Public Health Emergencies:

Use of Real-time Mobile Communications

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Disclaimer

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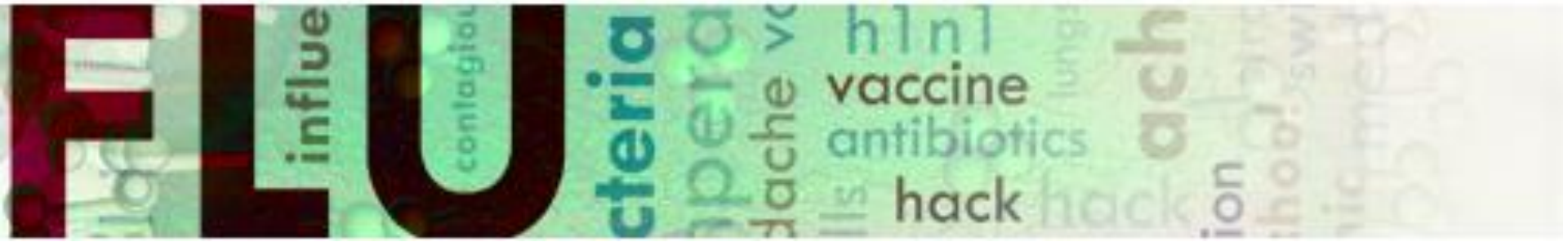
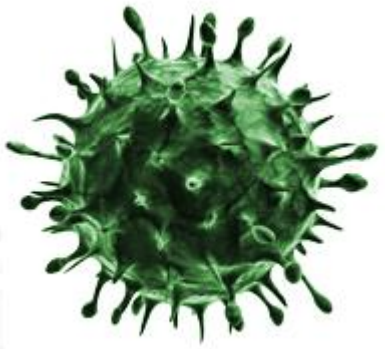


NATIONAL PUBLIC HEALTH EMERGENCY PREPAREDNESS:

2009 H1N1 INFLUENZA A PANDEMIC



2009 H1N1 Influenza Pandemic

A novel flu strain evolved from a combination of genetic elements from avian, pig, and human virus strains

US Secretary of DHHS declared a public health emergency on April 26, 2009.

WHO declared a global pandemic on June 11, 2009.

By end of August 2009, cases reported in >180 countries.

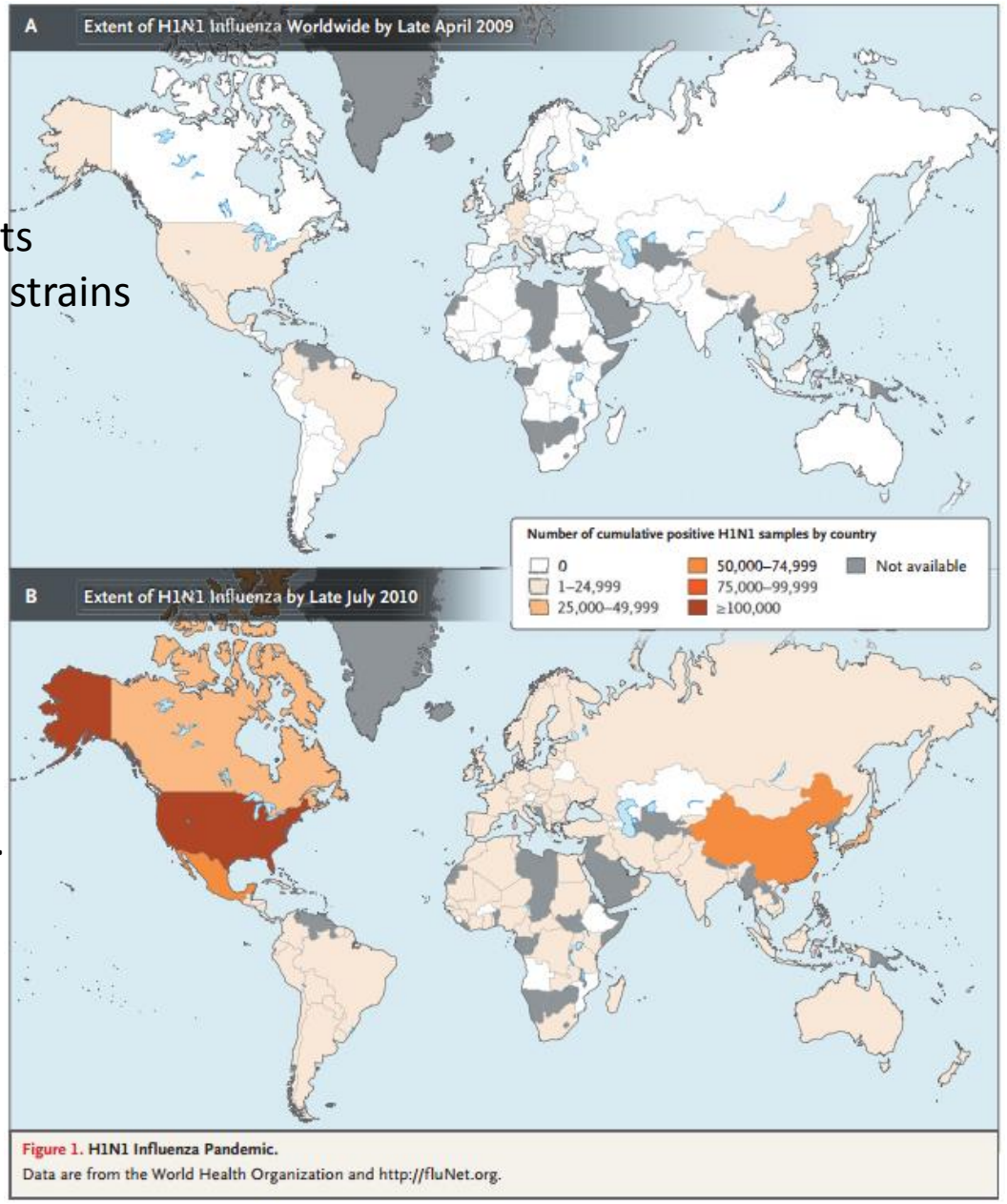


Figure 1. H1N1 Influenza Pandemic.
Data are from the World Health Organization and http://fluNet.org.

Fineberg HV. N Engl J Med 2014;370:1335-1342

H1N1

Cases reported in Mexico
April 2009

CDC starts candidate vaccines
Apr. 21

CDC starts releasing MCMs from SNS
Apr. 26

Discussions well underway:
- Vaccine EUA/lic.
- Vaccine safety
- Antivirals

May 2009

Resistance to oseltamivir & zanamivir found
July 2009

FDA approves 4 H1N1 vaccines
Sept. 2009

Peramivir EUA
Oct. 2009

CDC confirms US cases
Apr. 15

WHO declares PHEIC
Apr. 25

US declares PHE
Apr. 26

FDA issues 1st EUAs for flu antivirals & diagnostics
Apr. 27

Vaccine distribution planning well underway
June 2009

ACIP meeting for recommendations
July 2009

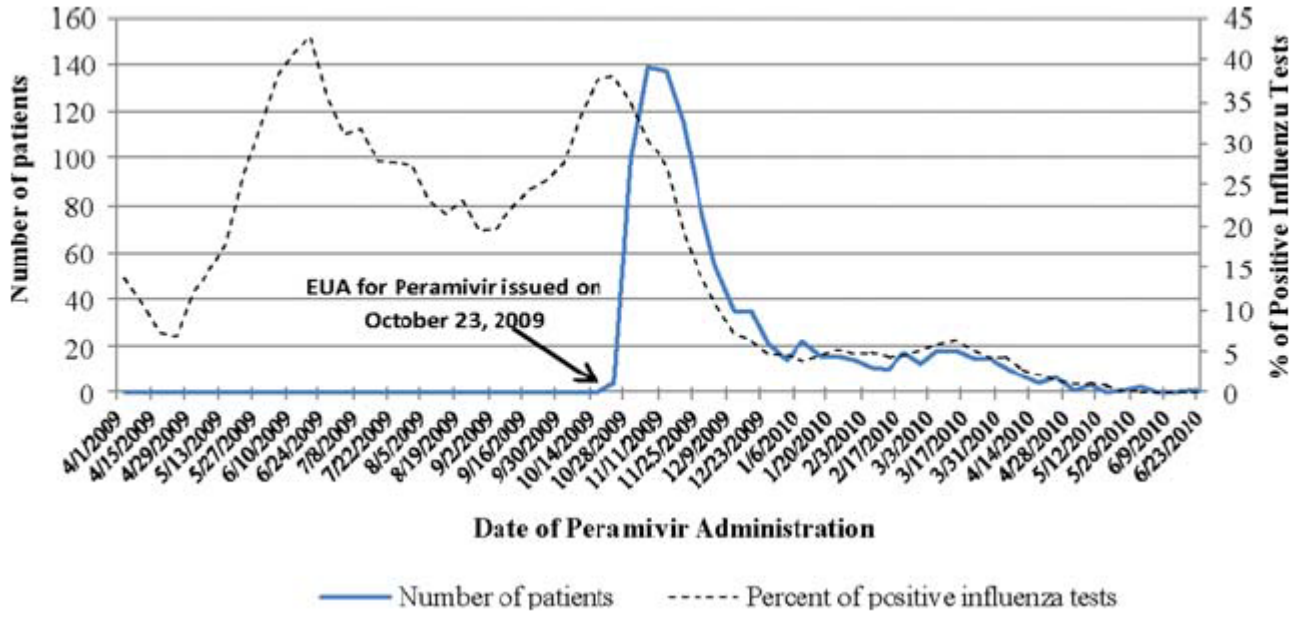
NIH starts clinical trials
July 2009

NIH announces trial results
Sept. 2009

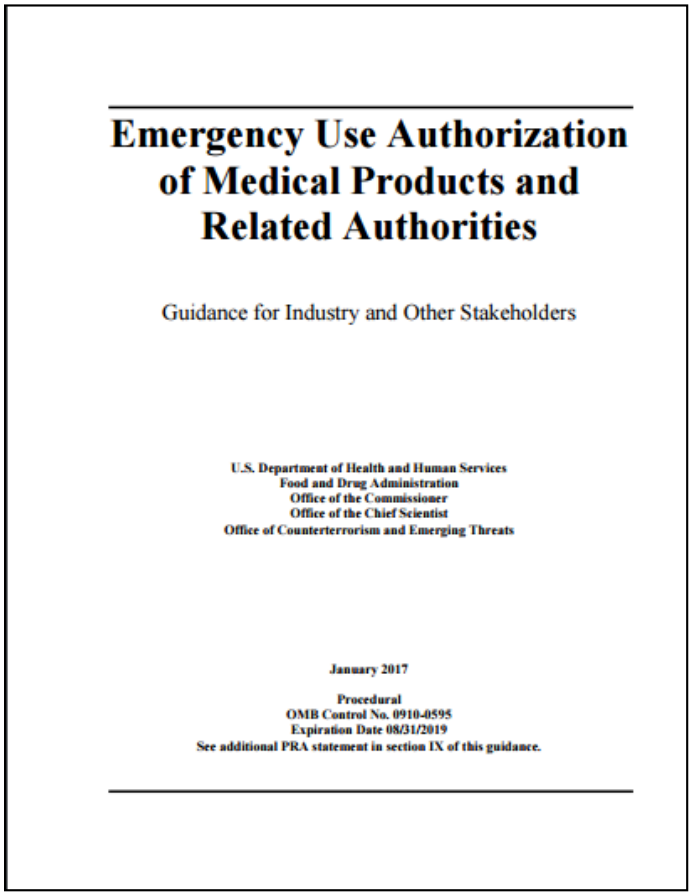
Sources:
FDA 2009 H1N1 (Swine) Flu Page (archived)
H1N1 EUAs – Archived Information (FDA)
Historical Information about Device Emergency Use Authorizations (FDA)
CDC 2009 H1N1 Pandemic: Summary Highlights, April 2009 – April 2010 (archived)

2009 H1N1 Influenza A Pandemic in the US

FDA Commissioner issues an EUA for peramivir on October 23, 2009.



