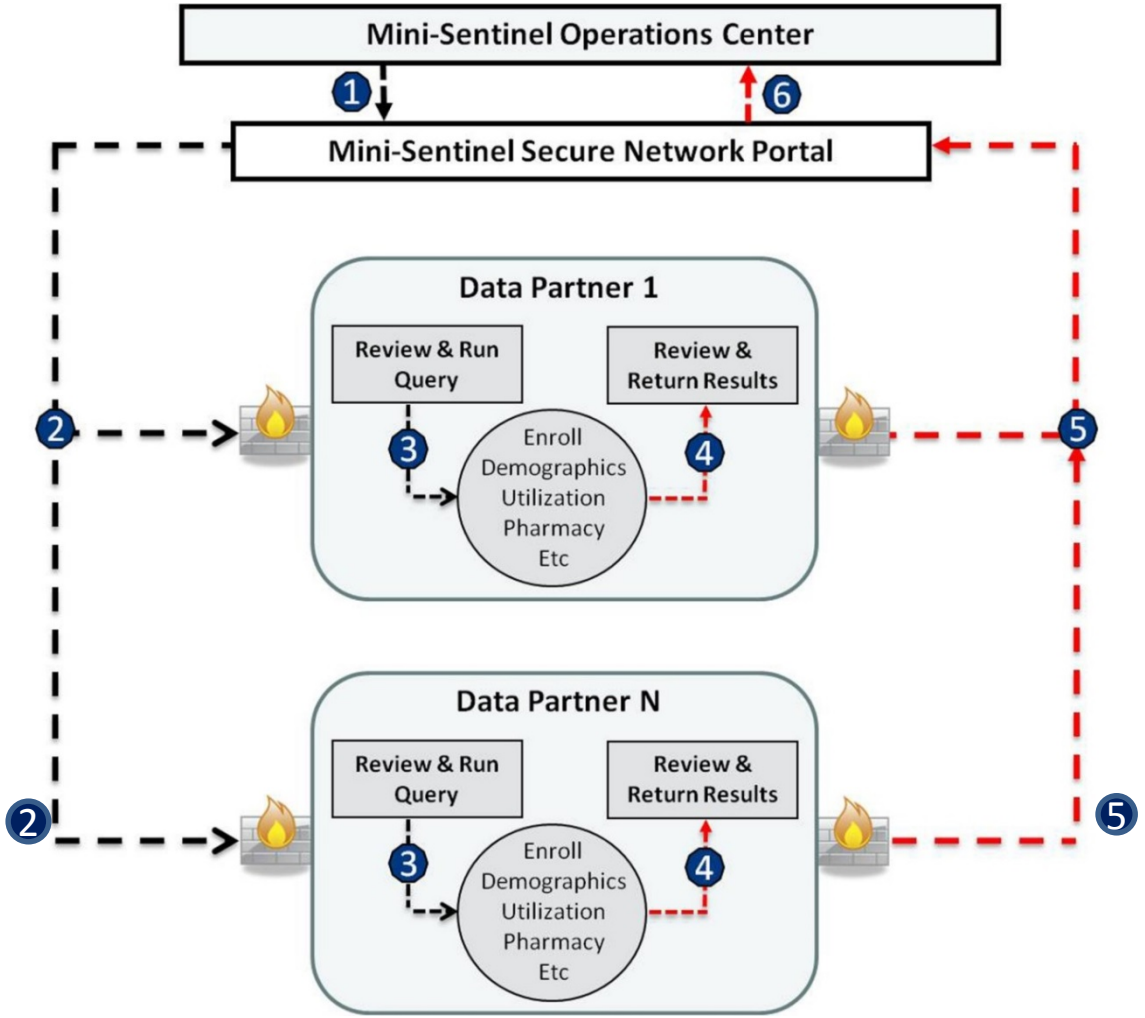
Sentinel

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/

Analysis in Sentinel's Distributed Data Network



1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6- Results are aggregated

ARIA is Comprised of Modular Programs

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The FDA Sentinel Initiative — An Evolving National Resource

Richard Platt, M.D., Jeffrey S. Brown, Ph.D., Melissa Robb, M.S., Mark McClellan, M.D., Ph.D., Robert Ball, M.D., M.P.H., Michael D. Nguyen, M.D., and Rachel E. Sherman, M.D., M.P.H.

