U.S. FOOD & DRUG ADMINISTRATION

Public Stakeholder Meeting on Prescription Drug User Fee Act (PDUFA) Reauthorization

November 20, 2020

Dr. Theresa Mullin
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research
Food and Drug Administration

Outline for this meeting

- Welcome and Roll Call
- Presentation Topics:
  - Enhancement And Modernization of the FDA Drug Safety System
  - Update on the Sentinel Initiative
  - Real World Evidence (RWE)
- Discussion
- Topics for upcoming meetings
- Recap and Closing

Enhancement And Modernization of the FDA Drug Safety System

November 20, 2020

Terry Toigo and Bob Ball
Center for Drug Evaluation and Research
Food and Drug Administration

PDUFA VI Drug Safety Overarching Goal

K. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

"FDA will continue to use user fees to enhance and modernize the current U.S. drug safety system, including adoption of new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, standardization and integration of REMS into the healthcare system, enhancing communication and coordination between postmarketing and pre-market review staff, and improving tracking, communication and oversight of postmarketing safety issues. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to enable access to needed medical products."

PDUFA VI Drug Safety Commitments

K. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

User fees will provide support for

- Timely and effective evaluation and communication of postmarketing safety findings related to human drugs, and
- Advancing postmarketing drug safety evaluation through expansion of the Sentinel System and integration into FDA pharmacovigilance activities

PDUFA VI Drug Safety Commitments: Timely and Effective Evaluation and Communication

Outline

- Discuss status of 4 commitments related to timely and effective evaluation and communication of postmarket safety findings
- Share resources for important information about the safety and availability of drug and biological products.

PDUFA VI Drug Safety Commitments: Timely and Effective Evaluation and Communication

1. *FDA will use user fee funds to continue to support the review, oversight, tracking, and communication of postmarketing drug safety issues.*
2. *FDA will make improvements to its current processes that capture and track information, including enhancements to its information technology systems, as needed, in order to support the management and oversight of postmarketing drug safety issues.*

April 30, 2020: FDA posted MAPP 4121.3 Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)

- Explains CDER's new process for tracking and managing the resolution of postmarket safety signals.
- Supported by a new workflow management tool (Lifecycle Signal Tracker (LiST)) to capture and manage all CDER safety signals for marketed drugs.

PDUFA VI Drug Safety Commitments: Timely and Effective Evaluation and Communication

3. *By the end of FY 2019, FDA will update existing policies and procedures (MAPPs and SOPPs) concerning tracking postmarketing safety signals to include consistent and timely notification to a sponsor (1) when a serious safety signal involving a product is identified and (2) to the extent practicable, not less than 72 hours before public posting of a safety notice under section 921 of the Food and Drug Administration Amendments Act of 2007.10*

September 9, 2019: CDER updated MAPP 6700.9 FDA Posting of Potential Signals of Serious Risks Identified by the FDA Adverse Event Reporting System and CBER Updated SOPP 8420: FDAAA Section 921: Posting of Potential Signals of Serious Risk

> Sponsors of an approved new drug application or biologics license application are notified at the time a safety signal will be evaluated and a second notification is sent to the sponsor at least 72 hours before the time of the quarterly Web posting.

A new report will be made available each quarter showing newly identified potential signals of serious risks/new safety information identified from the FAERS database during the previous quarter.

January - March 2020 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)

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Questions and Answers on FDA's Adverse Event Reporting System (FAERS)

FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files

FDA Adverse Event Reporting System (FAERS) Public Dashboard

FDA Adverse Event Reporting System (FAERS) Electronic

Product Name: Trade (Active Ingredient) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of June 12, 2020)
Bridion (sugammadex) injection	Arteriospasm coronary (coronary vasospasm)	FDA is evaluating the need for regulatory action.
• Bydureon (exenatide) • Bydureon BCise (exenatide) • Byetta (exenatide)	Thrombocytopenia	The "Contraindications," "Warnings and Precautions," "Adverse Reactions," "Patient Counseling Information," and "Medication Guide," sections of the exenatide labeling were updated in February 2020 to include thrombocytopenia. Example: Bydureon labeling

Content current as of:
06/26/2020

Regulated Product(s)
Drugs

Topic(s)
Adverse Event Reporting

PDUFA VI Commitments: Timely and Effective Evaluation and Communication

4. *By the end of FY 2022, FDA will conduct, or fund by contract, an assessment of how its data systems and processes, as described in MAPPs and SOPPs, support review, oversight, and communication of postmarketing drug safety issues.*

Status: To Be Completed

Providing the public with important information about the safety and availability of drug and biological products.

Safety & Availability (Biologics)

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- Safety & Availability (Biologics)
- Biologic Product Security
- Blood Safety & Availability
- CBER-Regulated Products: Shortages and Discontinuations
- Pandemics & Emerging Diseases
- Tissue Safety & Availability
- Vaccine Safety & Availability
- HIV Home Test Kits
- Recalls (Biologics)
- Report a Problem to the Center for Biologics Evaluation & Research

Content current as of: 02/20/2020

Regulated Product(s): Biologics

This webpage was developed to provide the public with important information about the safety and availability of biological products.

Safety communications older than 2 years are available on FDA Archive.

Biologics Safety and Availability Communications

- 2020 Safety and Availability Communications

Drug Safety and Availability

Share | Tweet | LinkedIn | Email | Print

- Drug Safety and Availability
- Information about Nitrosamine Impurities in Medications
- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- FDA Drug Safety Podcasts
- Information by Drug Class

Information for consumers and health professionals on new drug warnings and other safety information, drug label changes, and shortages of medically necessary drug products.

Download the **Drug Shortages Mobile Application**

Download on the App Store | ANDROID APP ON Google play

Drug Safety Communications

- Current Drug Safety Communications

Drug Safety-related Labeling Changes

- Drug Safety-related Labeling Changes
- More information about the database

Drug Recalls

- Drug Recalls

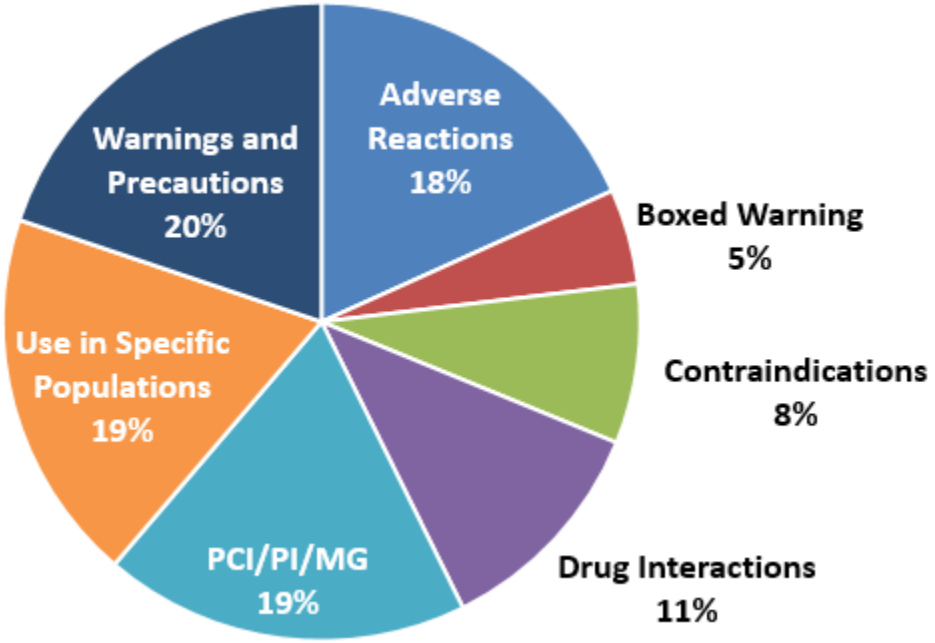
Providing the public with important information about the safety and availability of drug and biological products.

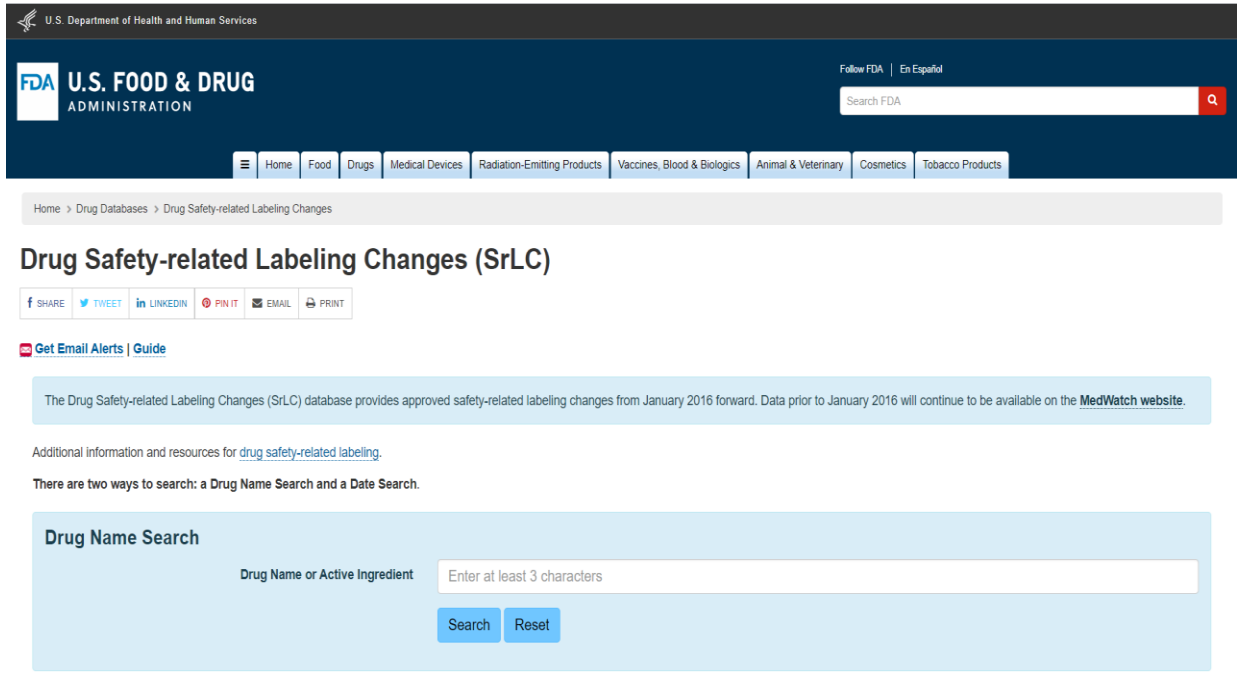
CDER Drug Safety Priorities annual report details CDER's key safety programs and activities, and describes several of CDER's most important efforts in drug safety science, surveillance, and oversight.