FROM: Yu Y, Garg S, Yu P, et. al . Clin Infect Dis 2012; 55(1):8-15.



Emergency Use Authorization of Medical Products and Related Authorities

Guidance for Industry and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of the Chief Scientist
Office of Counterterrorism and Emerging Threats

January 2017

Procedural
OMB Control No. 0910-0595
Expiration Date 08/31/2019
See additional PRA statement in section IX of this guidance.

An EUA :

1. May be issued by FDA Commissioner based on HHS Secretary declaration of an emergency or threat of an emergency

2. Allows FDA to facilitate availability and unapproved use of MCMs to prepare for and respond to CBRN emergencies

3. Authorizes access to a drug or device subject to specified conditions

4. Is not considered a clinical trial of an unapproved drug or device

5. May include unapproved products or approved products intended for unapproved use(s)

Medical countermeasures (MCM) refer to drugs, biologic products, antidotes, vaccines, in vitro diagnostic laboratory tests, and other drug products or devices

CBRN = chemical, biological, radiological, or nuclear, including emerging infectious diseases (pandemic influenza)

An **EUA** is separate from medical product use under investigational new drug application (IND) or investigational device exemption (IDE)

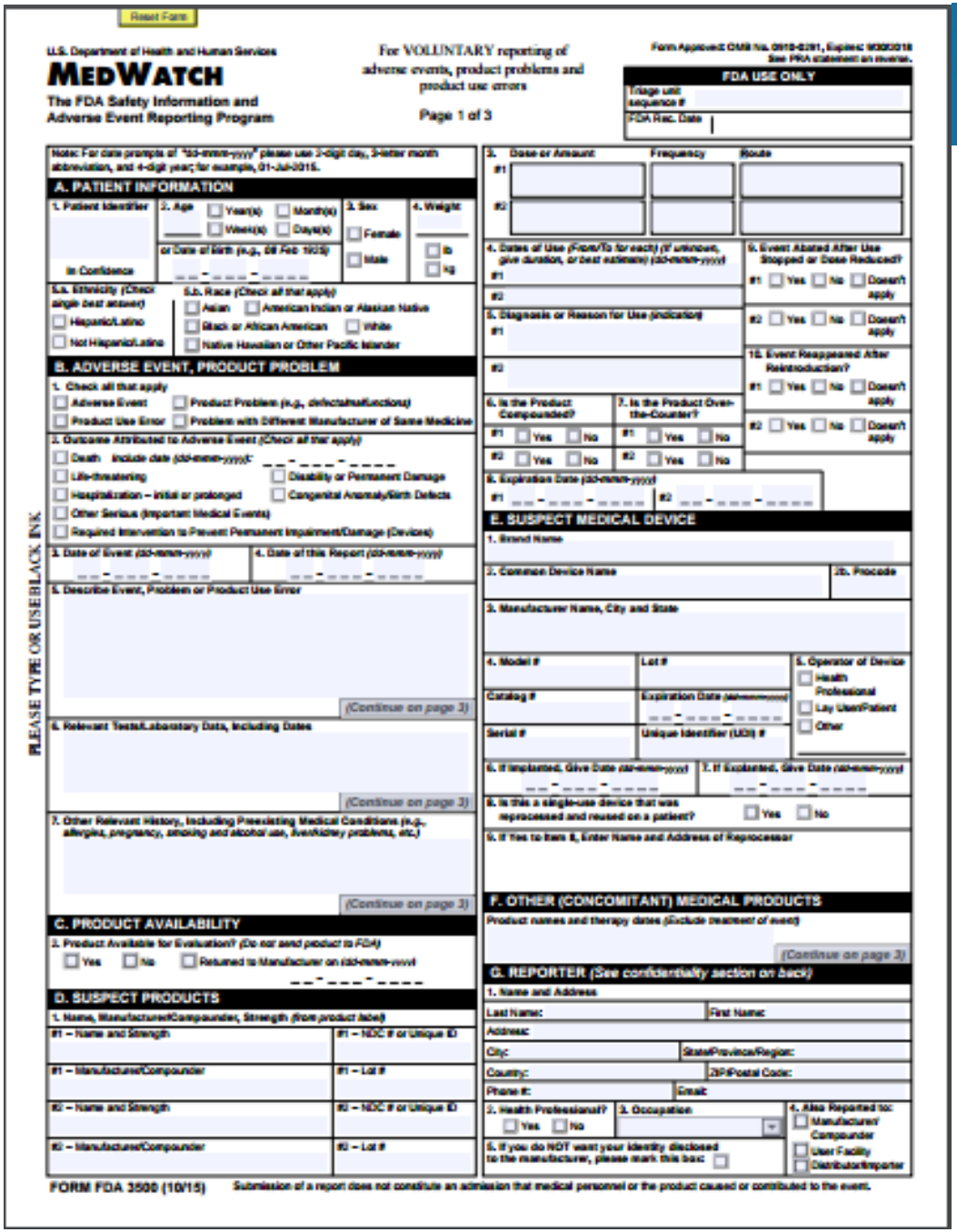
Criteria for Emergency Use Authorizations (EUAs), Investigational New Drug Applications (INDs), Emergency Investigational New Drug Applications (EINDS), and FDA-Approved Prescription Products.

	EUA, in General (and for Peramivir)	EIND	IND	FDA-Approved Prescription Product
Access	Broad or restricted according to the letter of authorization (peramivir: seriously ill, hospitalized patients)	Single patient with serious illness or immediately life-threatening condition	Limited to clinical trials or expanded access	By prescription
Use	According to the conditions of authorization (peramivir: intravenous administration in a hospital)	Limited to single patient	Limited to clinical trials or expanded access	According to labeling and practice of medicine
Efficacy requirements	Reasonable to believe based on totality of scientific evidence, including adequate and well-controlled trials as available (peramivir: benefit observed in patients with acute, uncomplicated influenza)	Rationale for intended use, risk from treatment should be no greater than risk from disease or condition	No efficacy requirements, but safety data from animal studies are needed	Substantial evidence based on adequate and well-controlled clinical trials
Prescriber safety reporting	According to the conditions of authorization (peramivir: mandatory)	Required per IND regulations	Required per IND regulations	Voluntary MedWatch reporting
Informed consent	No	Yes	Yes	No
Approval by institutional review board	No	Exempted but must be reported to institutional review board within 5 days	Yes	No

FROM: Birnkrant D, Cox E. N Engl J Med 2009;361:2204-7

FDA Adverse Event Reporting System (FAERS)

FDA Form 3500 (MedWatch)



Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018 See PRA statement on reverse.

FDA USE ONLY

Triage unit sequence #

FDA Rec. Date

Notes: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier / In Confidence
2. Age: Year(s) Month(s) Week(s) Day(s) / or Date of Birth (e.g., 09 Feb 1935)
3. Sex: Female Male
4. Weight: lb kg
5A. Ethnicity (Check single best answer): Hispanic/Latino; Not Hispanic/Latino
5B. Race (Check all that apply): Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

1. Check all that apply: Adverse Event; Product Problem (e.g., defect/malfunction); Product Use Error; Problem with Different Manufacturer of Same Medicine
2. Outcome Attributed to Adverse Event (Check all that apply): Death (include date dd-mmm-yyyy); Life-threatening; Disability or Permanent Damage; Hospitalization – initial or prolonged; Congenital Anomaly/Birth Defects; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event, Problem or Product Use Error (Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates (Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.) (Continue on page 3)

C. PRODUCT AVAILABILITY

1. Product Available for Evaluation? (Do not send product to FDA): Yes; No; Returned to Manufacturer on (dd-mmm-yyyy)

D. SUSPECT PRODUCTS

1. Name, Manufacturer/Compounder, Strength (from product label)

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

3. Dose or Amount / Frequency / Route: #1; #2
4. Dates of Use (From/To or best estimate) (dd-mmm-yyyy): #1; #2
5. Diagnosis or Reason for Use (Indication): #1; #2
6. Is the Product Compounded? #1 Yes No; #2 Yes No
7. Is the Product Over-the-Counter? #1 Yes No; #2 Yes No
8. Expiration Date (dd-mmm-yyyy): #1; #2
9. Event Abated After Use Stopped or Dose Reduced? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
10. Event Reappeared After Reintroduction? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
2B. Procode
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (dd-mmm-yyyy) / Serial # / Unique Identifier (UDI) #
5. Operator of Device: Health Professional; Lay User/Patient; Other
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (Exclude treatment of event) (Continue on page 3)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Last Name: / First Name:
Address:
City: / State/Province/Region:
Country: / ZIP/Postal Code:
Phone #: / Email:
2. Health Professional? Yes No
3. Occupation
4. Also Reported to: Manufacturer/Compounder; User Facility; Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box:

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/15)