The Food and Drug Administration (FDA) Sentinel Initiative,[1] which was launched in 2008, has matured from a pilot program designed to assess potential drug-safety signals in insurance claims into a core component of the agency's evolving safety surveillance system. Sentinel is a flexible and robust program that provides evidence on the effects of medical products while protecting secure querying system, created a very large rigorously curated and updated distributed health information data set, and developed tools permitting rapid, customized analysis.

Distributed data systems, in which data partners maintain physical and operational control over their data, provide a high level of protection for the privacy and security of patients' health viding guidance on the best use of their data. Although data partners have chosen to respond to nearly all questions sent to them, their ability to opt out of specific queries remains an important contributor to their willingness to participate in the program.

Administrative claims data are the foundation of the Sentinel infrastructure because they are the most reliable and readily avail-

https://www.nejm.org/doi/full/10.1056/NEJMp1809643

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

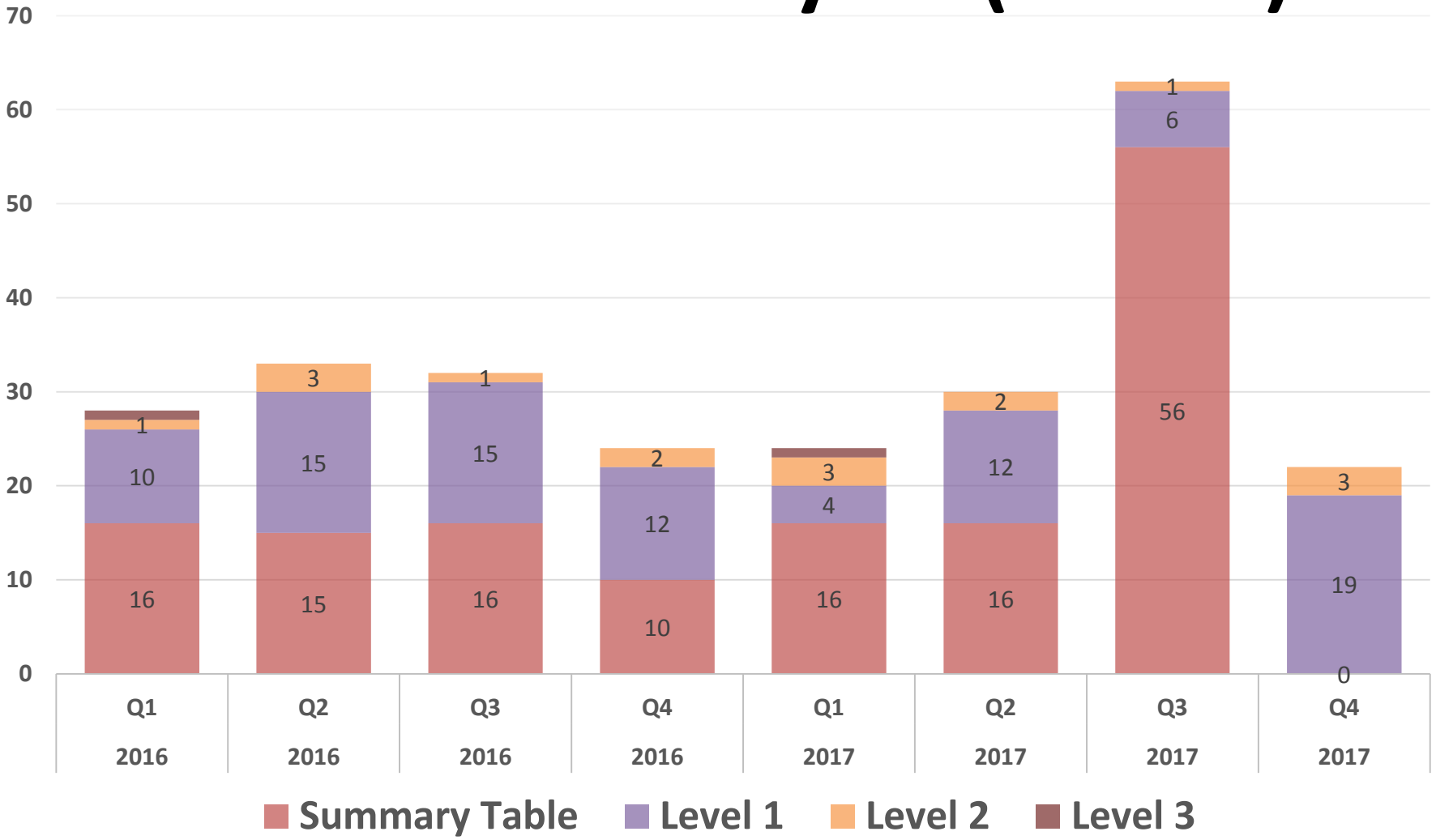
Just as the Sentinel Initiative looks very different today than it looked 5 years ago, in 5 to 10 years the system will have improved capabilities and will use new data sources and methods.