Providing the public with important information about the safety and availability of drug and biological products.

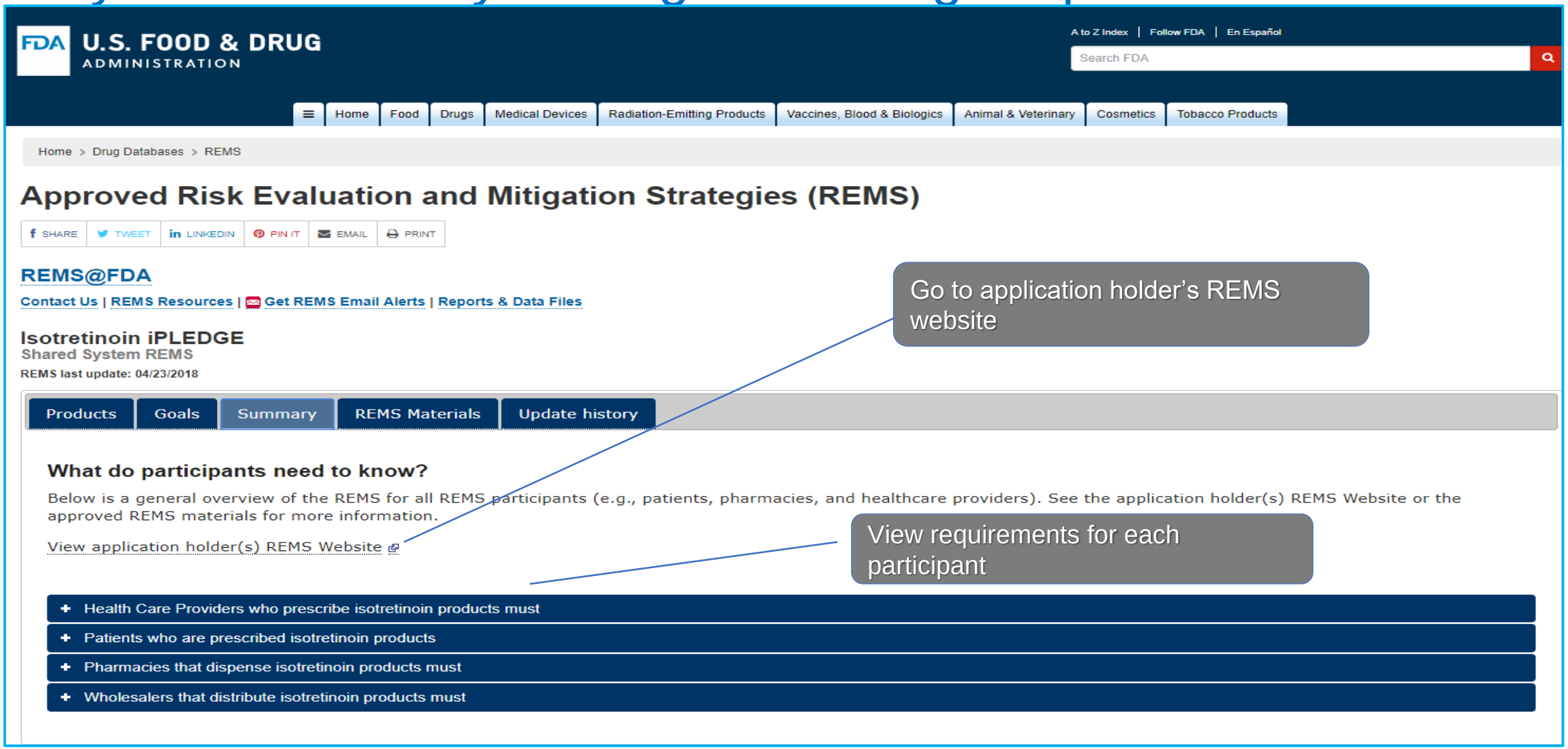
Drug Safety related Labeling Changes (SrLCs)

4,801 SrLCs were entered in 2019





Providing the public with important information about the safety and availability of drug and biological products.



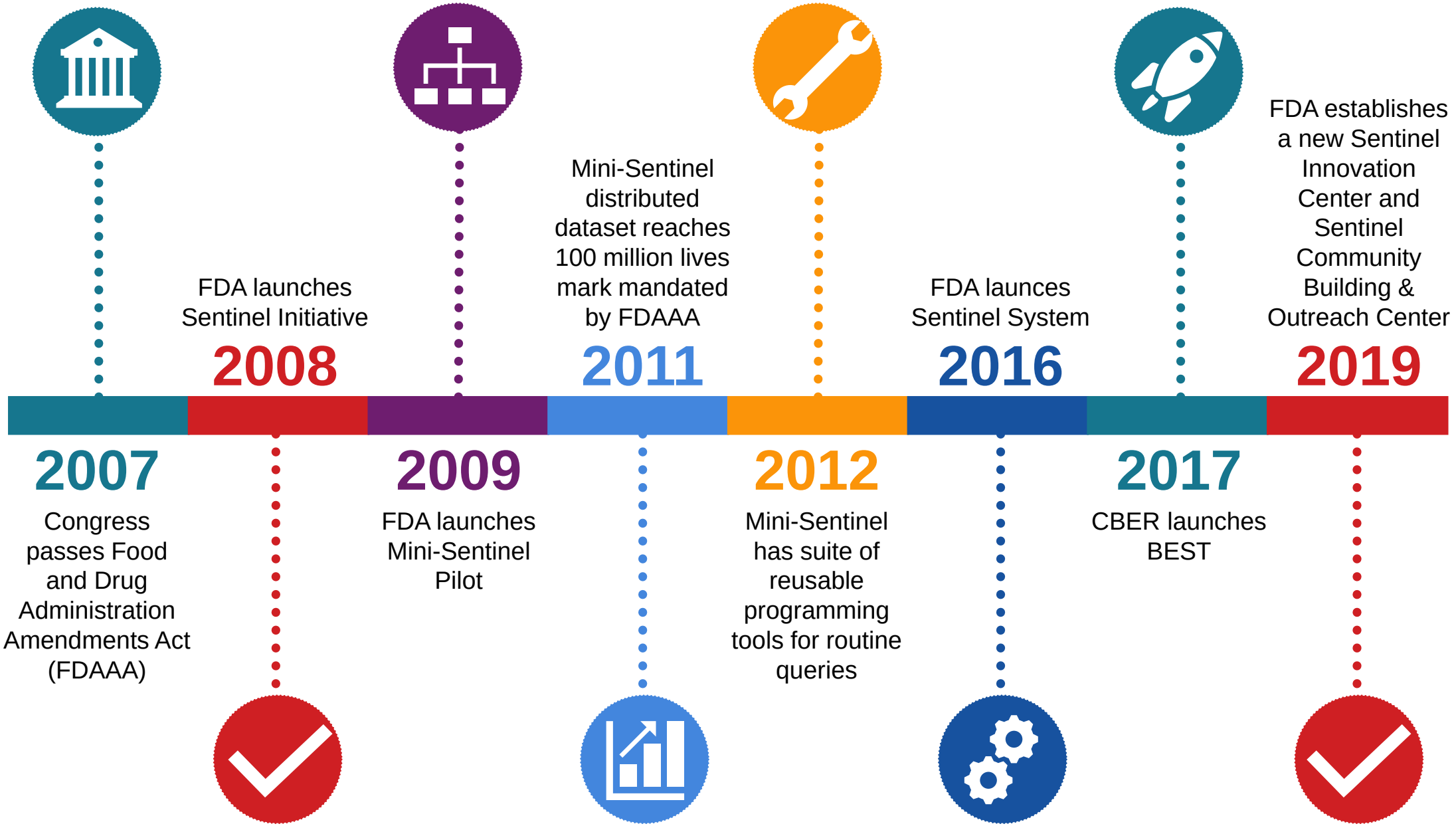
Questions?