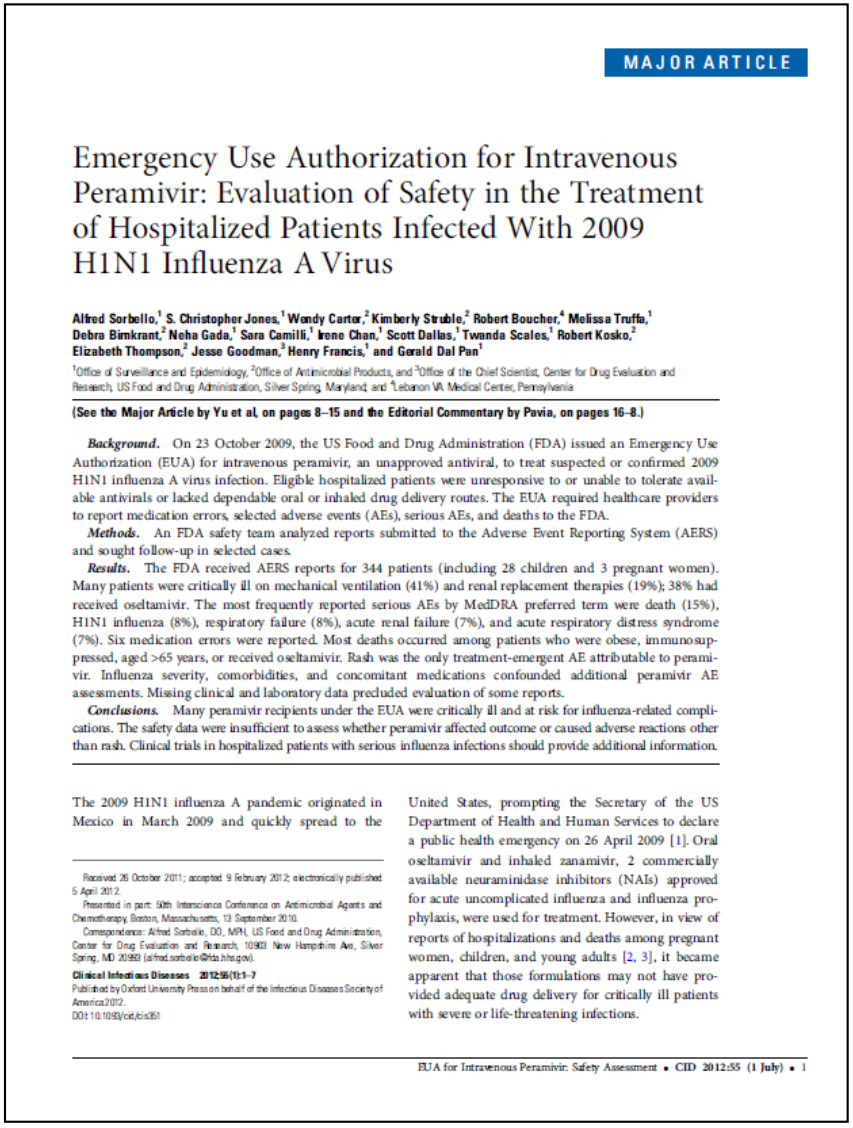
Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

FDA evaluation of the safety of peramivir during the H1N1 influenza A pandemic

- **The EUA for intravenous peramivir in October 2009 was the first EUA authorized for an unapproved drug product** in the US

- The **MedWatch reports served as the primary source of safety information** for FDA.

- **MedWatch reporting was subject to underreporting and missing data. The data was confounded in some instances** by severity of influenza, concomitant drugs, and concurrent medical disorders.



MAJOR ARTICLE

Emergency Use Authorization for Intravenous Peramivir: Evaluation of Safety in the Treatment of Hospitalized Patients Infected With 2009 H1N1 Influenza A Virus

Alfred Sorbello,[1] S. Christopher Jones,[1] Wendy Carter,[2] Kimberly Struble,[2] Robert Boucher,[4] Melissa Truffa,[1] Debra Birnkrant,[2] Neha Gada,[1] Sara Camilli,[1] Irene Chan,[1] Scott Dallas,[1] Twanda Scales,[1] Robert Kosko,[2] Elizabeth Thompson,[2] Jesse Goodman,[3] Henry Francis,[1] and Gerald Dal Pan[1]

[1]Office of Surveillance and Epidemiology, [2]Office of Antimicrobial Products, and [3]Office of the Chief Scientist, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland; and [4]Lebanon VA Medical Center, Pennsylvania

(See the Major Article by Yu et al, on pages 8–15 and the Editorial Commentary by Pavia, on pages 16–8.)

Background. On 23 October 2009, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for intravenous peramivir, an unapproved antiviral, to treat suspected or confirmed 2009 H1N1 influenza A virus infection. Eligible hospitalized patients were unresponsive to or unable to tolerate available antivirals or lacked dependable oral or inhaled drug delivery routes. The EUA required healthcare providers to report medication errors, selected adverse events (AEs), serious AEs, and deaths to the FDA.

Methods. An FDA safety team analyzed reports submitted to the Adverse Event Reporting System (AERS) and sought follow-up in selected cases.

Results. The FDA received AERS reports for 344 patients (including 28 children and 3 pregnant women). Many patients were critically ill on mechanical ventilation (41%) and renal replacement therapies (19%); 38% had received oseltamivir. The most frequently reported serious AEs by MedDRA preferred term were death (15%), H1N1 influenza (8%), respiratory failure (8%), acute renal failure (7%), and acute respiratory distress syndrome (7%). Six medication errors were reported. Most deaths occurred among patients who were obese, immunosuppressed, aged >65 years, or received oseltamivir. Rash was the only treatment-emergent AE attributable to peramivir. Influenza severity, comorbidities, and concomitant medications confounded additional peramivir AE assessments. Missing clinical and laboratory data precluded evaluation of some reports.

Conclusions. Many peramivir recipients under the EUA were critically ill and at risk for influenza-related complications. The safety data were insufficient to assess whether peramivir affected outcome or caused adverse reactions other than rash. Clinical trials in hospitalized patients with serious influenza infections should provide additional information.

The 2009 H1N1 influenza A pandemic originated in Mexico in March 2009 and quickly spread to the United States, prompting the Secretary of the US Department of Health and Human Services to declare a public health emergency on 26 April 2009 [1]. Oral oseltamivir and inhaled zanamivir, 2 commercially available neuraminidase inhibitors (NAIs) approved for acute uncomplicated influenza and influenza prophylaxis, were used for treatment. However, in view of reports of hospitalizations and deaths among pregnant women, children, and young adults [2, 3], it became apparent that those formulations may not have provided adequate drug delivery for critically ill patients with severe or life-threatening infections.

Received 26 October 2011; accepted 9 February 2012; electronically published 5 April 2012.

Presented in part: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, Massachusetts, 13 September 2010.

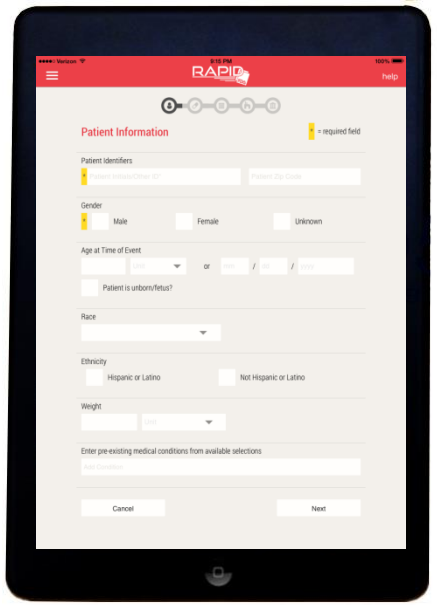
Correspondence: Alfred Sorbello, DO, MPH, US Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Silver Spring, MD 20993 (alfred.sorbello@fda.hhs.gov).

Clinical Infectious Diseases 2012;55(1):1–7
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.
DOI: 10.1093/cid/cis351

Lessons learned: pandemic preparedness

- **MedWatch reports were time consuming** for reporters, and analysis was limited by **variable quality of reporting and missing data**
- **Need for systems to handle real-time reporting** of safety concerns, changes in clinical condition, and patient outcomes
- **Limited technical tools** to extract, analyze, and share information in real-time for surveillance and decision making purposes
- **Need for a dedicated data management platform** for integrating and analyzing information from multiple data streams
- **Need for real-time bidirectional communication** during a declared national emergency to foster communication and information sharing

Real Time Application for Portable Interactive Devices



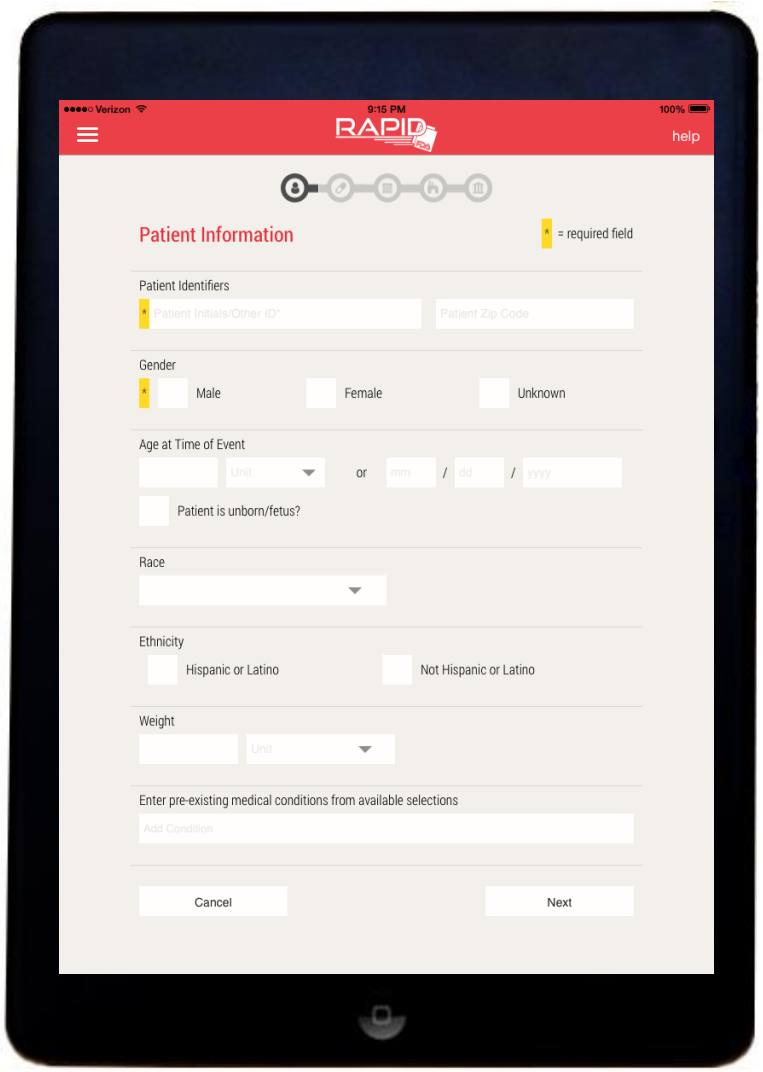
Henry Francis, M.D.
FDA/CDER/OTS

- RAPID is the FDA's first bidirectional communication system.
- Mobile applications for data collection
- Data lake to store diverse data resources, including information on adverse drug reactions, and analytics to enable FDA to detect emerging drug safety signals
- Changes how FDA will conduct post-market product surveillance
- Enhances emergency preparedness and response involving medical countermeasures (MCM)