The Sentinel Initiative can become a critical component of the FDA's implementation of its mandates under the 21st Century Cures Act by providing data and expertise to support the incorporation of real-world data into regulatory decision making in other areas in addition to safety assessments.

https://www.nejm.org/doi/full/10.1056/NEJMp1809643

Sentinel Strategic Plan

Sentinel ARIA Analyses (N=256)



Drug Safety in Pregnancy in a Large, Multisite Database: Advances in Analytic Methods, Querying Tools, and Supplemental Data Collection from Patients

Danijela Stojanovic, Liz Suarez, Susan Andrade, David Martin

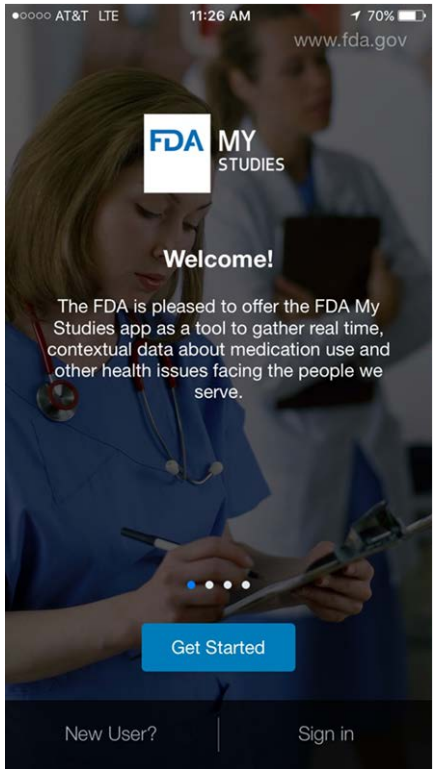
Friday, November 30, 10-11am EDT

1	2	3	4
Danijela Stojanovic	Liz Suarez	Susan Andrade	David Martin
New Mother-Infant Linkage	**New ICD-10 Gestational Age Algorithm**	**Validation of ICD-10 Stillbirth Algorithm**	**Open Source Mobile App for Data Collection**

https://www.sentinelinitiative.org/communications/sentinel-initiative-events/drug-safety-pregnancy-large-multisite-database-advances

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System

FDA My Studies



- Mobile App
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
  - Gateway capability
- Web-based configuration portal
- Secure Storage Environment
  - FISMA complaint
  - Partitioned for distributed research
  - Responses can be downloaded in broadly compatible formats (e.g., for use in SAS, Excel, etc.)

Signal Detection Approaches Available in Sentinel

Pre-Specified Panel of Select Outcomes

Prospective sequential surveillance tool (Level 3)

One Product, All Outcomes

TreeScan

One Outcome, All Products

DrugScan

All Products, All Outcomes

No existing tool in Sentinel

Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data **Prescribing Information**

Signal identification led by **Divisions of Pharmacovigilance** and Sentinel Program Team

Follow up investigations to be conducted by **Divisions of Epidemiology**

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

Identify Outcome for Further Evaluation (if any)

Advancing the Sentinel System

- **Explore opportunities to leverage advances in machine learning, natural language processing, artificial intelligence**
- **Expand the Sentinel Common Data Model**
- **Enhance existing data sources, particularly with electronic health records**

https://healthpolicy.duke.edu/events/improving-efficiency-outcome-validation-sentinel-system
https://healthpolicy.duke.edu/events/public-webinar-planned-next-steps-advance-sentinel-system

FDA's Sentinel Initiative - News and Events

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FDA is committed to an open public process that will enable information to be disseminated and stakeholder contributions to be gathered as it explores the scientific, technical, and policy issues that will affect the Sentinel System's development.

