Sentinel

Real-world evidence: Trends and application of real-world data in drug development and safety

The Sentinel Experience

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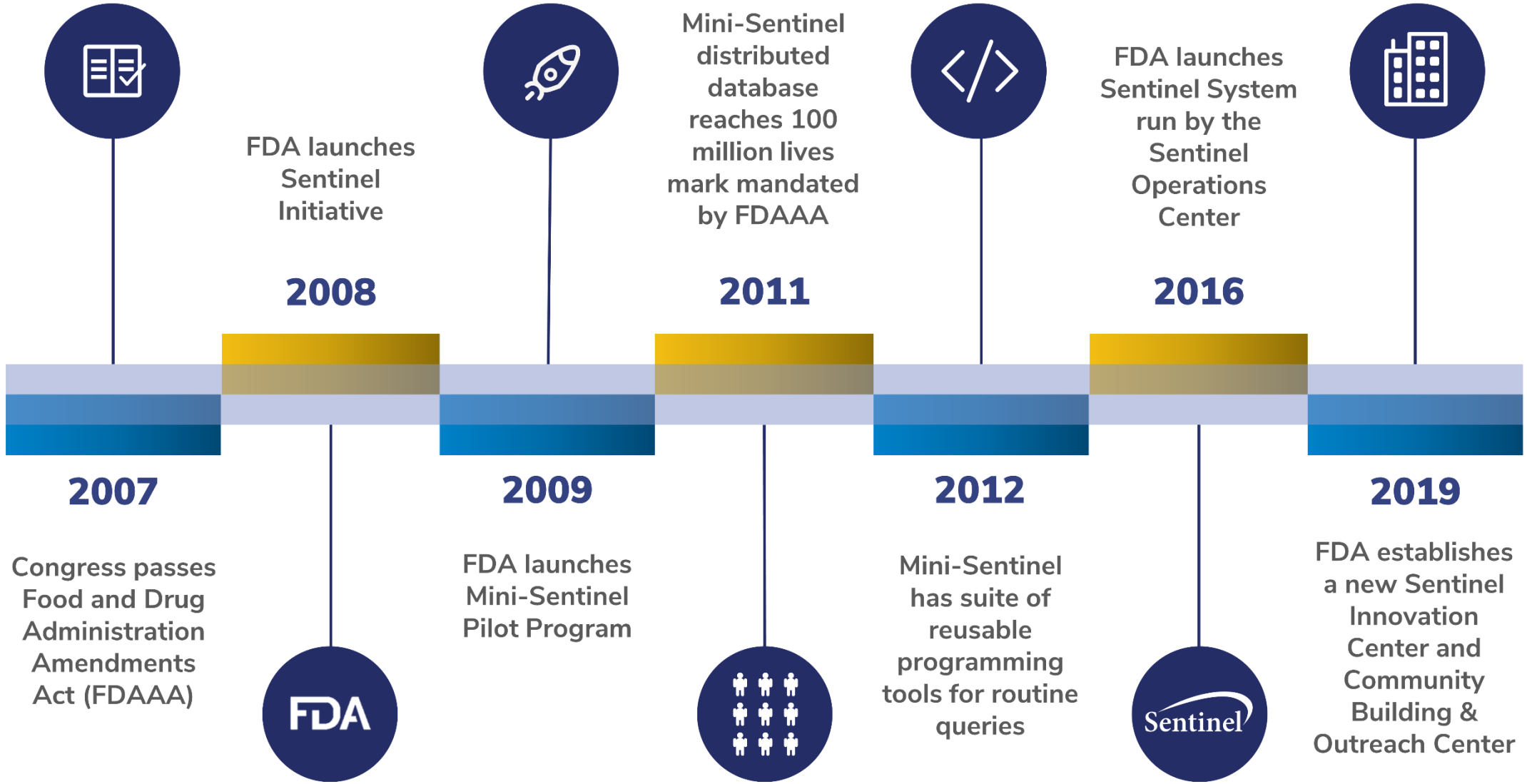
July 10, 2021