FDA requires a real-time active surveillance application to support pharmacovigilance and adverse event reporting in MCM situation

The Solution

- Real-time Application for Portable Interactive Device (RAPID) will facilitate the real-time collection, analysis, and communication of MCM product and health information during national public health emergencies
- Flexible Mobile platform to use during MCM events
- Flexible FDA cloud design complementary to FAERS
- Adaptable data management and analysis system
- Bidirectional CDER multimedia communications
- Decision maker data work bench



FOOD & DRUG
NISTRATION

RAPID

Home

Home > Summary > Case Details > **Send Message**

Selected Drug: Peramivir ×

To: Case #1114 Reporter | All Peramivir Reporters

Enter Message:

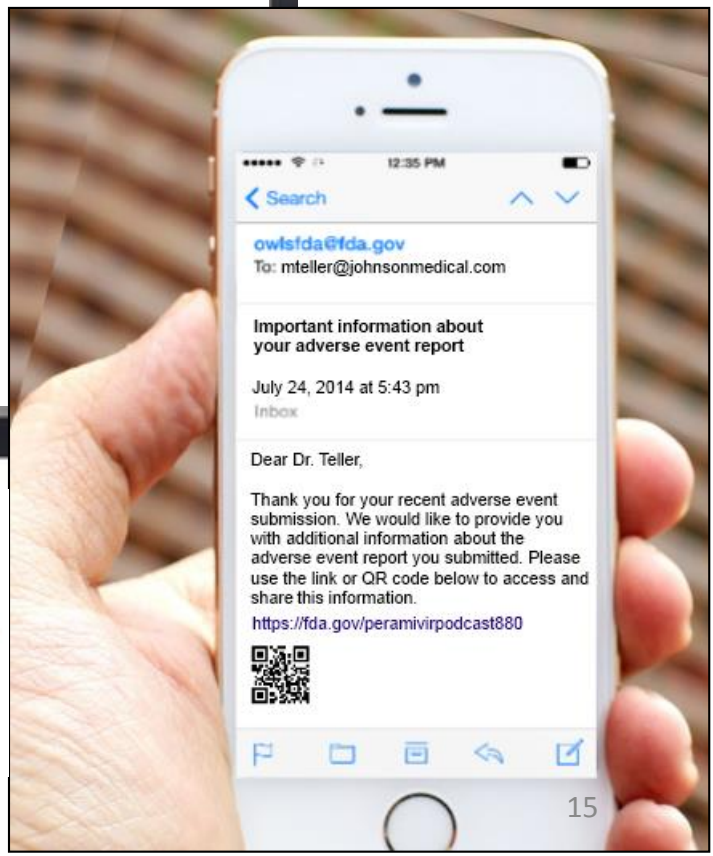
Dear Dr. Teller,

Thank you for your recent adverse event submission. We would like to provide you with additional information about the adverse event report you submitted. Please use the link or QR code below to access and share this information.

https://fda.gov/peramivirpodcase880

Thank you,
FDA

Cancel | Send Message



RAPID

- Organized in four tiers:
  - Mobile app for collection of incoming diverse information
  - A data lake to store diverse data resources, including information on adverse drug reactions, and analytics to enable FDA to detect emerging drug safety signals
  - Data visualization dashboards to assess patterns in data and allow emerging issues to be explored
  - Presents information and analyses to leadership to support decision making and guidance to ensure patient safety

The cloud-based RAPID Bio-surveillance System will support collaboration between FDA and other Federal agencies to enhance monitoring emerging health threats

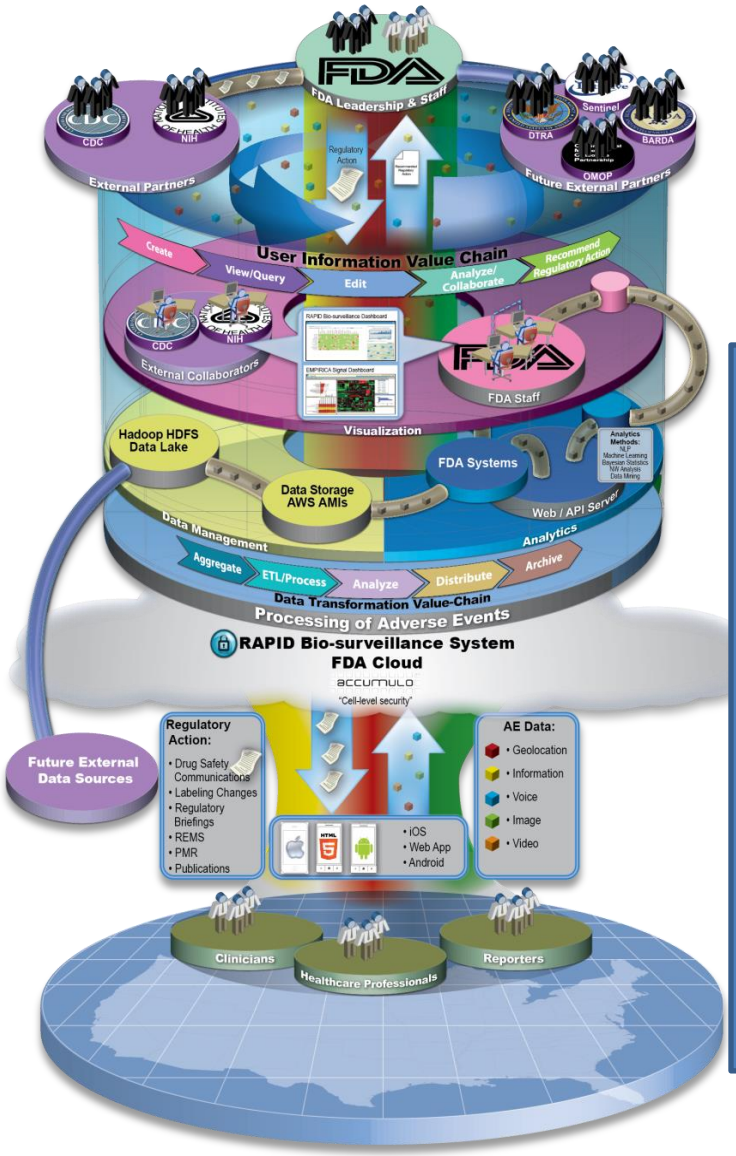
RAPID Biosurveillance System

Tier 1: Regulatory Action/Guidance
- FDA and external partners issue guidance to ensure patient safety

Tier 2: Data Visualization
- Dashboards summarizing key information provide safety alerts
- Disproportionality metrics and detailed analyses allow FDA and collaborators to understand emerging issues

Tier 3: Data Management & Analytics
- RAPID data is combined with existing MedWatch and Medwatcher reports and data from external collaborators
- Advanced analytics support AE signal detection

Tier 4: Processing of Adverse Events
- Healthcare professionals submit AE data via the RAPID mobile app
- AE data is stored in a "data lake" to support real-time access

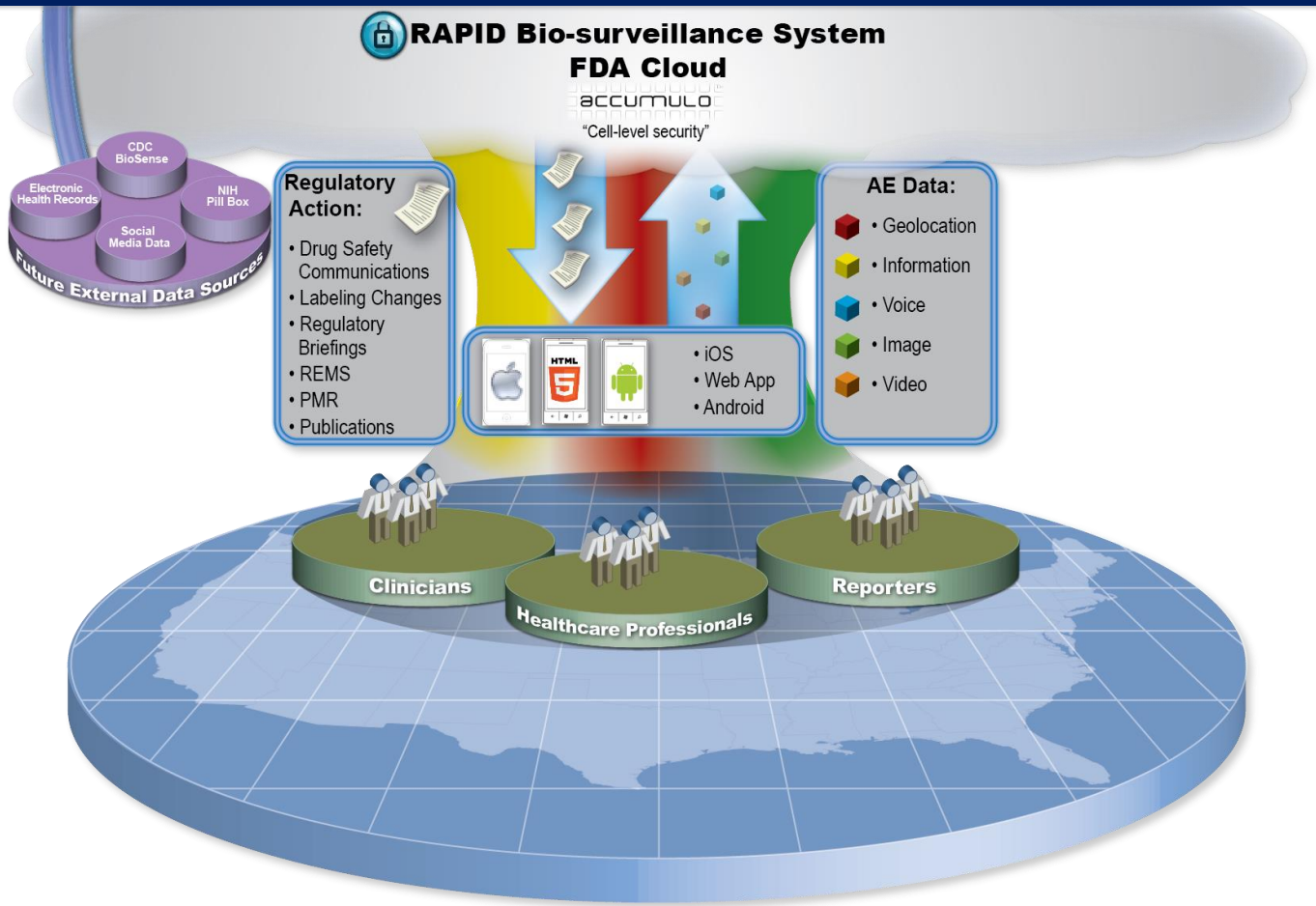


Tier 4 of the cloud-based RAPID Biosurveillance System includes the processing of adverse events submitted by clinicians, healthcare professionals and other reporters