Sign up for E-mail Updates

Upcoming Events

Eleventh Annual Sentinel Initiative Public Workshop

The Sentinel Initiative was launched in response to the Food and Drug Administration Amendments Act of 2007 (FDAAA) and is comprised of several components including the Sentinel System, the Active Risk Identification and Analysis, the Biologics Effectiveness and Safety System (BEST IDIQ #1, BEST IDIQ #2) and FDA Catalyst. The Food and Drug Administration (FDA) is committed to facilitating stakeholder engagement on approaches to modernize the Sentinel Initiative's capabilities. The Annual Public Workshop is a gathering of the Sentinel community and leading experts to share recent developments within the Sentinel Initiative, provide training on Sentinel System's tools and data infrastructure, and promote engagement and collaboration with patients, industry, academia, and consumers. This year marks the Eleventh Annual Sentinel Initiative Public Workshop and will be a two-day event. Please note that there are separate registrations for each day of the meeting and there are two different locations for Days 1 and 2. Day 3 is by invitation only for international regulators.

https://www.fda.gov/Safety/ucm149341.htm

Sentinel Annual Meeting | Day 1

DAY 1 | Sentinel Initiative Public Workshop, April 3, 2019

Registration: Open to everyone. Please register through this Duke Margolis link.
Location: Hyatt Regency Bethesda
1 Bethesda Metro Center
Bethesda, MD 20814

Agenda and Details: Day 1 will be convened by the Robert J. Margolis, MD, Center for Health Policy at Duke University under a cooperative agreement with FDA. The workshop will feature updates on how the Sentinel Initiative is being used by FDA as a core safety surveillance program from leaders at FDA and from investigators within the Sentinel Initiative. Discussion will also highlight strategic initiatives and potential future directions for continued improvements to the distributed data infrastructure. There will be opportunities throughout the day's discussion for stakeholders to provide input and ask questions.

Sentinel Annual Meeting | Day 2

DAY 2 | Sentinel System Analysis Tools Training: Hands-On Workshop, April 4, 2019

Registration: Open to everyone. Please register through this Day 2 link.
Location: FDA White Oak Campus
10903 New Hampshire Avenue
Building 31, Room 1503 A (the Great Room)
Silver Spring, MD 20993

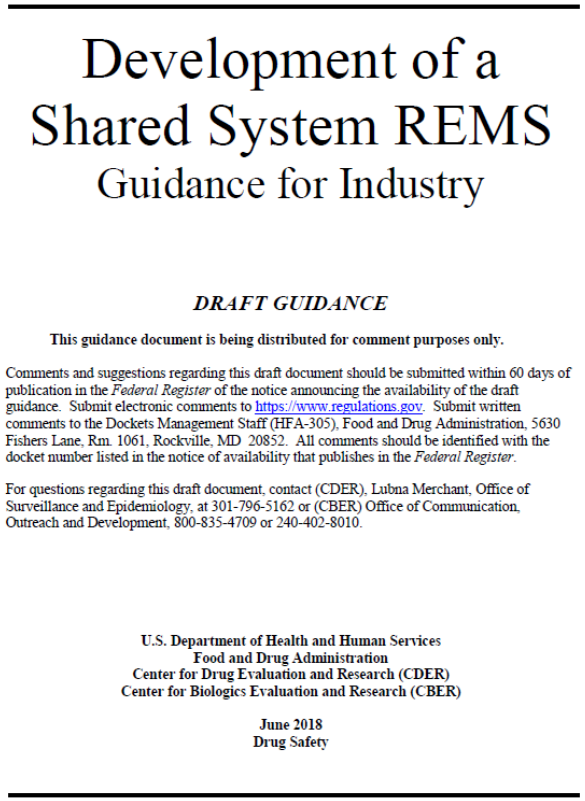
Agenda and Details: Day 2 will be the third public training sponsored by FDA and the Sentinel Operations Center targeting researchers who have prior experience executing epidemiologic analyses with claims data using SAS statistical packages and programming. Registrants are expected to have either attended the prior Sentinel Public Training Events held in July 2017 (Part 1) and February 2018 (Part 2) or viewed the recorded contents online prior to attending. This workshop will build on these prior trainings using a hands-on laboratory format. Attendees should bring a laptop to the training to participate. Due to the interactive nature of the training, no online participation will be available.

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategies

Development of a Shared System REMS

- This draft guidance is meant to enhance clarity and transparency of the development process for shared system REMS, specifically it:
  - Provides recommendations for industry on the development of a shared system REMS for multiple prescription drug products, including biological products
  - Provides information about the benefits of shared system REMS
  - Describes situations in which a shared system is not required under the statute, but the Agency may encourage manufacturers to develop one to reduce burden on the healthcare system



Development of a
Shared System REMS
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*.