Update on the Sentinel Initiative

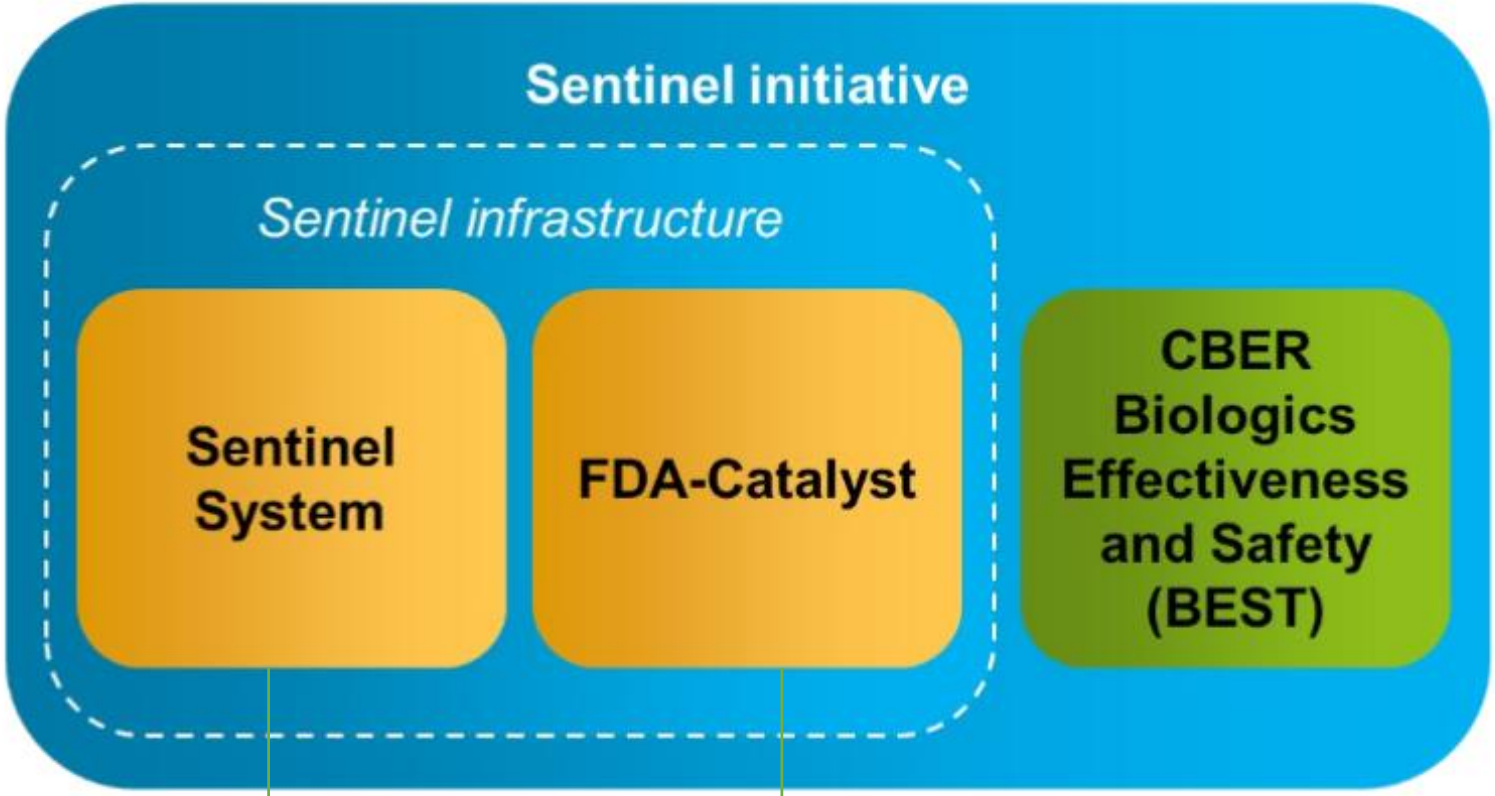
Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
November 20, 2020

Outline

- Brief history of Sentinel Initiative
- PDUFA VI accomplishments
- From strategic plan to new Sentinel System structure
- Biologics Effectiveness and Safety (BEST) Program


2007
Congress passes Food and Drug Administration Amendments Act (FDAAA)
2008
FDA launches Sentinel Initiative
2009
FDA launches Mini-Sentinel Pilot
2011
Mini-Sentinel distributed dataset reaches 100 million lives mark mandated by FDAAA
2012
Mini-Sentinel has suite of reusable programming tools for routine queries
2016
FDA launces Sentinel System
2017
CBER launches BEST
2019
FDA establishes a new Sentinel Innovation Center and Sentinel Community Building & Outreach Center

Components of Sentinel Initiative

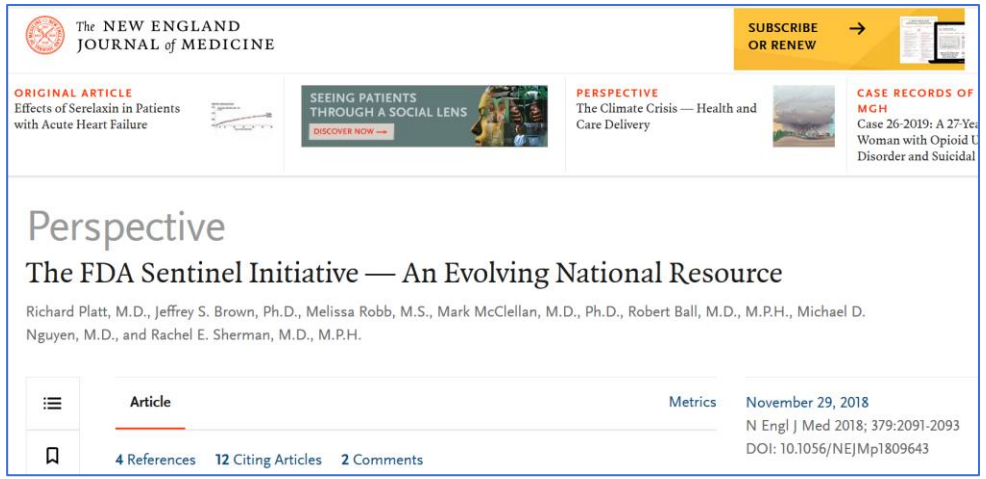


Queries using predefined analytic tools and distributed data network

Routine queries + interventions or interactions with health plan members

Scientific and Regulatory Impact

- >160 scientific papers published since 2009
- >400 analyses completed since 2016
- >30 regulatory outcomes posted online
- >21 adverse events, across 11 different drugs studied in Sentinel in lieu of a sponsor led PMR study since 2015



https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda

PDUFA VI Commitment for Sentinel	Actions Taken to Meet Commitment	Status
a. Expand sources of data and enhance core capabilities	• Created 5-year strategic plan to improve access to EHR, incorporate advanced analytics • Added PCORnet and TriNetX to Sentinel System, many other potential resources available in SOC and IC • Sentinel IC is developing a new EHR based distributed data network • Addition of BEST by CBER added several new claims and EHR data partners and scientific collaborators, with EHR data for over 50 million patients and linked claims-EHR data for over 5 million patients • BEST is developing new technologies to extract clinical information from EHR data	
b. Enhance communication with sponsors and the public on methodologies for Sentinel queries	• Formalized existing policies and processes for sponsor notification in MAPP • Continue to post all results, analytic packages, analysis tools • Hosting Sentinel Annual Meeting with public trainings on tool use • Updated Sentinel website	
c. Facilitate public and sponsor access to Sentinel	• Sharing analytic center with IMEDS • Supported 15 IMEDS queries • IMEDS benefits from FDA's routinely curated data network and only incurs marginal costs for queries	
d. Hold a public meeting engaging stakeholders	• Annual Sentinel Public Workshops, with public training on tools • Improving the Efficiency of Outcome Validation (July 2018) • Signal Detection meeting (Dec 2018)	

PDUFA VI Commitment for Sentinel	Actions Taken to Meet Commitment	Status
e. Establish policies and procedures to facilitate informing sponsors about the planned use of Sentinel	• Developed and posted sponsor notification MAPP	✓
f. Facilitate integration of Sentinel into the human drug review program	• ARIA sufficiency process now integral to original and supplemental drug reviews and integrated into Approval Letter • Developed ARIA templates to improve consistency of implementation • PMR industry guidance revised • CBER revised SOPP 8415 to formalize sentinel sufficiency assessments in the drug review program	✓
g. Develop a comprehensive training program for review staff on Sentinel	• Module-based training program	✓
h. By the end of FY 2022, analyze and report on FDA's use of Sentinel for regulatory purposes	• Multiple public presentations • Ongoing updates to 3 ARIA webpages describing ongoing queries, completed queries and regulatory impact • Ongoing updates to "Assessing ARIA's Ability to Evaluate a	✓

Active Risk Identification and Analysis (ARIA) System

- Creation of ARIA mandated by Section 905 of FDAAA 2007
- Linked to PMR in Section 901(3)(D)(i):
  - "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)."
- "…create a robust system to identify adverse events and potential drug safety signals"

Defining ARIA

ARIA uses a subset of Sentinel System's full capabilities to fulfill the FDAAA mandate to conduct active safety surveillance