https://www.sentinelinitiative.org/about

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

Healthagen

aetna

HealthCore

Anthem

OPTUM

Humana Healthcare Research

RTI INTERNATIONAL

veradigm

TriNetX

TennCare

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

OPTUMLabs

pcornet

MASSACHUSETTS

BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

KAISER PERMANENTE

Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington

ADVANCE Collaborative

Booz | Allen | Hamilton

CAPriCORN

GPC Greater Plains Collaborative

Marshfield Clinic Research Institute

HCA Healthcare

GDIT

NYC-CDRN New York City Clinical Data Research Network

UF College of Pharmacy UNIVERSITY of FLORIDA

VANDERBILT UNIVERSITY MEDICAL CENTER

The Meyers Primary Care Institute

RUTGERS

OneFlorida Clinical Research Consortium

REACHnet Research Action for Health Network

IBM Watson Health

UAB

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

PaTH Network patient empowered research

PEDSnet A Pediatric Learning Health System

HealthPartners Institute

SCHOOL OF PUBLIC HEALTH UNIVERSITY of WASHINGTON

STAR Stakeholders, Technology, and Research CRN

Duke Clinical Research Institute

THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH

Penn Medicine

Male, 55 Years Old, From Boston

Has Appendectomy

Diagnosed with Hypertension

Routine Office Visit

2017 | 2018 | 2019 | 2020

1/1/2017

Encounter

Office Visit Diagnosis:
Influenza with pneumonia

Dispensings

Prescription:
Antibiotic

3/15/2018

Encounters

Emergency Department Procedure:
Appendectomy

3/15/2018 - 3/18/2018

Hospital:
Inpatient Stay

12/11/2018

Encounter

Office Visit Diagnosis:
Hypertension

Dispensings

Prescription:
Anti-hypertensive

10/31/2019

Encounter

Office Visit Diagnosis:
Hypertension

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	zip
PatID1	2/2/1964	F	N	5	32818

DISPENSING

PATID	RXDATE	NDC	RXSUP	RXAMT
PatID1	10/14/2005	00006074031	30	30
PatID1	10/14/2005	00185094098	30	30
PatID1	10/17/2005	00378015210	30	45
PatID1	10/17/2005	54092039101	30	30
PatID1	10/21/2005	00173073001	30	30
PatID1	10/21/2005	49884074311	30	30
PatID1	10/21/2005	58177026408	30	60
PatID1	10/22/2005	00093720656	30	30
PatID1	10/23/2005	00310027510	30	15

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2004	Y	N
PatID1	1/1/2005	12/31/2005	Y	Y

DEATH

PATID	DEATHDT	DTIMPUTE	SOURCE	CONFIDENCE
PatID1	12/27/2005	N	S	E

ENCOUNTER

PATID	ENCOUNTERID	ADATE	DDATE	ENCTYPE
PatID1	EncID1	10/18/2005	10/20/2005	IP

DIAGNOSIS

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	DX	DX_CODETYPE	PDX
PatID1	EncID1	10/18/2005	Provider1	IP	296.2	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	300.02	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	305.6	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	311	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	401.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	493.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	715.9	9	S

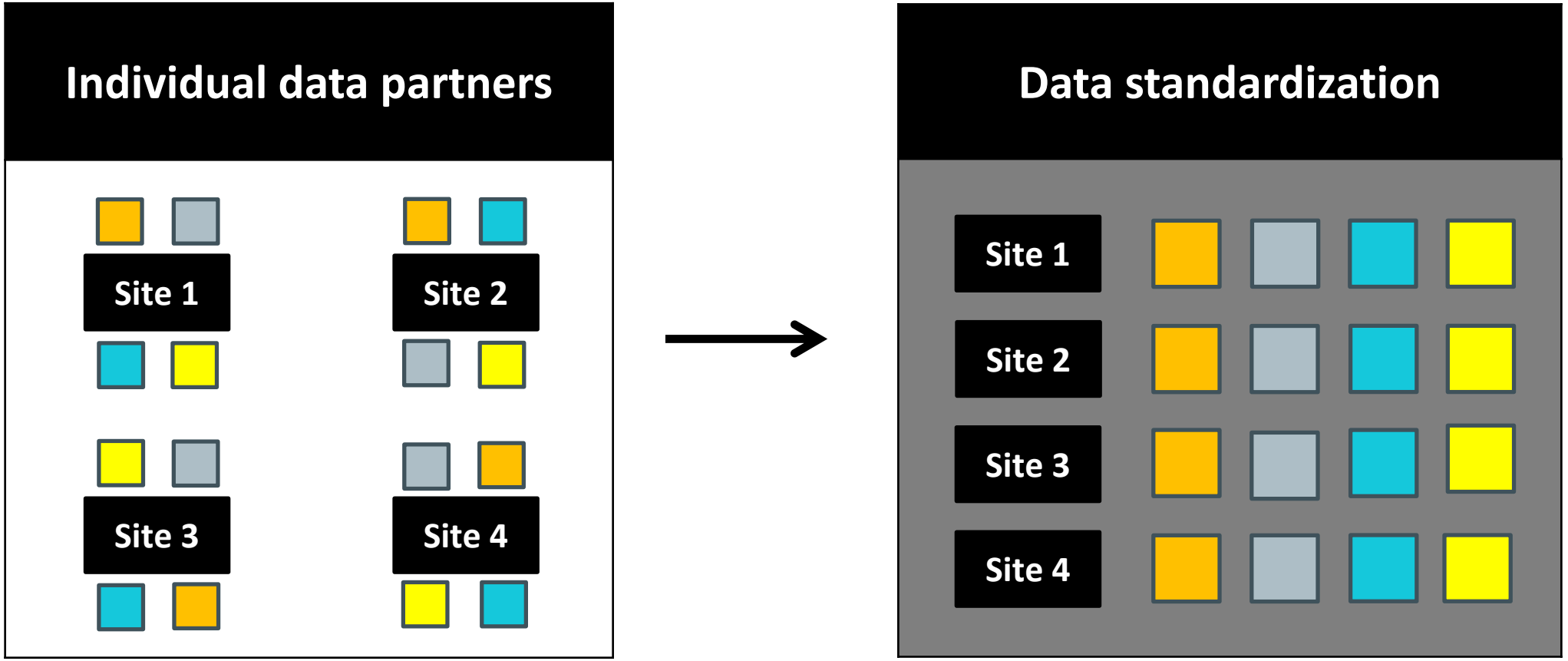
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99222	C4
PatID1	EncID1	10/18/2005	Provider1	IP	99238	C4
PatID1	EncID1	10/18/2005	Provider2	IP	27445	C4