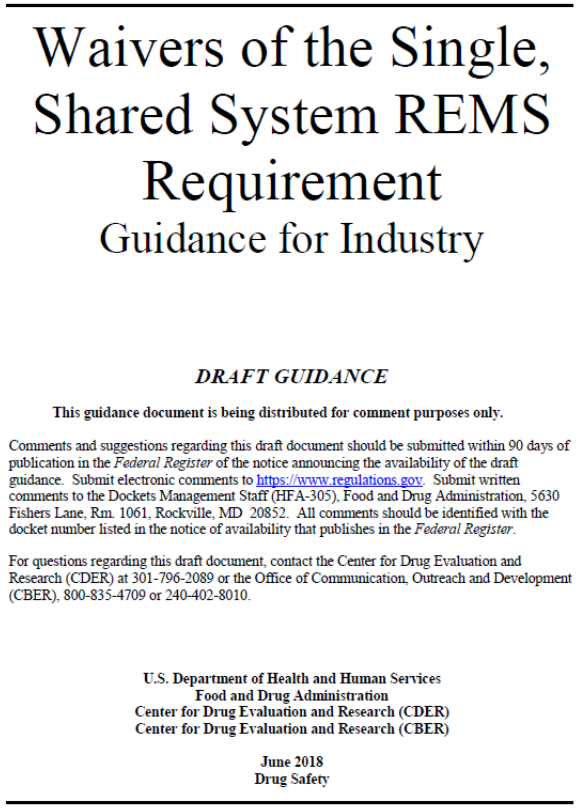
For questions regarding this draft document, contact (CDER), Lubna Merchant, Office of Surveillance and Epidemiology, at 301-796-5162 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

June 2018
Drug Safety

Waivers of the Single, Shared System REMS Requirement

- This guidance is meant to provide clarity to help alleviate the delays in ANDA approvals that can be caused by prolonged negotiations over the development of a single, shared system REMS, specifically it:
  - describes the factors FDA will consider in evaluating a request for a waiver of the single, shared system requirement
  - provides recommendations to ANDA applicants regarding the submission and content of waiver requests
  - addresses the requirement that any separate system use a different, comparable aspect of the ETASU



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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 Drug Evaluation and Research (CBER)

June 2018
Drug Safety

FDA issued its report on the use of accredited CE as a method to implement HCP education under a REMS

- Part of the REMS Integration Initiative
- FDA looked at the feasibility of using Continuing Education for individual REMS
- Report concluded that CE can be a useful too to implement HCP education:
  - Will likely require FDA to provide a *blueprint* which serves as the basis for the content of the education
  - More practically implemented in the postapproval setting

REMS and Continuing Education for Health Care Providers

FDA Feasibility Report

FDA REMS Resources Portal

- Launched in 2018 in response to stakeholder requests for easier access and to improve their understanding of REMS

FDA U.S. FOOD & DRUG ADMINISTRATION

New REMS Webpages Launched

Today the U.S. Food and Drug Administration (FDA) is launching a new set of web pages that aims to provide a one-stop source for general information about Risk Evaluation and Mitigation Strategy (REMS) programs. These webpages organize general REMS information according to audience (i.e., patients, health care professionals and industry) and most pages are presented in a short question and answer format.

In 2007, the Food, Drug Administration Amendments Act gave FDA the authority to require a REMS when FDA determines it is necessary to ensure the benefits of the drug outweigh the risks. Over the past decade, REMS have enabled FDA to approve drugs that otherwise might not have been approvable. However, REMS can also place a burden on the healthcare delivery system.