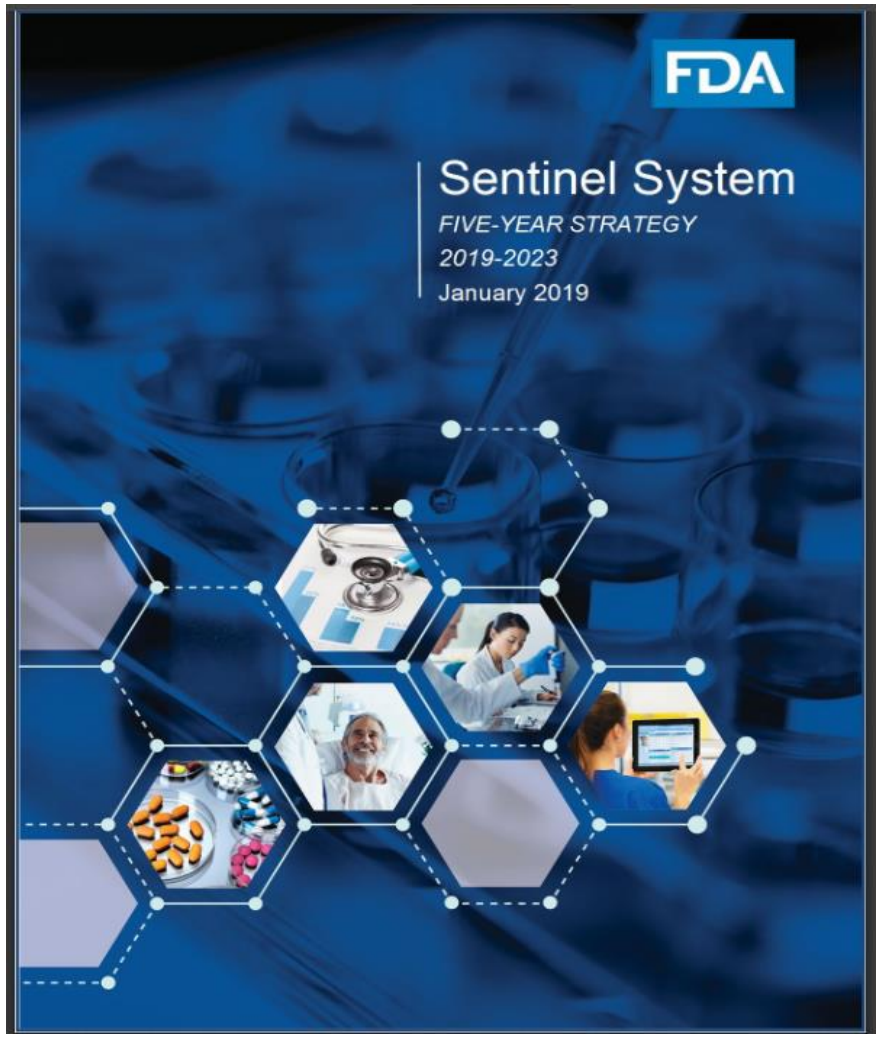
* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol based assessments with customized programming)

† Electronic claims data, without manual medical record review

What is Sufficiency?

- Adequate data
  - Drug/biologic of interest and comparator
  - Confounders and covariates
  - Health outcome of interest
- Appropriate methods
- To answer the question of interest
  - assess a known serious risk related to the use of the drug/biologic
  - assess signals of serious risk related to the use of the drug/biologic
  - identify an unexpected serious risk when available data indicate the potential for a serious risk
- To lead to a satisfactory level of precision

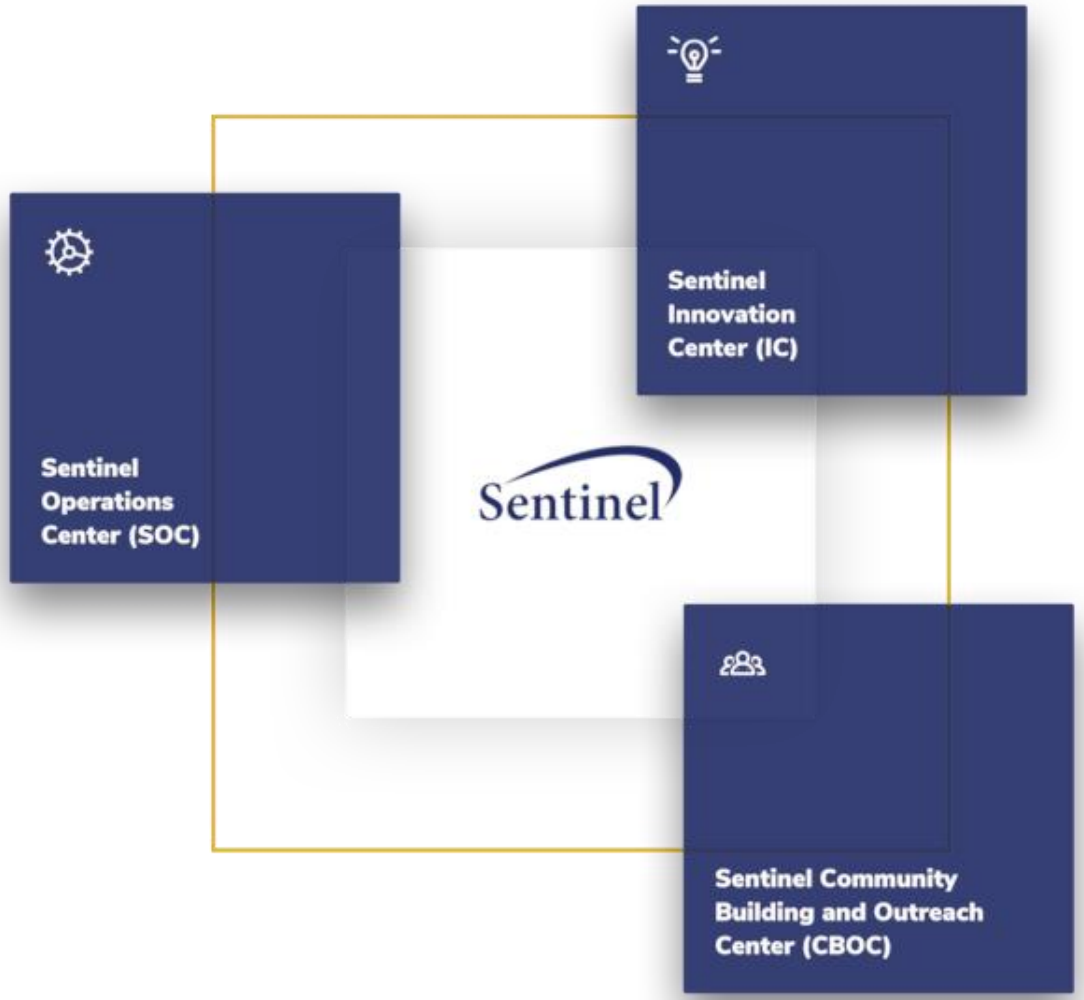
Key Messages from Strategic Plan



- Maintain and enhance the foundation of the Sentinel System, preserving FDA's long term investment in Sentinel's analysis tools and data infrastructure
- Diversify data sources, especially EHRs and claims linked to EHR's
- Incorporate advanced analytics
- Broaden touch points for participating in Sentinel's development
- Establish a Sentinel scientific community and disseminate knowledge to improve public health

New Sentinel System Structure

Conduct analyses and Enhance the Infrastructure



Advance the Science

Engage the Community

Biologics Effectiveness and Safety (BEST) Program

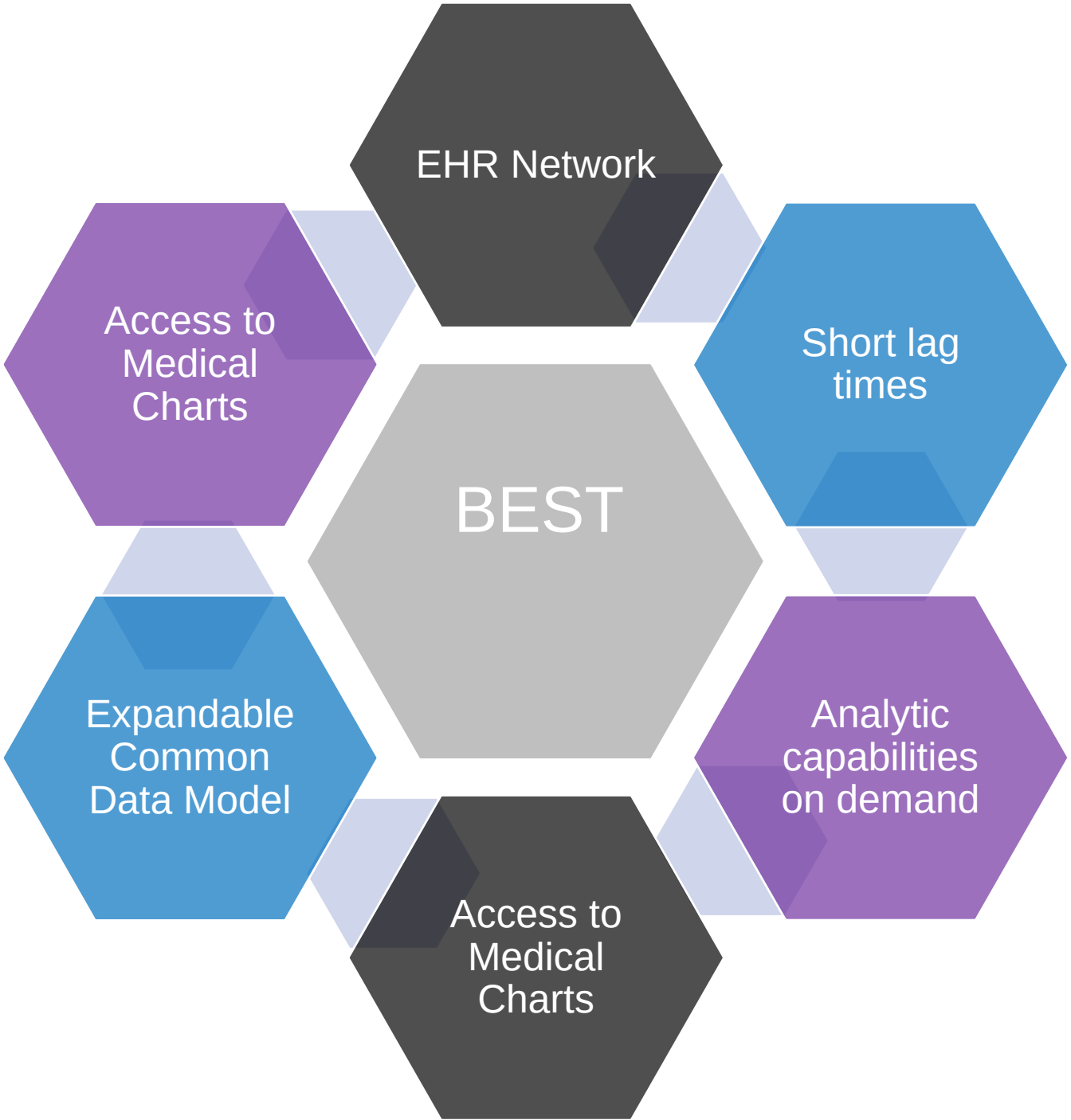
- BEST launched September 2017
- Emphasis on Electronic Health Records (with some claims data)
- Rapid access to clinical data via EHRs: address specific CBER product needs and regulatory questions
  - Claims data useful but can be limited– less clinical details and more time lag
- CBER Goals:
  - rapid queries with handling of complex confounders,
  - semi-automate chart review with new technology,
  - mine EHR data for outcomes and AEs

What is BEST?