CAUSE OF DEATH

PATID	COD	CODETYPE	CAUSETYPE	SOURCE	CONFIDENCE
PatID1	J18.0	10	U	S	E

Hypothetical numbers; for illustrative purposes only


Individual data partners
Site 1
Site 2
Site 3
Site 4
Data standardization
Site 1
Site 2
Site 3
Site 4

Types of Data Quality Checks and Examples

Level 1 Checks:
Single table checks

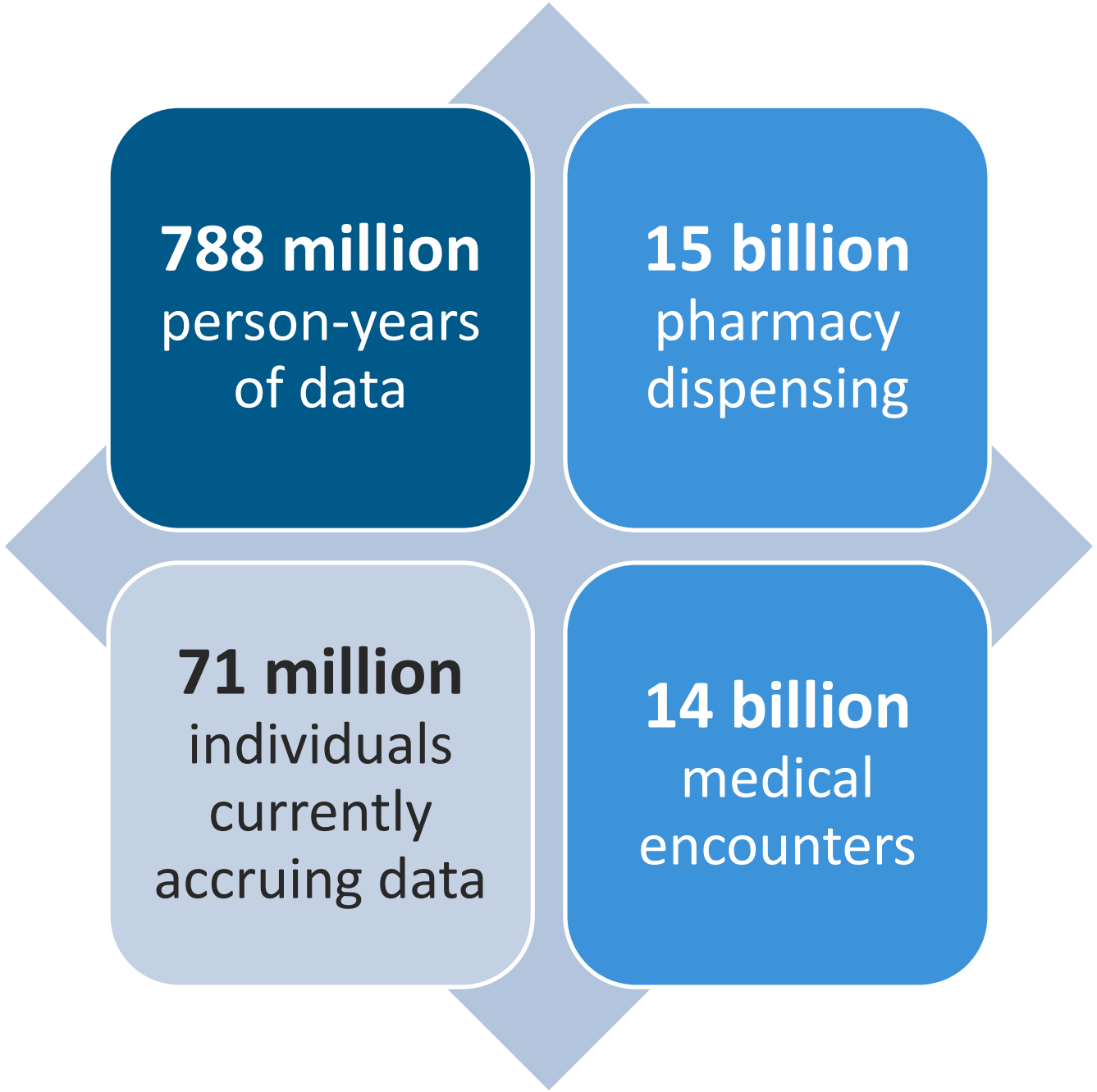
- **Completeness**
  Admission date is not missing value
- **Validity**
  Admission date is in date format