RAPID Biosurveillance System

Tier 4: Processing of Adverse Events

- Healthcare professionals submit AE data via the RAPID mobile app
- AE data is stored in a "data lake" to support real-time access

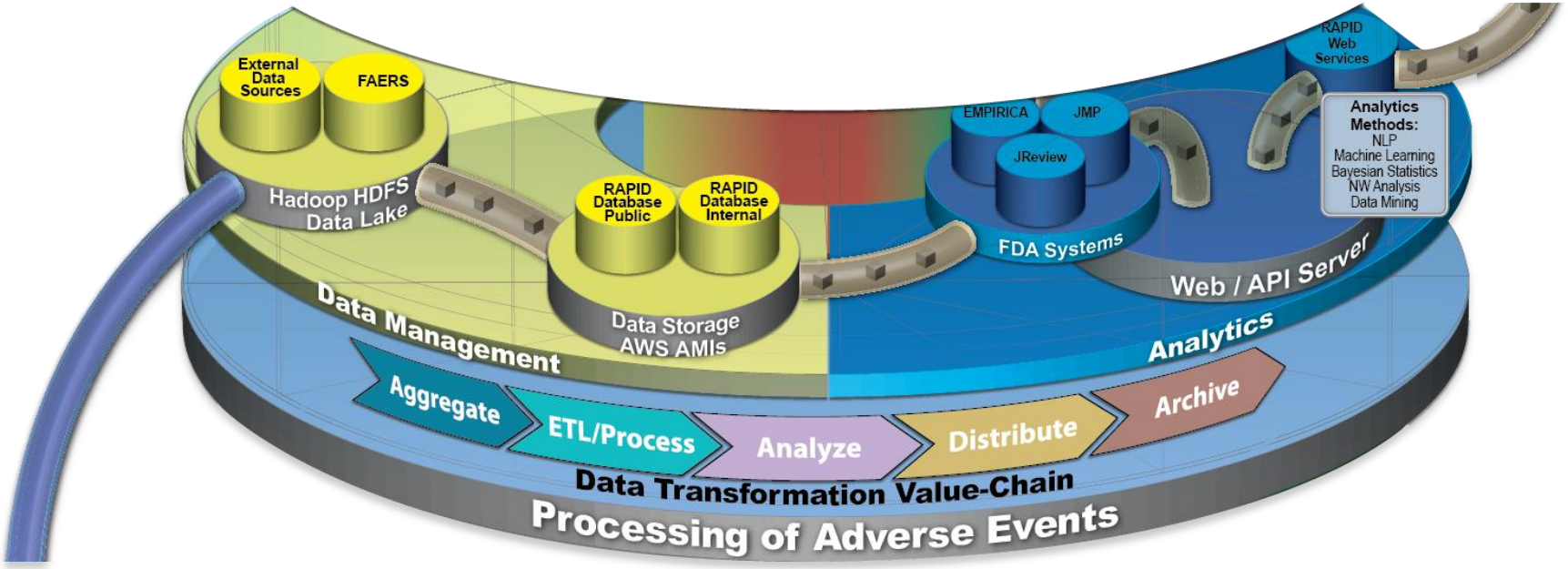


Tier 3 of the cloud-based RAPID Biosurveillance System includes data storage, data integration, and advanced analytics to support adverse event signal detection

RAPID Biosurveillance System

Tier 3: Data Management & Analytics

- RAPID data is combined with existing MedWatch reports and data from external collaborators
- Advanced analytics support AE signal detection

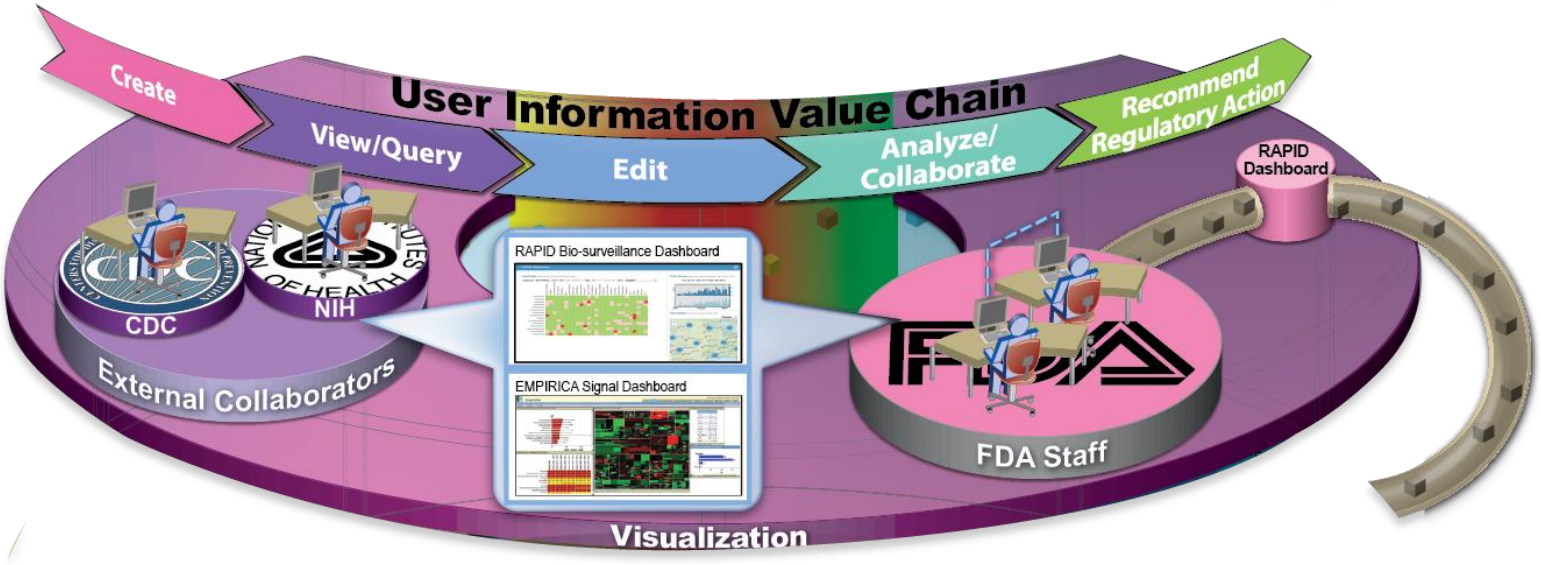


Tier 2 of the cloud-based RAPID Biosurveillance System includes visualization of adverse event trends for interpretation by FDA staff and external collaborators

RAPID Biosurveillance System

Tier 2: Data Visualization

- Dashboards summarizing key information provide safety alerts
- Disproportionality metrics and detailed analyses allow FDA and collaborators to understand emerging issues



The cloud-based RAPID Biosurveillance System will support collaboration between FDA and other Federal agencies to enhance monitoring of investigational therapies for Ebola and other emerging health threats

RAPID Biosurveillance System

Tier 1: Regulatory Action/Guidance

- FDA and external partners issue guidance to ensure patient safety

FDA collaborators in MCM events

- Federal agencies
- Healthcare providers
- Healthcare facilities
- Individuals
- Sponsors

RAPID use cases

- Non-MCM
  - Product Safety Surveillance
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Medication Errors
- MCM related
  - Real time patient outcome and safety data collection
  - Streaming data
  - Merging data resources, e.g. weather and disease patterns

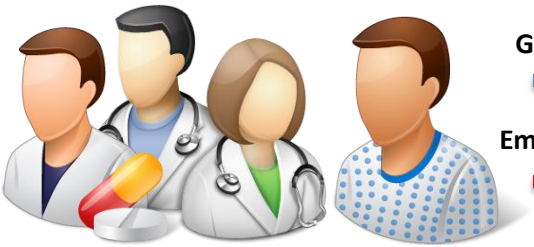
MCM = medical countermeasures

- Cloud-based storage in a data lake (can accommodate streaming information while minimizing need for physical servers)
- Analytics dashboard, including geolocation functionalities
- Secure data broker to allow approved outside collaborators to view mirrored information

DPV - Adverse Event Report Use Case

1

Healthcare Professionals and consumers submit regular and emergency surveillance adverse event reports



General Surveillance

Emergency Surveillance

2

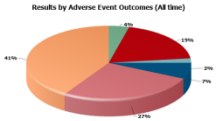
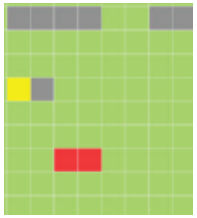
4

RAPID External Data (Future)

5

3

Adverse Event Analytical Tools

RAPID AE Dashboard & Data	Geovisualization
	
RAPID Heatmap	**Empirica**
	

1 **Mobile Data Collection:** Clinicians, reporters, and patients create general surveillance and emergency surveillance reports

2 **Data Transferred to FDA:** Data is submitted from mobile device and sent over Cellular network or WiFi to FDA GovCloud via web services

3 **Perform Analytics :** Utilize RAPID Dashboard, location based data, and Empirica (signal detection) for analysis

4 **Response Sent to Reporter:** Within 24 hours a targeted response is sent via email containing links to multimedia files like images and podcasts

5 **Obtain External Data:** Data will be shared from external sources via web services (ex. HL7 ICSR) and increase the effectiveness of analysis performed using RAPID analytical tools

Dashboard: Homepage for Regulatory Review

RAPID | Adverse Events | REMS Survey | Medication Errors | John Doe

Search the RAPID database

Filter the list of adverse event reports shown in the dashboard.