- Electronic Healthcare data from multiple partner organizations:
  - Claims (billing) data
  - Electronic Health Records (EHR)
  - Claims-EHR linked data
- Data from partner organizations is transformed into a common data model (CDM)
- BEST operates as a distributed data network: data providers retain control over their data which remain behind local firewalls
- Coordinating Centers work with FDA to define parameters of the data needed, access the data from the partners, and return results to FDA

Why the BEST Initiative?

A modern surveillance system that is able to perform a diversity of queries and studies.



Summary

- FDA has met PDUFA VI commitments for Sentinel
- FDA has implemented ARIA assessments, deferred PMR's, and routinely uses Sentinel for regulatory decision making
- Continued PDUFA VI resources are needed to maintain and enhance the foundation of the Sentinel System, preserve the long term investment in Sentinel's analysis tools and data infrastructure, conduct routine analyses, train staff, periodically update training, guidance, processes and procedures, and communicate with the public and industry
- FDA's Sentinel strategic plan and new contracts contemplate broad areas for continued improvement
- New PDUFA VII resources could take advantage of strategic infrastructure building to focus on further development in specific areas of mutual interest to FDA and industry

Thank You

Questions?

FDA'S REAL-WORLD EVIDENCE PROGRAM

John Concato, MD, MS, MPH

Office of Medical Policy

Center for Drug Evaluation and Research

Food and Drug Administration (FDA)

20 November 2020

Objectives

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- Provide an overview of real-world data (RWD) and real-world evidence (RWE)

- Highlight key takeaways from FDA's RWE Framework for drugs and biologics

- Offer insight into RWE-related FDA activities involving:
    - internal Agency activities
    - external stakeholder engagement
    - demonstration projects
    - guidance development

Statutory Basis – 21st Century Cures Act (2016)

- FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  - approval of new indication for a drug approved under section 505(c)
  - satisfy post-approval study requirements
- Ongoing RWE program is based on December 2018 “RWE Framework”:
  - describes priority areas, remaining challenges, and potential pilot opportunities that the FDA RWE program will address
- Draft Guidance anticipated to be issued by December 2021
- Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA) VI

Enhancing the Use of RWE

- PDUFA VI Commitment Letter - Enhancing Use of RWE for the Use of Regulatory Decision Making

  -Initiate appropriate activities (e.g., pilot studies or *methodology development projects*) to address key issues in the use of RWE for regulatory decision making purposes

  -Publish *draft guidance* on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions (e.g., supplemental applications, post-marketing applications)

Definitions

From FDA Real-World Evidence Framework (2018):

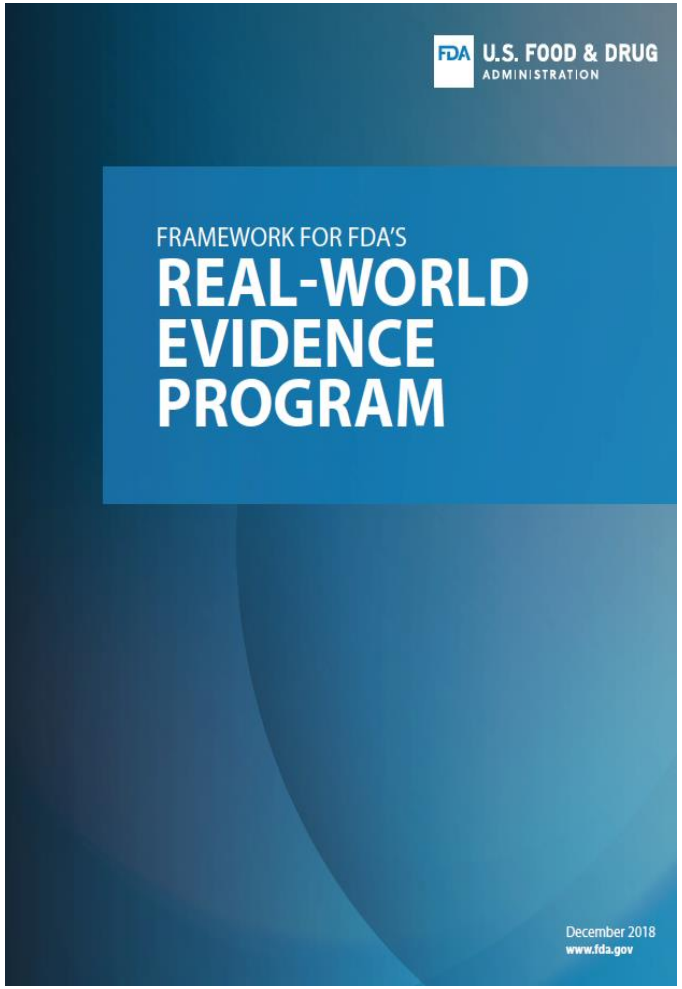
Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Example of FDA Drug Approval Involving RWE

- Blinatumomab = Bispecific T-cell Engager (BiTE) antibody; evaluated as treatment for Philadelphia chromosome-negative, relapsed-and-refractory B-cell precursor acute lymphoblastic leukemia
- Studied in single-arm trial (N=189): primary outcome of complete remission/partial hematological recovery in 43% (95% CI 35–50%)
- Results compared to historical data extracted from Europe and United States, with weighted analysis and propensity scoring used to balance compared populations: complete remission 24% (95% CI 20-27%) among n=694 patients in historical arm
- FDA-approved in Dec 2014

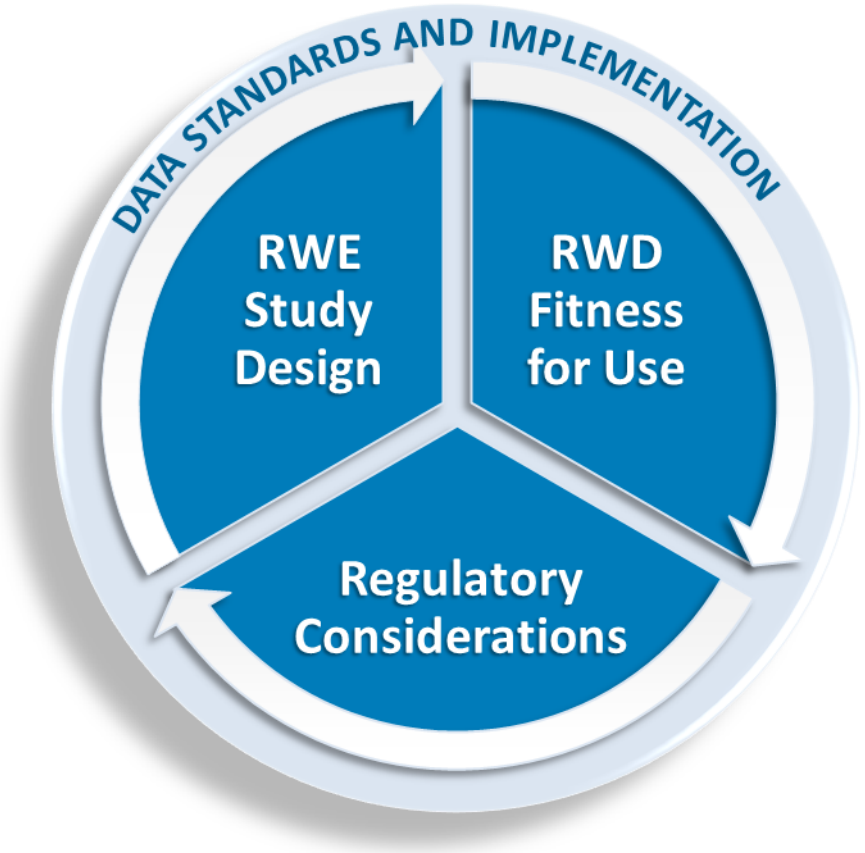
FDA RWE Framework



- Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)
- Conceptual approach to RWE ←
- Multifaceted program to implement RWE:
  - internal processes
  - external stakeholder engagement
  - demonstration projects
  - guidance development