Level 2 Checks:
Cross-table checks

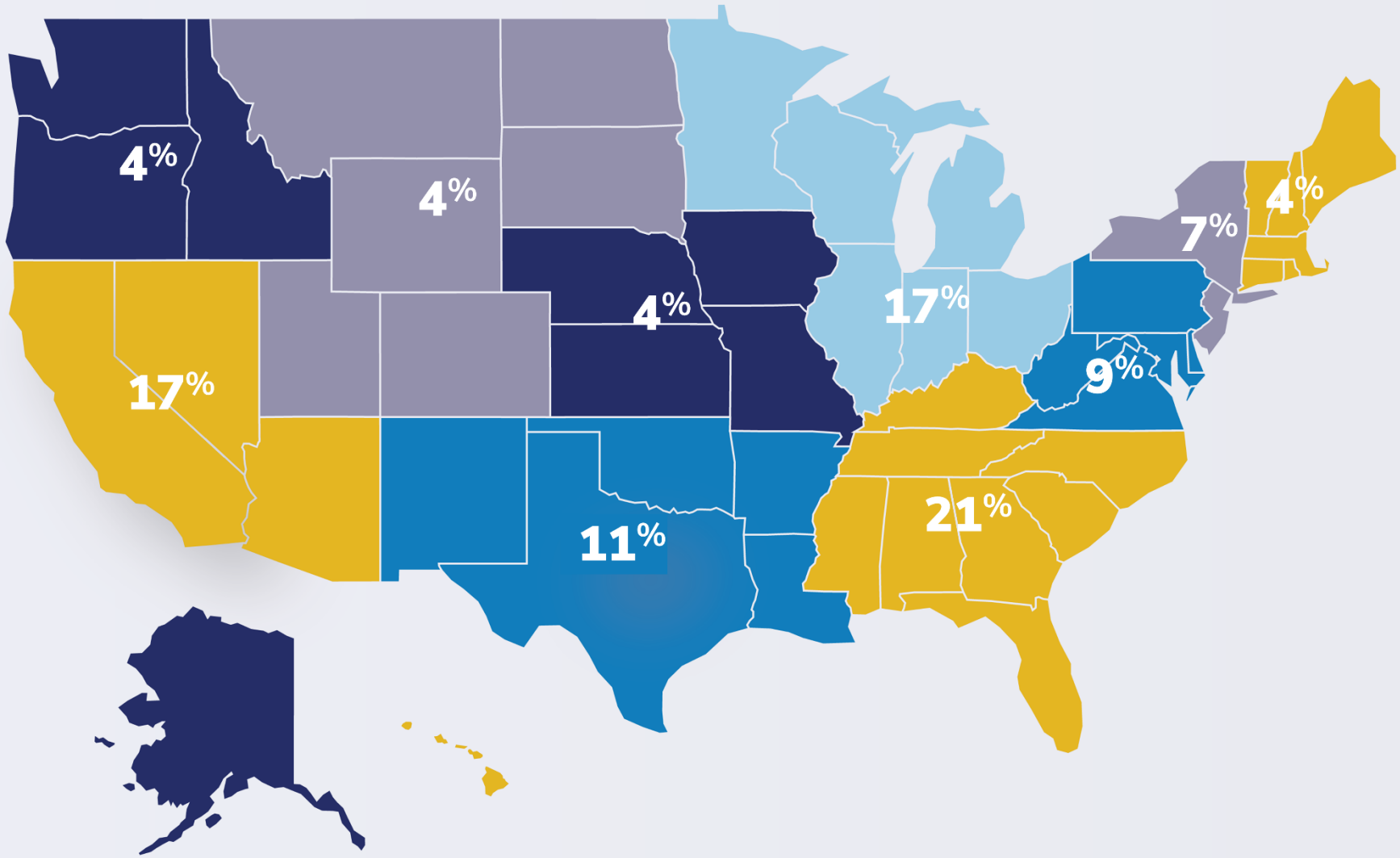
- **Accuracy**
  Admission date occurs before the patient's discharge
- **Integrity**
  Admission date occurs within the patient's active enrollment period