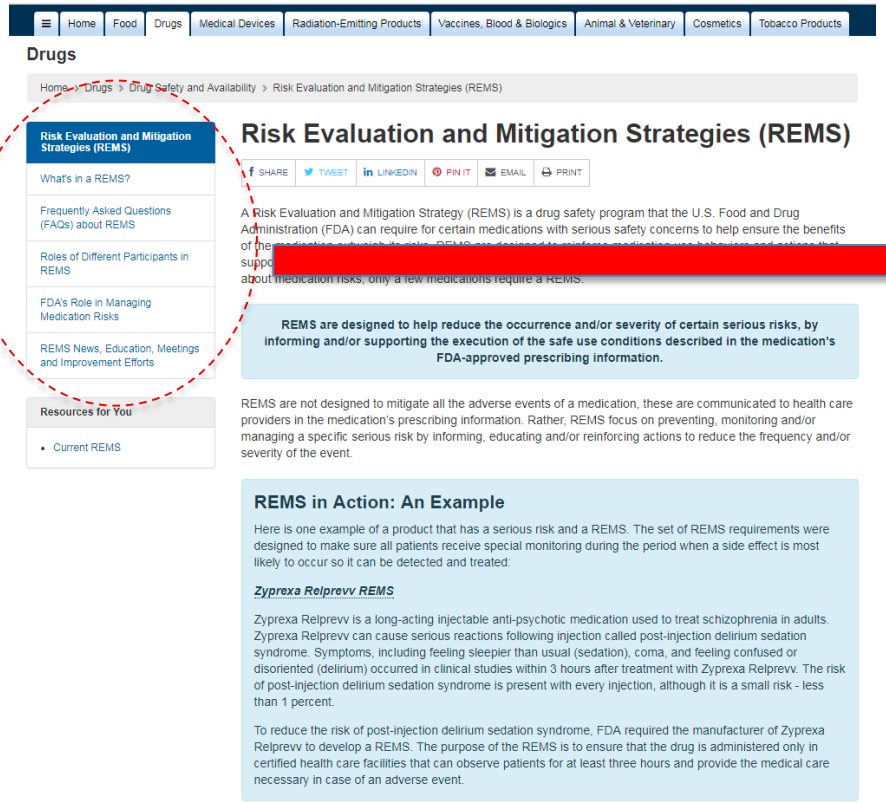
One piece of value feedback FDA has received regarding REMS is that information on drug-specific REMS, and on REMS more generally, can be difficult to locate on the web. REMS information will now be easier to find, relevant and ultimately more useful because organization of the new web content is based on the role a person might have in a REMS program. Also, other newly created pages guide visitors to current information about REMS programs, FDA guidances, public meetings, and educational resources.

Our goal is to enable easier compliance with these programs so that patient access to drugs with REMS can be maintained, while still preserving their safe use.

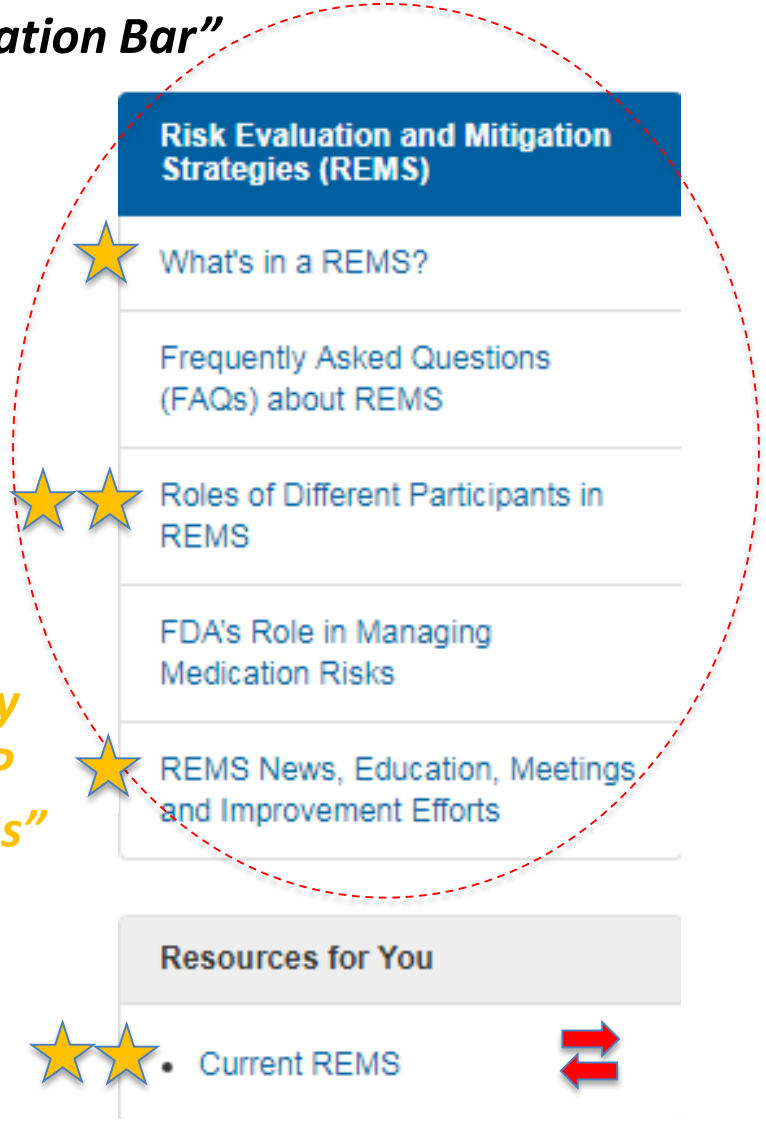
As always, FDA welcomes feedback. Please use the Contact REMS Form to send us any comments you have on the newly created REMS webpages.