https://www.fda.gov/media/120060/download

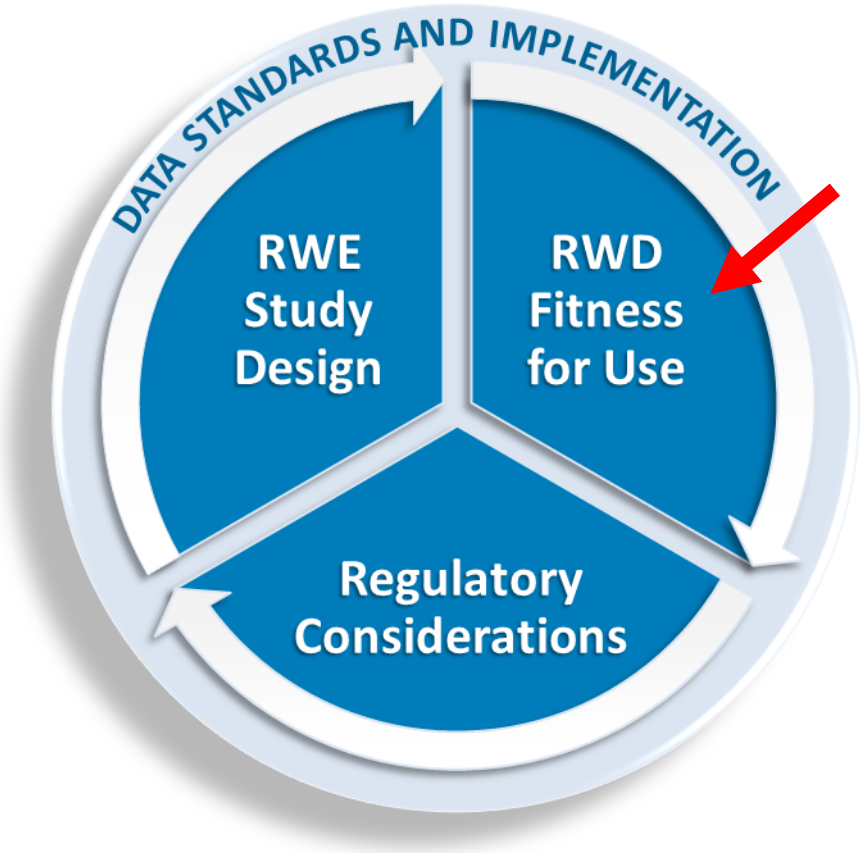
FDA RWE Framework – Key Take-Home Points



Considerations:

- Whether the RWD are fit for use
- Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements

RWE Framework: Data



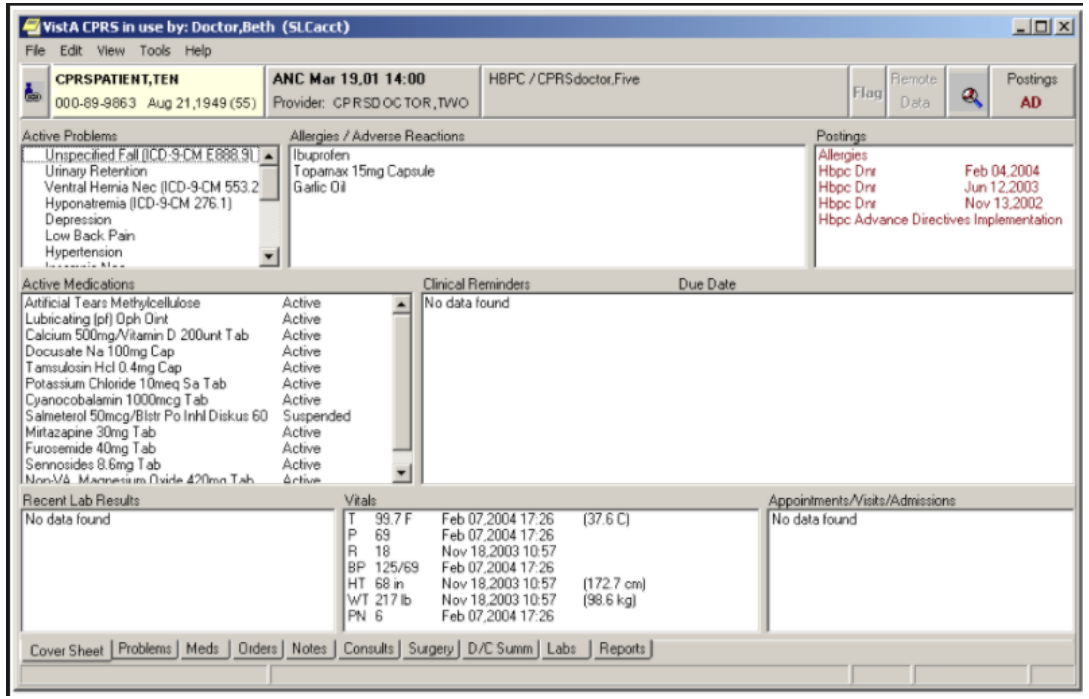
Considerations:

- Whether the RWD are fit for use,

  with RWD sources including administrative claims, electronic health records, registries, device-generated data, and patient-generated data

Real-World Data – Electronic Health Records (EHRs)

- Advantages:
  - Capture more complete (“granular”) clinical picture vs. claims data
  - Include labs/imaging/pathology reports
- Challenges:
  - Data in pathology/radiology/clinical notes often unstructured (≈80%)
  - Typed note ≠ consistency or complete documentation
  - Clinical outcome measures suitable for drug approvals may not be used or recorded consistently in practice
  - Interoperability issues



Evolving Digital Health Technology

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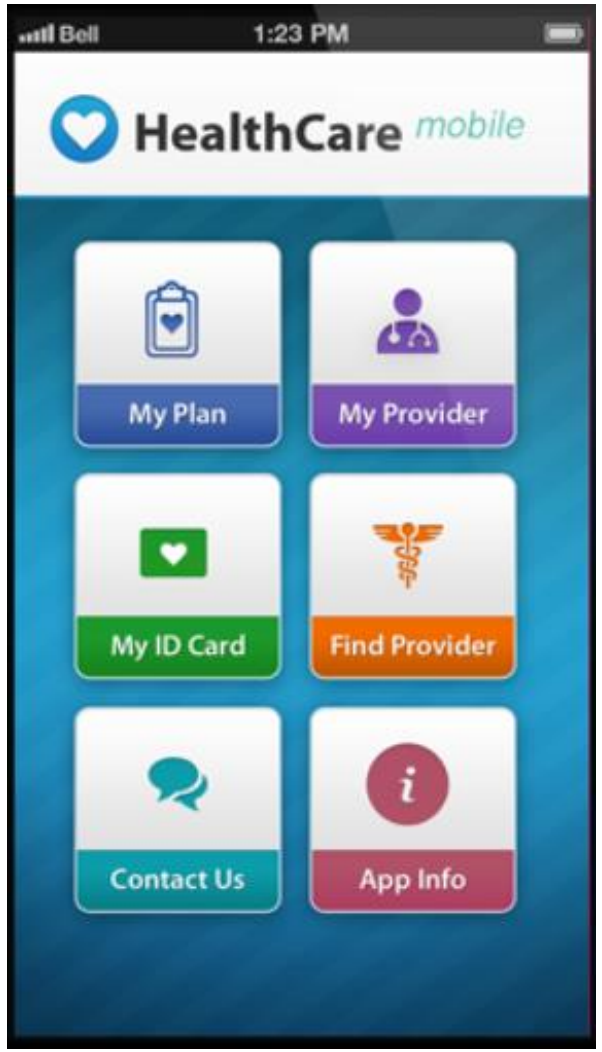
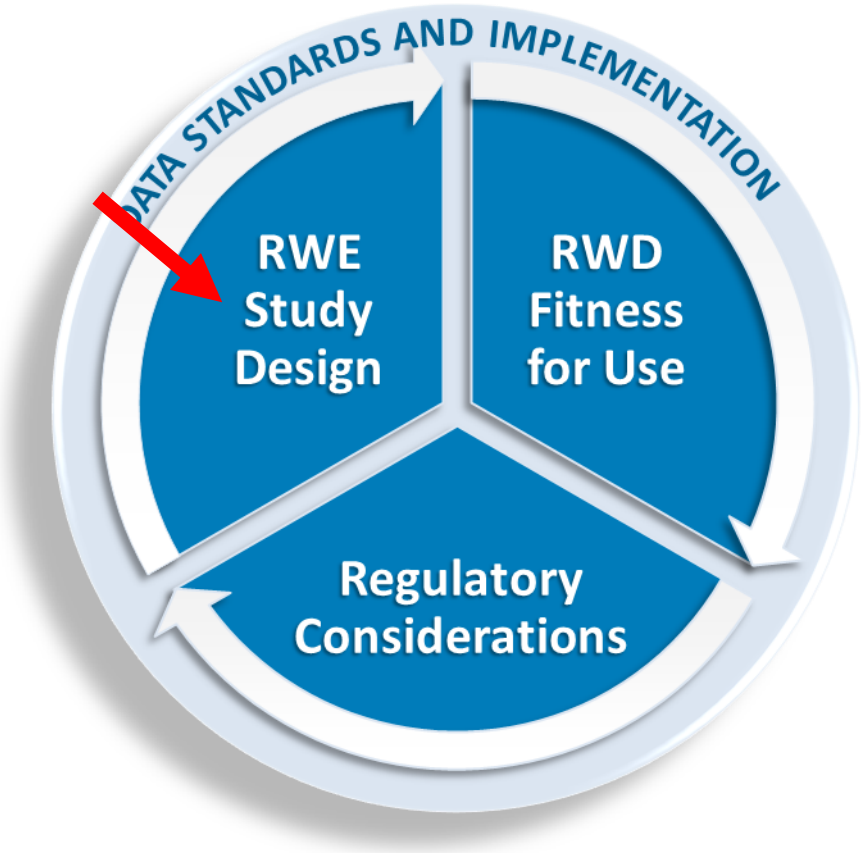


RWE Framework: Design



Considerations:

- Whether the RWD are fit for use
- Whether the clinical trial or (observational) study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

Study Design Based on ‘Intervention’ and ‘Data’

Randomized, observational, interventional, and real-world—What's in a name?