Level 3 Checks:
Cross-time checks

- **Consistency of Trends**
  There is no sizable percent change in admission date record counts by month-year


788 million
person-years
of data
15 billion
pharmacy
dispensing
71 million
individuals
currently
accruing data
14 billion
medical
encounters

Member Distribution of the Sentinel Distributed Database by Geographic Region

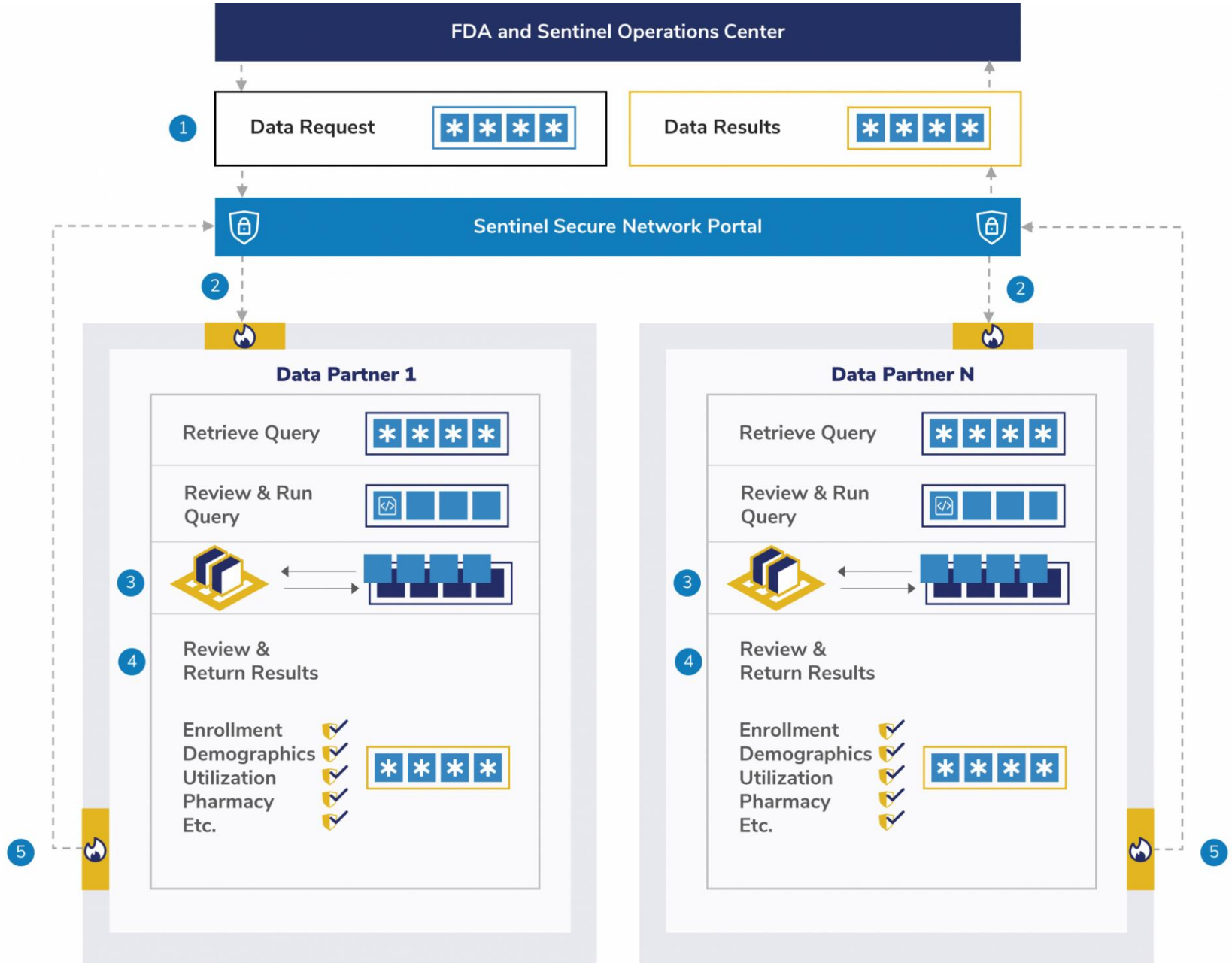


1. FDA data request sent to Data Partners via FISMA-compliant secure network portal
2. Data Partners retrieve query
3. Data Partners review and run query against their local data behind their firewalls
4. Data Partners review results for accuracy and privacy compliance
5. Data Partners return de-identified results to SOC via secure portal