Navigating Within the Portal

"Landing page"



"Navigation Bar"



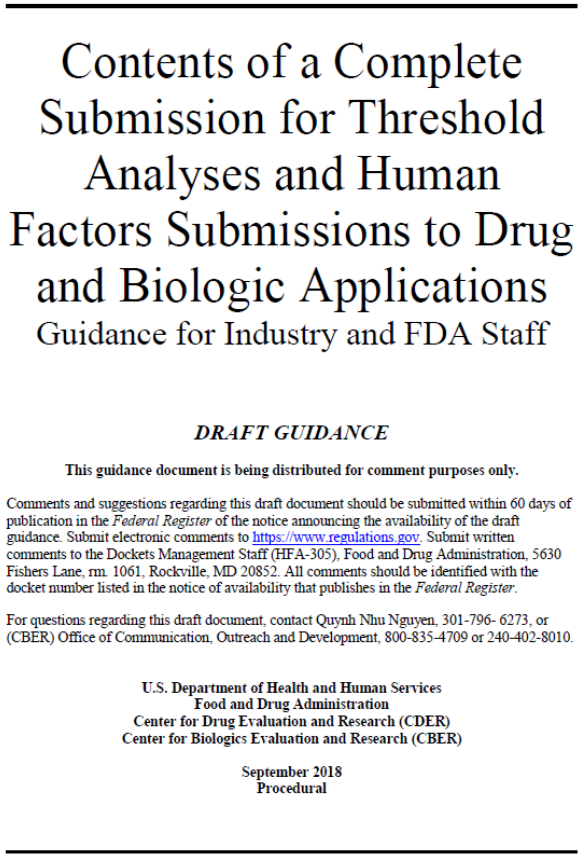
"Key HCP Pages"

U.S. FOOD & DRUG ADMINISTRATION

Medication Error Prevention Program

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions

- Draft issued in September 2018
- Describes to industry and FDA staff the contents of and submission procedures for threshold analyses and human factors submissions that will support efficient Agency review, and presents timelines for FDA's review of such submissions.



Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

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For questions regarding this draft document, contact Quynh Nhu Nguyen, 301-796- 6273, 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 2018
Procedural

Phonetic Orthographic Computerized Analysis (POCA) Database Update

- First released to public in Spring 2009 as a search tool to identify similar drug names
  - Assigns similarity scores
  - Searches databases listing approved product names and internal databases listing proposed proprietary names*
- FDA has adapted the POCA tool to include a database of suffixes that are incorporated within the nonproprietary name of approved biological products.
- The new features of the POCA enable reviewers to
  - compare a suffix candidate to drug names (brand or established names) to avoid the suffix candidates that are too similar to other drug names, or
  - conduct target comparisons of suffix candidates to the suffix component of biological nonproprietary names.