	Interventional	Non-Interventional
Primary data collection for research	• traditional RCTs • decentralized RCTs	• registry-based analyses*
Secondary use of clinical data	• pragmatic RCTs • cluster RCTs	• health records- or claims-based analyses*

*Non-interventional research designs include observational cohort and case-control studies; RCT = randomized, controlled trial.

Pharmacoepidemiol Drug Saf. 2020;1–4. DOI: 10.1002/pds.5123

Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness

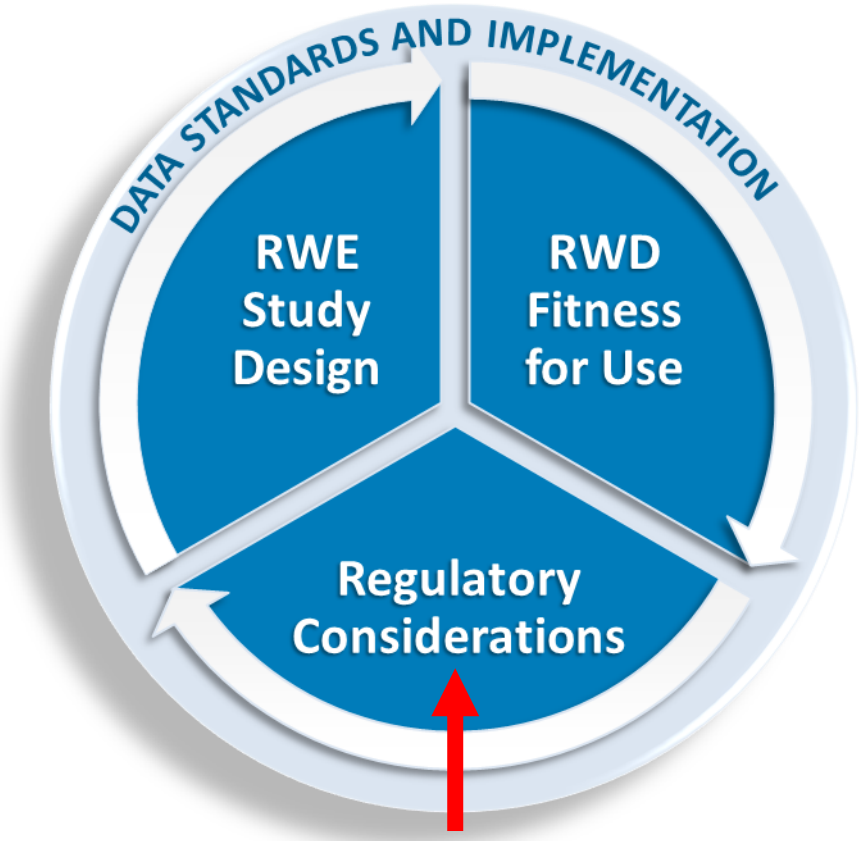
Jacqueline Corrigan-Curay, JD, MD
Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland.

Leonard Sacks, MD
Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland.

Janet Woodcock, MD
Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland.

Take-home message: "Further research is needed to determine when large data sets and statistical methods are sufficient to correct for systematic bias in sampling, ascertainment, or missing data that may arise in observational studies—a particular problem with retrospective studies in which less well-characterized patients limit adjustments for confounding."

RWE Framework: Regulatory



Considerations:

- Whether the RWD are fit for use
- Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements

U.S. Regulatory Standard

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- Code of Federal Regulations – Sec. 314.126 “Adequate and well-controlled studies”
  - Goal is to distinguish the effect of the drug from other influences, such as spontaneous change in disease course, placebo effect, or biased observation

- “Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs”

- Established practices, using traditional randomized controlled trials, include probabilistic control of confounding through randomization, blinding, standardized outcome assessment, adjudication criteria, and audits of study data

- *Note: Observational methods are currently being evaluated in this context*

Contradictory Observational Studies

JAMA The Journal of the American Medical Association

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Cardwell et al.

JAMA, August 11, 2010—Vol 304, No. 6

Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with

BMJ

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

BMJ 2010;341:c4444

The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal

Studies evaluating the **same drug** and the **same outcome**, using the **same source of data** and over a **similar time** period, yielded discordant results

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials

Cochrane Collaboration – 2014:

- "[…] on average, there is little evidence for significant effect estimate differences between observational studies and RCTs […]"
- "Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies"

Citation: Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

Conclusions: Our findings suggest that the discrepancies between the Women's Health Initiative and Nurses' Health Study ITT estimates could be largely explained by differences in the distribution of time since menopause and length of follow-up.

(*Epidemiology* 2008;19: 766–779)

RWD/RWE: Need for Transparency

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

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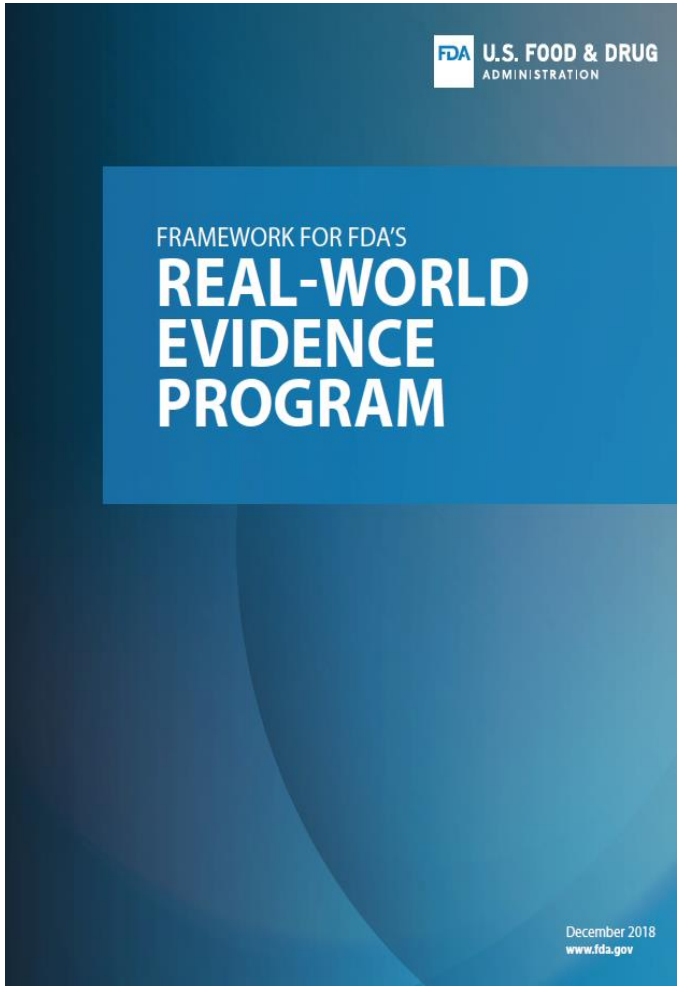
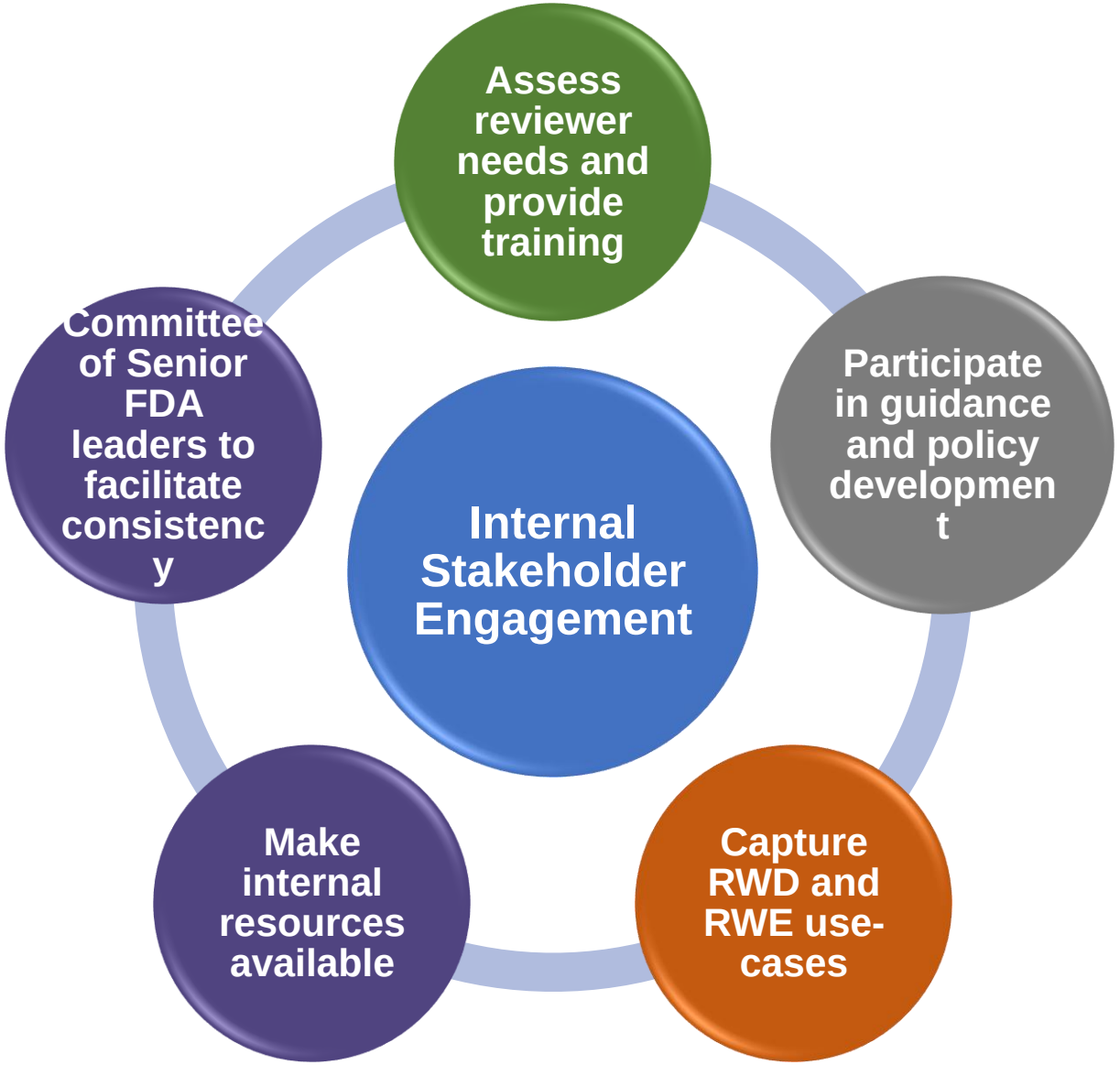
Transparency about study design and analysis, *before* execution, is critical for ensuring confidence in results