Firewall

Local Data

Privacy Compliance



Sentinel's Multi-Modal Response System

Claims (with Limited EHR Network)

Active Risk Identification and Analysis (ARIA)*

- Sentinel Distributed Database
- IBM® MarketScan® Research Databases

- Sentinel Common Data Model
- Sentinel Analytic Tools
- Access to Medical Records within the Sentinel Distributed Database

EHR Data Aggregators

- TriNetX
- IBM Watson Health

- Proprietary Common Data Models
- Web-Based Query Interface & Custom Programming
- Access to Medical Records varies by Source

EHR Data Warehouse

- HCA Healthcare
- Veradigm

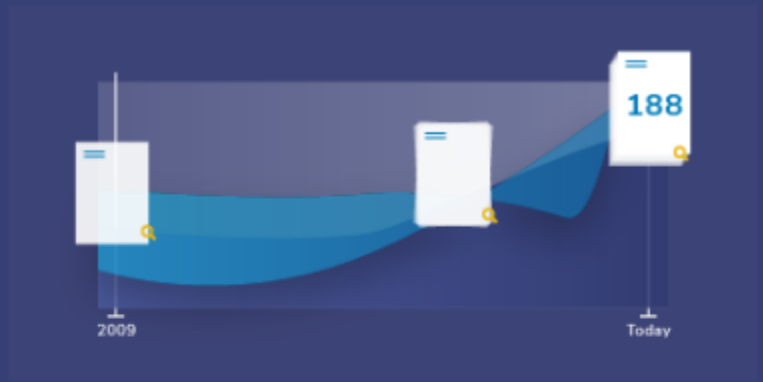
- Data Warehouse for Multiple Healthcare Organizations in a System
- Custom Programming
- Access to Medical Records

EHR Networks

- PCORnet

- PCORnet Common Data Model
- PCORnet Analytic Tools
- Access to Medical Records

**Note: The Active Risk Identification and Analysis (ARIA) System is comprised of the Sentinel Distributed Database, the Sentinel Common Data Model, and Sentinel analytic tools.*