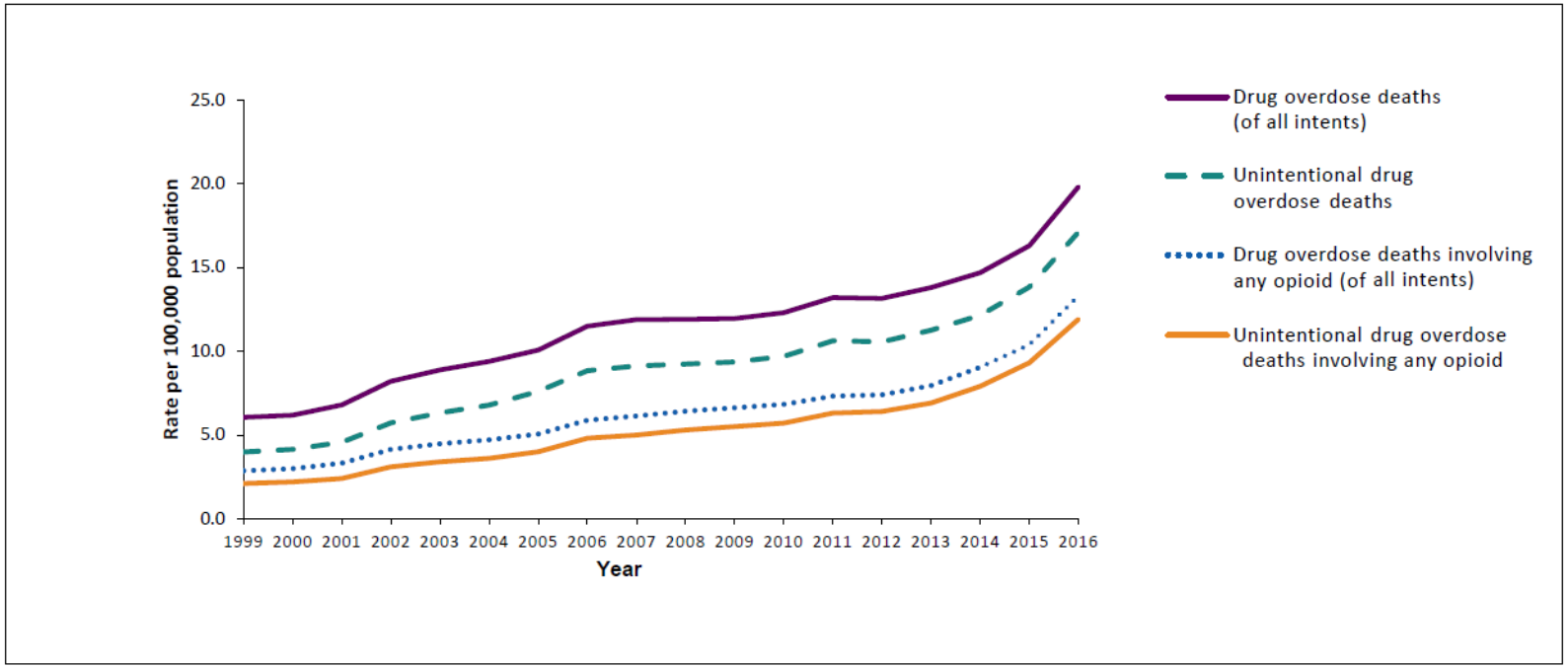
**proposed proprietary name and biological product suffix listings are only available to FDA - not the public*

U.S. FOOD & DRUG ADMINISTRATION

Prescription Opioid Abuse

Trends in Drug Overdose Deaths

FIGURE 2A **Age-adjusted rates[a] of drug overdose deaths[b] and drug overdose deaths involving any opioid[c] for all intents and for unintentional intent by year — United States, 1999–2016**

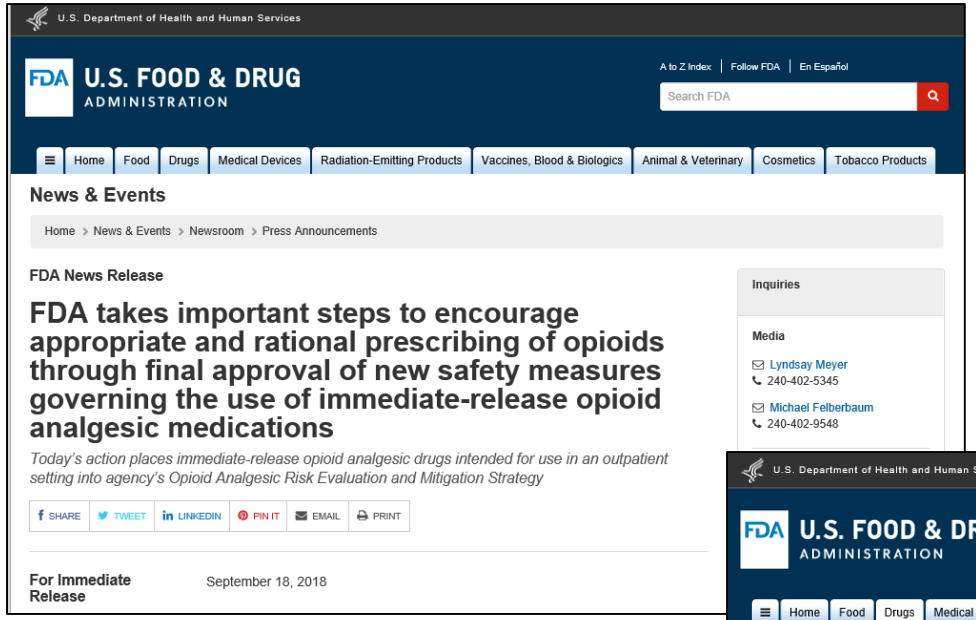


Source: https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf

Opioids

- Another busy year!
- Seven of nine Drug Safety and Risk Management Advisory Committee meetings 2018 concerned opioids
- Increasing public health focus

Opioids REMS

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