FDA RWE Framework



- Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)
- Conceptual approach to RWE
- Multifaceted program to implement RWE:
  - internal processes
  - external stakeholder engagement
  - demonstration projects
  - guidance development

Internal Stakeholder Engagement



Internal (cont'd) and External Engagement

- **Real-World Evidence Subcommittee internal activities (membership comprised of FDA staff from multiple CDER and CBER Offices) include:**
  - **providing oversight of policy development on RWE (e.g., guidances)**
  - **offering resources and leadership (e.g., to review divisions)**
  - **other activities**

- **RWE Subcommittee external activities include:**
  - **providing feedback on early-stage proposals from sponsors, vendors, etc.**
  - **discussing initiatives presented to Subcommittee for consideration**

- **Additional activities, beyond the Subcommittee, include:**
  - **holding FDA- or Center-level public meetings on RWE-related topics**
  - **conducting FDA Small business & industry webinars, speaking engagements**

Demonstration Project – Example

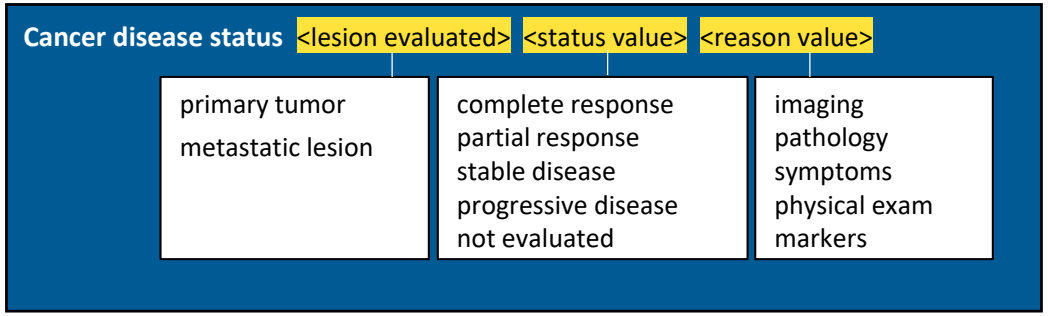
ICAREdata: Develop and validate EHR-based outcome measures in oncology

Cancer disease status

Clinical Assessment

Based on the data available today (at the time of evaluation), categorize the patient's disease extent.

ICAREdata Question Format



Sample Resulting Structured Phrase*

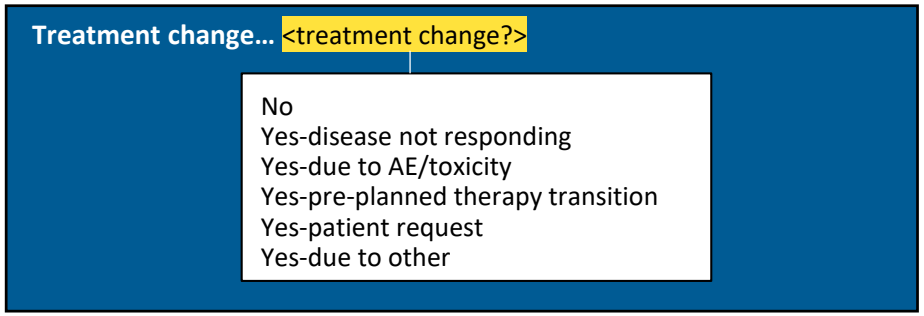
#Cancer disease status observed for #primary tumor was #progressive disease based on #imaging and #symptoms

Treatment change

Clinical Assessment

Based on your evaluation today, are you making a change in treatment?

ICAREdata Question Format



Sample Resulting Structured Phrase*

#Treatment change #yes-disease not responding

* Blue font denotes controlled vocabularies

Other RWE Demonstration Projects

- HARMONY-OUTCOMES ancillary study
  - whether EHRs are suitable for trial recruitment, baseline assessment, and endpoint ascertainment (>9,000 participants in original trial)
- IMPACT-Afib study
  - proof of concept for conducting randomized trials using FDA Sentinel infrastructure, involving distributed database and common data model (17 data partners; >300M unique patient IDs; >70M pts accruing data)
- RCT-DUPLICATE
  - longitudinal insurance claims data are being used in observational cohort analyses to emulate randomized controlled trials on the same topic (n > 30 trials)

New RWE Demonstration Projects

Funding Opportunity Title

Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making (U01) Clinical Trials Optional RFA-FD-20-030

Number	Applicant	Project Title
1 U01FD007220-01	Critical Path Institute	Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project
1 U01FD007206-01	Genentech, Inc.	Applying novel statistical approaches to develop a decision framework for hybrid RCT designs which combine internal control arms with patients' data from RWD sources
1 U01FD007213-01	Brigham and Women's Hospital	Enhancing evidence generation by linking RCTs to RWD
1 U01FD007172-01	Verantos, Inc.	Transforming RWE with Unstructured and Structured data to advance Tailored therapy (TRUST)

FDA Guidance Development

- **Real-world evidence topics (from 2018 RWE Framework):**

Using Trials or Studies with RWD/RWE for Effectiveness Decisions.....13

Assessing Fitness of RWD for Use in Regulatory Decisions 14

Potential for Study Designs Using RWD to Support Effectiveness 19

Regulatory Considerations for Study Designs Using RWD 22

Data Standards — Appropriate Data Standards for Integration and Submission to FDA..... 24

- **"Submitting Documents Using RWD and RWE to FDA […]" Guidance, May 2019**

- **Ongoing work on other draft guidance documents (Dec 2021 target date)**

RWE Informs Effectiveness When Fit-for-Purpose

DRUG	INDICATION	APPROVED	DATA
Carbaglu *(carglumic acid)*	Treatment of NAGS deficiency	2010	▪ Retrospective, non-random, unblinded **case series of 23 patients compared to historical control group**
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	2012	▪ Approval based on open-label, **NIH expanded access protocol**
Blincynto *(Blinatumomab)*	Treatment of Acute Lymphoblastic Leukemia	2014	▪ Single-arm trial ▪ Reference group weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites***
Vistogard *(uridine triacetate)*	Overdose of chemotherapy drugs 5-fluorouracil (5-FU)	2015	▪ Two single-arm, open-label expanded access trial of **137 patients compared to case history control**

List not exhaustive

Bold = RWE

*https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html

RWE Informs Effectiveness When Fit-for-Purpose (cont'd)

DRUG	INDICATION	APPROVED	DATA
Defitelio *(defibrotide sodium)*	Severe hepatic veno-occlusive disorder	2016	▪ Two prospective clinical trials enrolling 179 patients and **an expanded access study with 351 patients**
Lutathera *(lutetium 177 dotate)*	Gastroenteropancreatic neuroendocrine tumours (GEP-NETs)	2017	▪ Open-label clinical trial ▪ **Analysis of a subset of 360 patients who participated in an investigator sponsored, open-label, single-arm, single institution study of 1214 patients that started as an expanded access program**
Zostavax *(Zoster Vaccine Live)*	Prevention of herpes zoster (shingles) in persons 50 years of age and older	2018	▪ **Prospective, observational cohort study using electronic health records in Kaiser Permanente Northern California (KPNC)** to characterize the duration of protection in persons 50 years of age and older
Ibrance *(palbociclib)*	Men with certain types of advanced or metastatic breast cancer	2019	▪ Data from electronic health records and postmarketing reports of the **real- world use of IBRANCE in male patients**

List not exhaustive

Bold = RWE

RWE and COVID-19 – Representative Comments

The pandemic is prompting widespread use–and misuse–of real-world data

www.pnas.org/cgi/doi/10.1073/pnas.2020930117

“The dangers of COVID-19 present an unprecedented opportunity to leverage diverse, real-world data sources to inform medical and regulatory responses. But researchers and clinicians must be careful not to sacrifice methodological rigor.”

Summary and Conclusions

- FDA's Real-World Evidence Program is advancing as outlined in the Agency's 2018 'RWE Framework'
- Ongoing efforts can identify attributes that promote generation of reliable and relevant real-world data as well as valid real-world evidence
- Alternative study designs can support and augment—but are not intended to replace—clinical trials for regulatory decision-making

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Questions?

Discussion

U.S. FOOD & DRUG ADMINISTRATION

PDUFA VII
Closing Remarks

November 20, 2020

Dr. Theresa Mullin
Office of the Center Director
Center for Drug Evaluation and Research
Food and Drug Administration

Upcoming Topics

Friday, December 11, 2020

10:30AM-12:30 PM EST

- CDER recent work to modernize new drug review information infrastructure (knowledge management) and reviewer talent management
- CBER cell and gene therapy review programs
- FDARA Section 905 provisions and implications for the future allocation of user fees to modernize infrastructure and support regulatory review