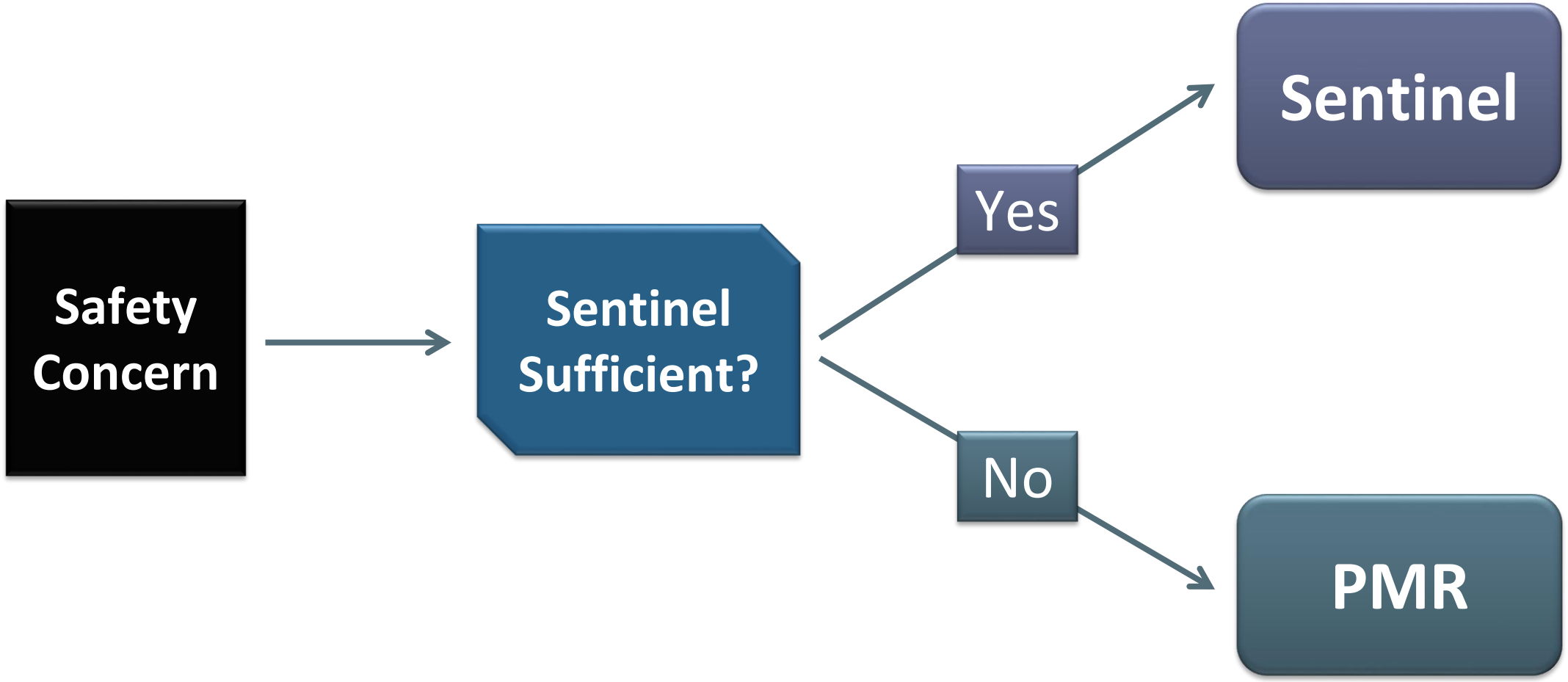


Since the founding of the Sentinel Initiative in 2009, 188 scientific papers have been published

Scientific Publications

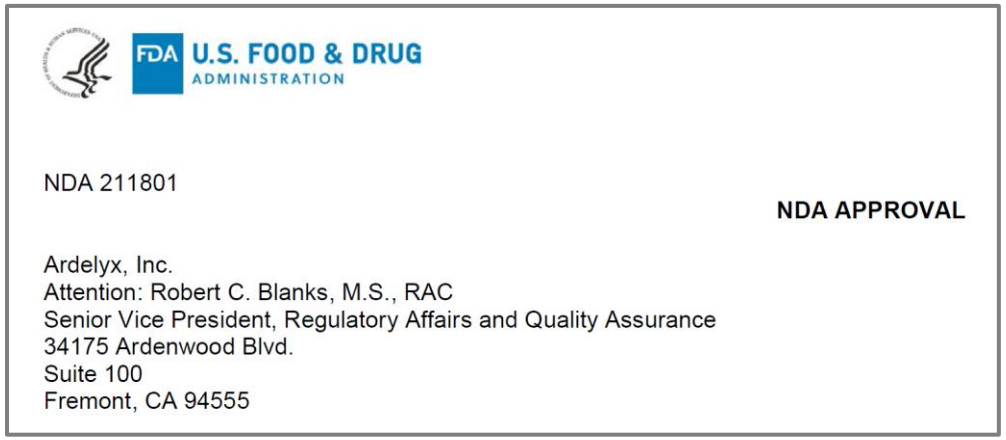
Since 2016, more than 30 Sentinel drug assessments have contributed to FDA regulatory actions or discussion

Drug Assessments



PMR: Post-market requirement

https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf



U.S. FOOD & DRUG ADMINISTRATION

NDA 211801

NDA APPROVAL

Ardelyx, Inc.
Attention: Robert C. Blanks, M.S., RAC
Senior Vice President, Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd.
Suite 100
Fremont, CA 94555

NDA approval letter

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate tenapanor in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: risk of inflammatory bowel disease.

The ARIA safety assessment will be posted to the Sentinel website.[3] Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/211801Orig1s000ltr.pdf

OXFORD

JNCI Cancer Spectrum (2021) 5(2): pkab009

doi: 10.1093/jncics/pkab009
First published online 4 February 2021
Article

Risk of Nonmelanoma Skin Cancer in Association With Use of Hydrochlorothiazide-Containing Products in the United States

Efe Eworuke, PhD,[1,*] Nicole Haug, MPH,[2] Marie Bradley, PhD,[1] Austin Cosgrove, BS,[2] Tancy Zhang, MPH,[2] Elizabeth C. Dee, MPH,[2] Sruthi Adimadhyam, PhD[2] Andrew Petrone, MPH,[2] Hana Lee, PhD,[3] Tiffany Woodworth, MPH,[2] Sengwee Toh, ScD[2]

Postmarketing Experience:

Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

Label change

https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=02e96a51-1d56-460c-8c20-3d6f37e0ce46

FDA Briefing Document

ARTHRITIS ADVISORY COMMITTEE
AND DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE MEETING
January 11, 2019

NDA 21856
Febuxostat
Xanthine oxidase (XO) inhibitor for the chronic management of hyperuricemia in patients with gout

Takeda

EXECUTIVE SUMMARY

Febuxostat (Uloric®), a selective inhibitor of xanthine oxidase, lowers serum uric acid levels by inhibiting the conversion of xanthine to uric acid. It was approved by the FDA in February 2009 for the management of chronic hyperuricemia in patients with gout. Preliminary results from a post-approval safety trial (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity (CARES)) showed an increased risk of cardiovascular-related death and all-cause death in febuxostat users. As a result, FDA issued a drug safety communication in November 2017. An advisory committee (AC) meeting is scheduled for January 11, 2019 to discuss potential regulatory action to address the safety of febuxostat. For context, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested the Division of Epidemiology (DEPI) to investigate the characteristics of the gout population and use of febuxostat and allopurinol in real-world settings using the Sentinel Distributed Database (SDD) since the CARES trial was enriched for patients with CVD.