Product Name

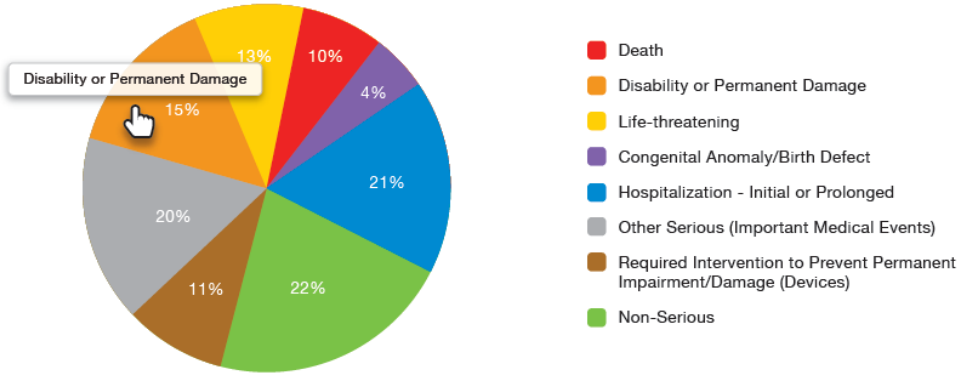
MedDRA terms (•) PT ( ) SOC

All PT
Angioedema
Aplastic anaemia
Delirium
Diarrhoea

Search | Clear Filter

Results by Adverse Event Outcomes

Past Year



Recent Submissions

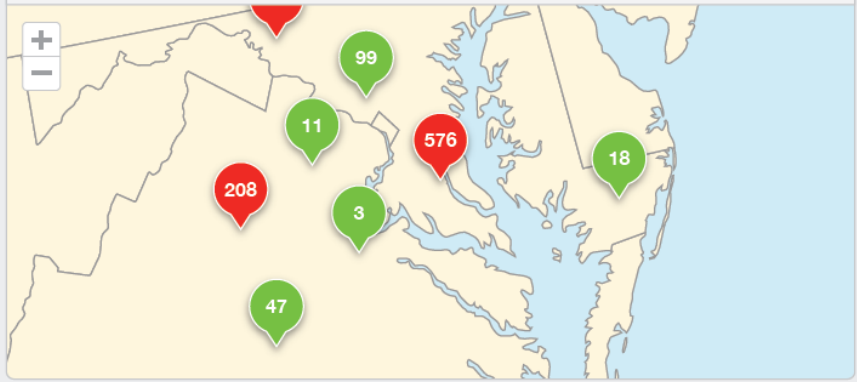
Show All >

120 cases submitted for PERAMAVIR since 05/15/2014

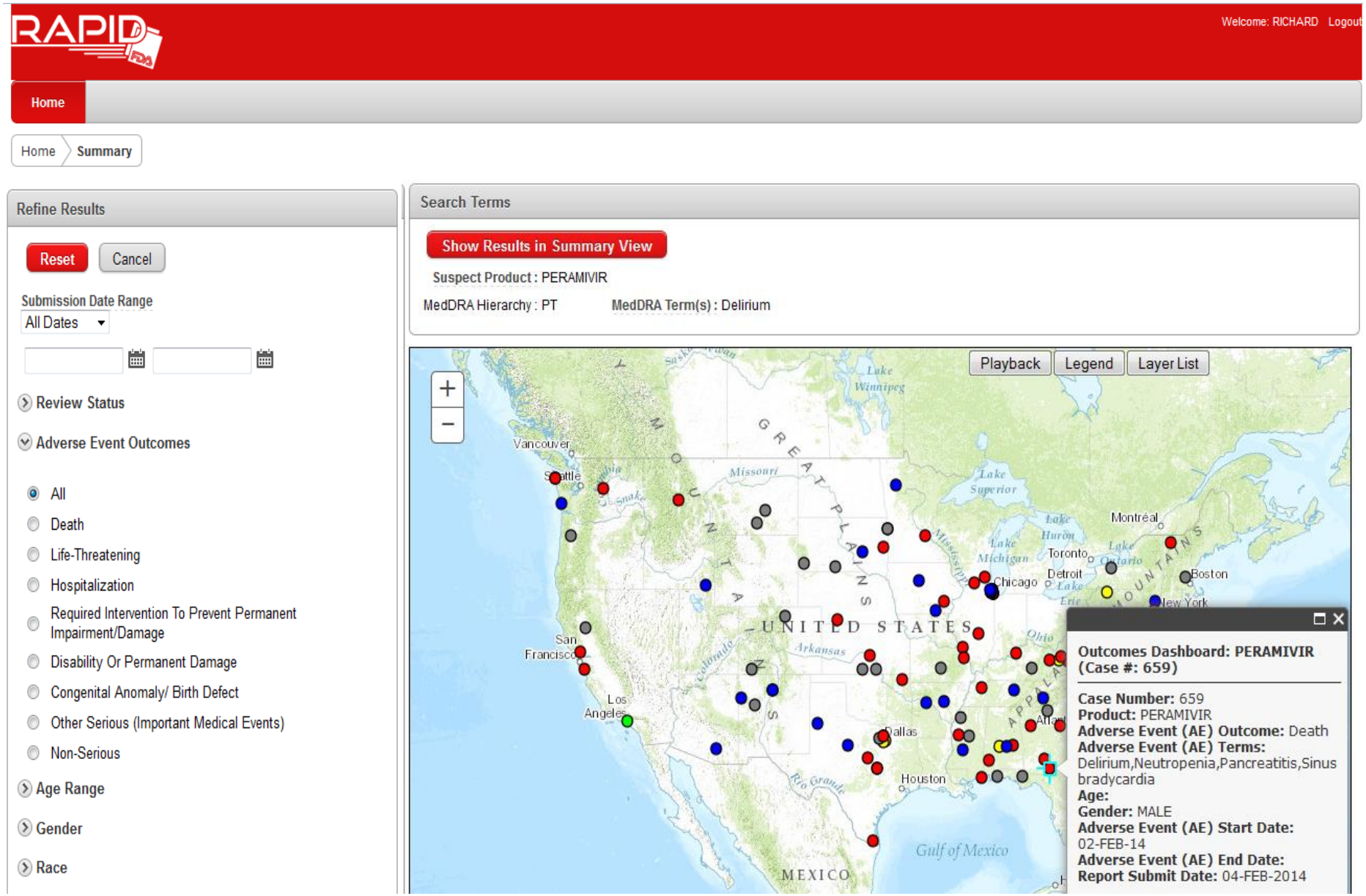
Case #	Suspect Product Name	Adverse Event Outcomes	PT	Submit Date
35241	PERAMIVIR	Non-Serious	Headache	12/03/2015
35241	PERAMIVIR	Non-Serious	Headache	12/03/2015
35241	PERAMIVIR	Non-Serious	Headache	12/03/2015
35241	PERAMIVIR	Non-Serious	Headache	12/03/2015

Map View

Past Year



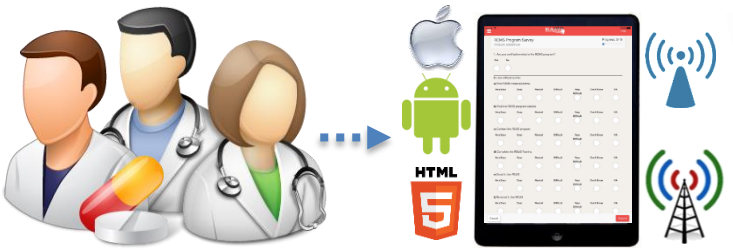
RAPID GIS Visualizing Functionality



DRISK - REMS Assessment Use Case

1

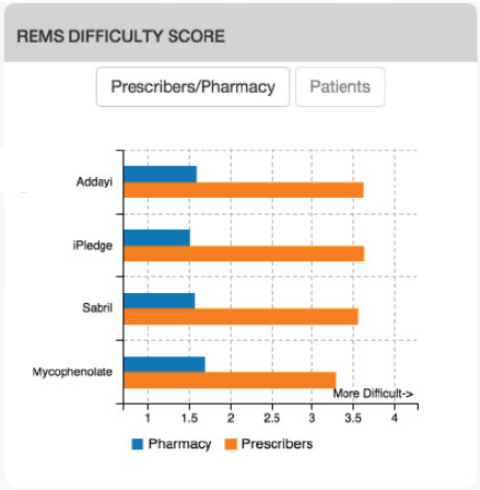
Prescribers & Pharmacists submit REMS Program Assessment



2

4

3 **REMS Program Dashboard**



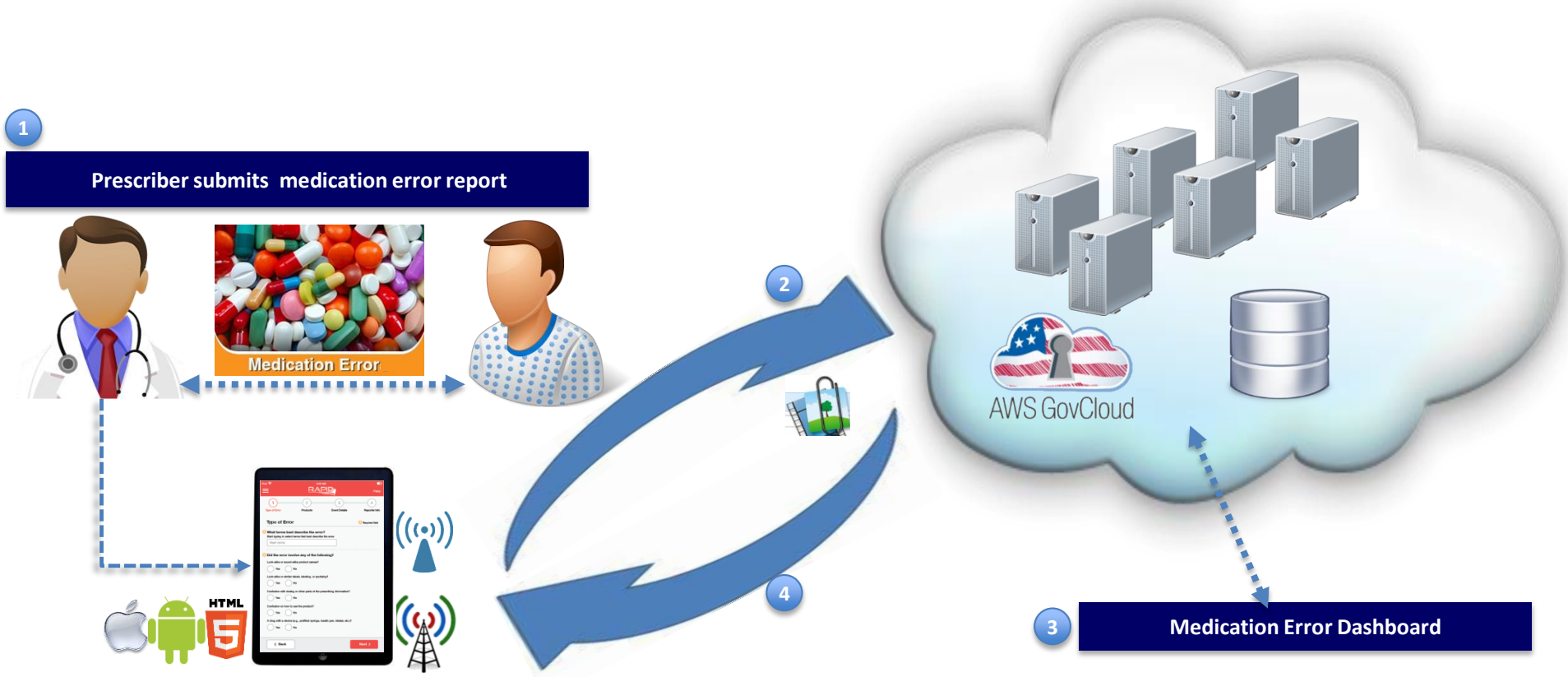
1 **Mobile Data Collection:**
Prescribers, pharmacists, and patients complete the REMS Assessment using the RAPID app on their mobile device

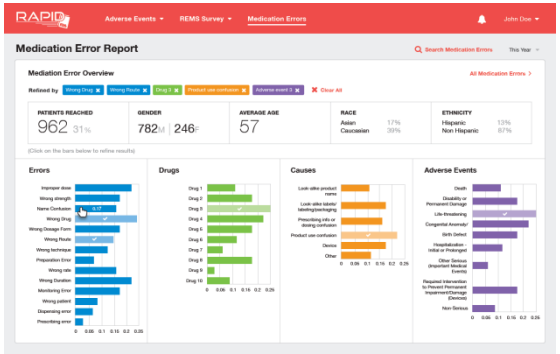
2 **Data Transferred to FDA:**
Data is submitted from mobile device and sent over Cellular network or WiFi to GovCloud via web services

3 **Perform Analytics :**
Utilize the REMS Dashboard to view composite scores, results by domain, and to perform additional analysis

4 **Response Sent to Reporter:**
Send email containing information about the REMS Program back to the user

DMEPA – Medication Error Use Case





1 **Mobile Data Collection:**
Prescriber completes a Medication Error Report and attaches an image using the RAPID app on their mobile device

2 **Data Transferred to FDA:**
Data is submitted from mobile device and sent over Cellular network or WiFi to GovCloud via web services

3 **Perform Analytics :**
Utilize the Medication Error Dashboard to view overview of the medication error reports that are being submitted

4 **Response Sent to Reporter:**
Send email containing information about the Medication Error back to the user

RAPID Dashboard for Agency Leadership

RAPID

Welcome: RICHARD Logout

Home

Search

Suspect Product: PERAMIVIR

Enter MedDRA Term(s): PT

All PT
Angioedema
Aplastic anaemia
Delirium
Diarrhoea

Search | Reset

PT Summary

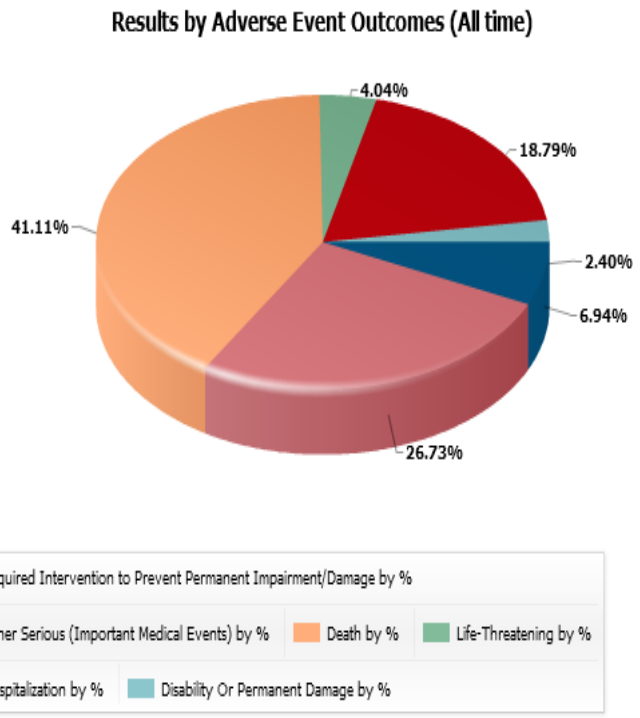
no data found

Recent Submissions

Case #	Suspect Product Name	Adverse Event Outcomes	PT	Submit Date
1271	PERAMIVIR	Disability Or Permanent Damage	Rash	06/04/2014
1273	PERAMIVIR	Life-Threatening	Headache	06/04/2014

1 - 2

Pie Chart



- Designed to streamline completion of FDA Form 3500A (MedWatch) more efficiently and in less time (from approximately 45 minutes to 5 minutes)
- Includes voice-recognition technology to capture dictated response information
- Captures pictures, small videos, and other image recordings taken with mobile phones
- Provides bi-directional communication functionality so that FDA can send back information (such as how to use the drug and potential side effects to be aware of)

The Real-time Application for Portable Interactive Devices (RAPID) System can inform decision-making at the physician, hospital and Federal level

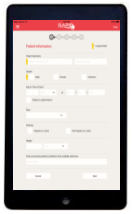
FDA U.S. FOOD & DRUG ADMINISTRATION

Data from RAPID combined with other systems

Key questions and capabilities that can be addressed with RAPID data

RAPID

RAPID Secure Data Broker (SDB) – ***Provides access to adverse event reports and electronic health records to inform decisions made by physicians, hospitals and the Assistant Secretary.***



RAPID Mobile Application

ASPR – *RAPID enables improved management of MCM stockpiles*

- Number and location of stockpiles (drugs, vaccines, diagnostics)
- Type, severity and location of potential CBRN threats
- Syndromic surveillance data from state/local public health agencies

Monthly

- How to manage stockpile inventory and location?
- How to get MCM resources to patients and at-risk populations?
- What types of threats are most likely to occur in the short- and long-term?

Geographic visualizations

Hospital Administrators – *RAPID supports allocation of healthcare resources*

- Number of occupied beds
- Patient characteristics (diagnoses, level of care, etc.)
- Patient status (waiting for treatment, ready for hospital discharge, etc.)

Daily

- How to manage current patient flow?
- How many patients are projected to require care in the short- & long-term?
- What number and type of medical equipment are required to diagnose and treat patients in short- & long-term?

Hospital Alerts

Physicians – *RAPID informs diagnosis and treatment of patients*

- Patient history data
- Physical exam data
- Laboratory data
- Medical equipment data (diagnostic, treatment, life support, monitors, etc.)

Streaming

- How to diagnose the patient based on symptoms, history, and data from others?
- How can data from other patients influence the current patient's treatment plan?
- What drugs, vaccines and/or diagnostics should be ordered to treat the patient?

Clinical Decision Support

RAPID Phase II

RAPID Biosurveillance Platform

- The proposed RAPID Biosurveillance Platform includes a **cloud-based open source big data analytic tool** to facilitate the detection of adverse event signals in near real-time.
- Additional data sources can be integrated to augment product safety information received via the RAPID mobile application.

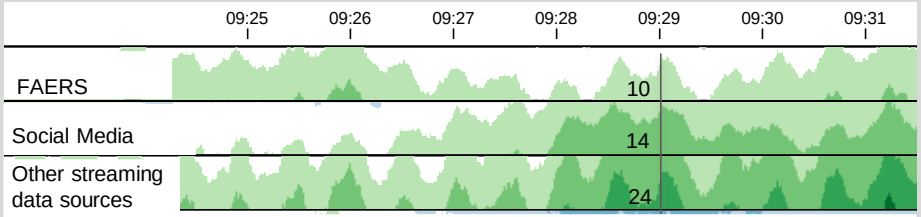
1 ***Alerts … Peramivir 3% Change in Number of Reports … Avandia 2.1% Change in Number of Reports …***

Drug-Event Tracker

2 Drug	% Change in Number of Reports (daily)	**3** Algorithm & Ranking Statistic (all data)
Peramivir-H1N1	3	2.0
Avandia-Diabetes	2.1	1.05
MPA-Steroid Injections	1.0	1.3
Zanamivir-H1N1	0.17	1
ALL	10	2.5

1) Alerts: Display drugs with > 50% increase in the number of reports in the last 2 weeks
2) Drug-AE Filter: Show drugs with AEs linked to fatal outcomes or pediatric populations
3) Disproportionality Metric Filter: Show ROR, PRR and other disproportionality metrics

Time Series Visualization for Number of Reports for Drug of Interest: Adverse Event Data and Social Media Data

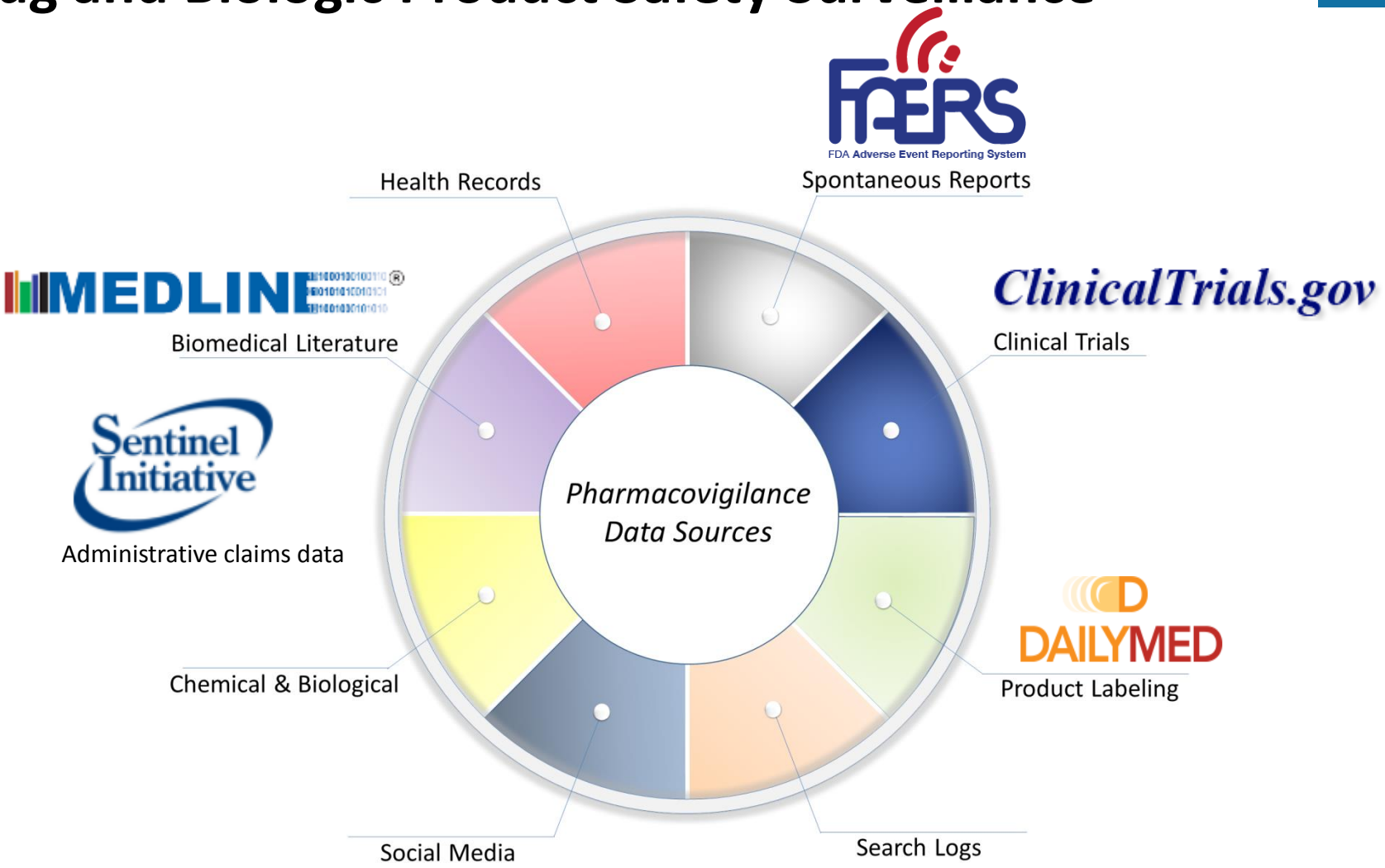


*Mouseover or use the arrow keys to inspect values

*Mouseover bubbles to view information on adverse events reported at different geographic locations