Advisory Committee briefing document

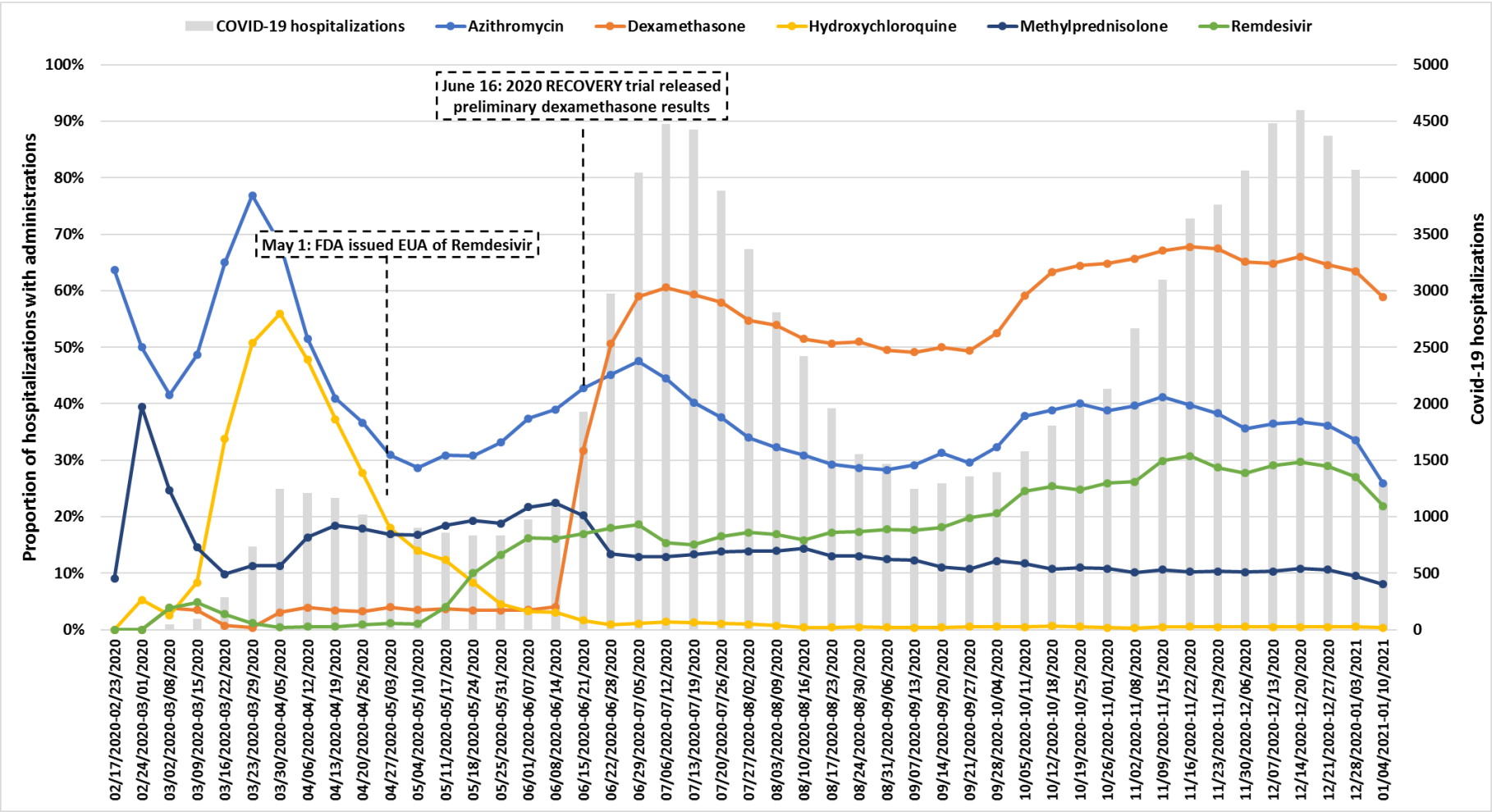
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM629362.pdf

Received: 3 March 2021 | Revised: 25 March 2021 | Accepted: 26 March 2021
DOI: 10.1002/pds.5240

REVIEW

WILEY

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

N Engl J Med 2011; 364:498-499

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.

N Engl J Med 2018; 379:2091-2093

Sentinel

Real-world evidence: Trends and application of real-world data in drug development and safety

The Sentinel Experience

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