Drug Safety Surveillance, Data Mining, and Data Analytics

Diverse Biomedical Resources for Drug and Biologic Product Safety Surveillance



FDA Adverse Event Reporting System (FAERS)

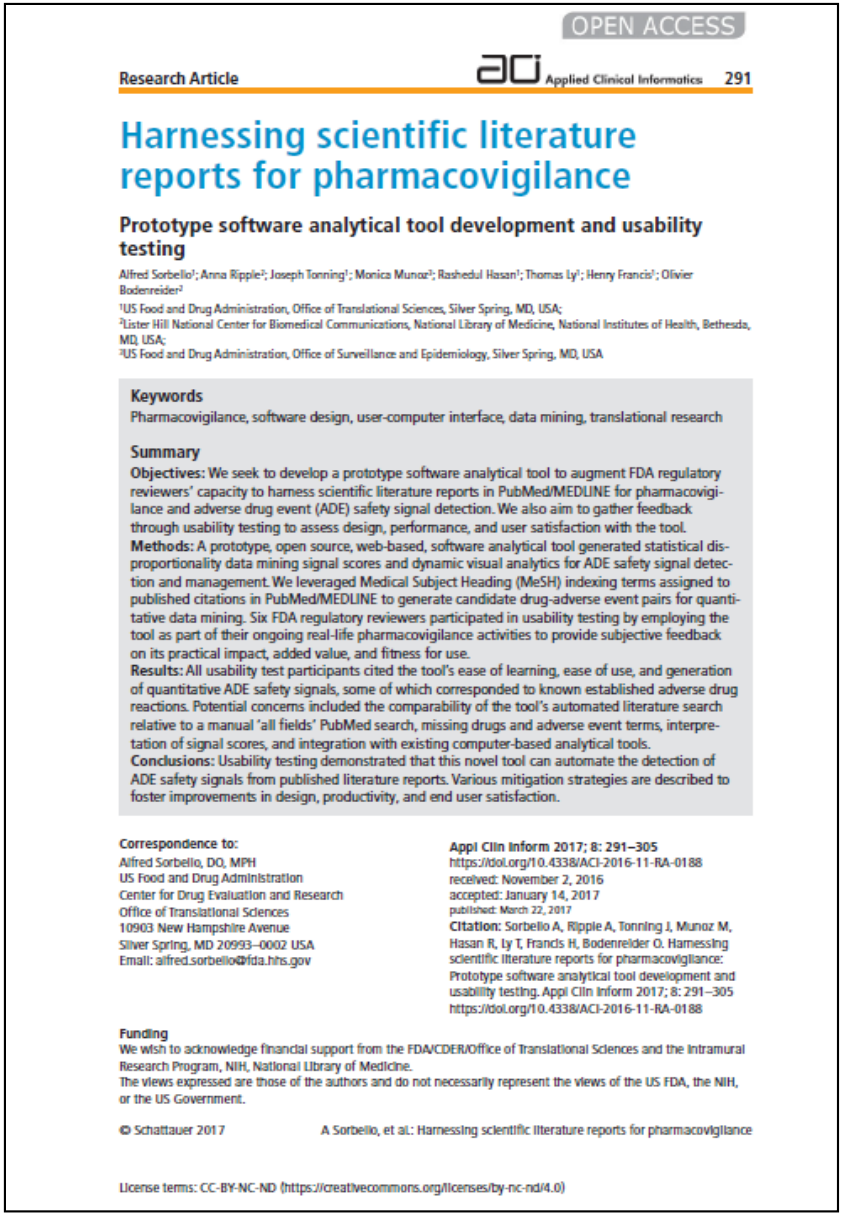
- Centralized repository of postmarket spontaneous adverse event reports submitted by manufacturers and consumers
- Human drugs and therapeutic biologic products
- >9 million reports since 1969
- approximately 1.5 million reports /year
- Detection of rare ADEs not observed in clinical trials

PubMed/MEDLINE

- Bibliographic database of more than 26 million biomedical citations
- Developed a novel prototype web-based tool (PEARL) that leverages Medical Subject Heading (MeSH) indexing terms to extract citations reporting adverse drug events (ADEs)
  - We used combinations of MeSH descriptors (and supplementary concepts) and qualifiers to identify drugs involved in ADEs (e.g., ofloxacin/adverse effects) and clinical manifestations reflecting an ADE (e.g., tendinopathy/chemically induced).
- Explored various statistical approaches for data mining to detect emerging ADE safety signals

PEARL web-based analytical tool

- First-of-its-kind information technology tool
- Builds capacity to harness biomedical resources to support pre-and post-market regulatory decisions
- Complementary to existing resources (e.g., FAERS)



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Research Article — Applied Clinical Informatics 291

Harnessing scientific literature reports for pharmacovigilance

Prototype software analytical tool development and usability testing

Alfred Sorbello[1]; Anna Ripple[2]; Joseph Tonning[1]; Monica Munoz[3]; Rashedul Hasan[1]; Thomas Ly[1]; Henry Francis[1]; Olivier Bodenreider[2]

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[2]Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA;
[3]US Food and Drug Administration, Office of Surveillance and Epidemiology, Silver Spring, MD, USA

Keywords
Pharmacovigilance, software design, user-computer interface, data mining, translational research

Summary

Objectives: We seek to develop a prototype software analytical tool to augment FDA regulatory reviewers' capacity to harness scientific literature reports in PubMed/MEDLINE for pharmacovigilance and adverse drug event (ADE) safety signal detection. We also aim to gather feedback through usability testing to assess design, performance, and user satisfaction with the tool.

Methods: A prototype, open source, web-based, software analytical tool generated statistical disproportionality data mining signal scores and dynamic visual analytics for ADE safety signal detection and management. We leveraged Medical Subject Heading (MeSH) indexing terms assigned to published citations in PubMed/MEDLINE to generate candidate drug-adverse event pairs for quantitative data mining. Six FDA regulatory reviewers participated in usability testing by employing the tool as part of their ongoing real-life pharmacovigilance activities to provide subjective feedback on its practical impact, added value, and fitness for use.

Results: All usability test participants cited the tool's ease of learning, ease of use, and generation of quantitative ADE safety signals, some of which corresponded to known established adverse drug reactions. Potential concerns included the comparability of the tool's automated literature search relative to a manual 'all fields' PubMed search, missing drugs and adverse event terms, interpretation of signal scores, and integration with existing computer-based analytical tools.

Conclusions: Usability testing demonstrated that this novel tool can automate the detection of ADE safety signals from published literature reports. Various mitigation strategies are described to foster improvements in design, productivity, and end user satisfaction.

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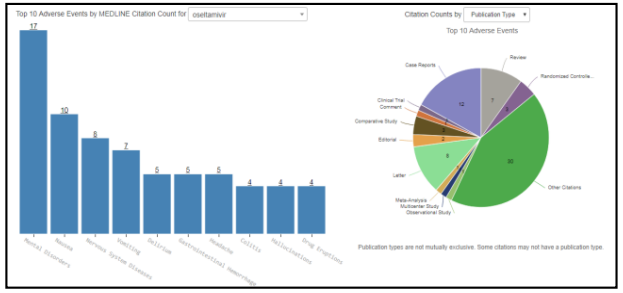
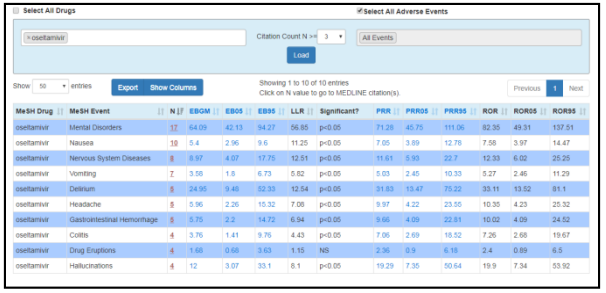
PEARL Web-based analytical tool: Featured visualizations

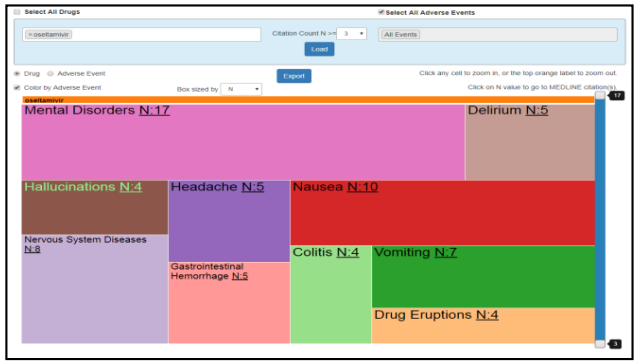
Top 10 Adverse Drug Events



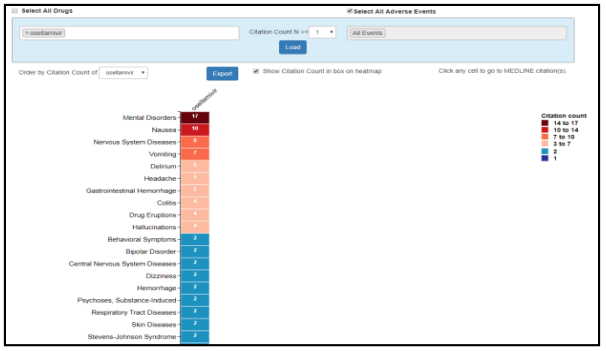
Exportable Data Mining Outputs



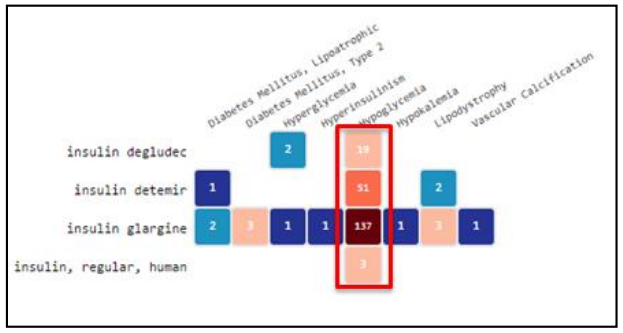
Tree Maps



Heat Maps

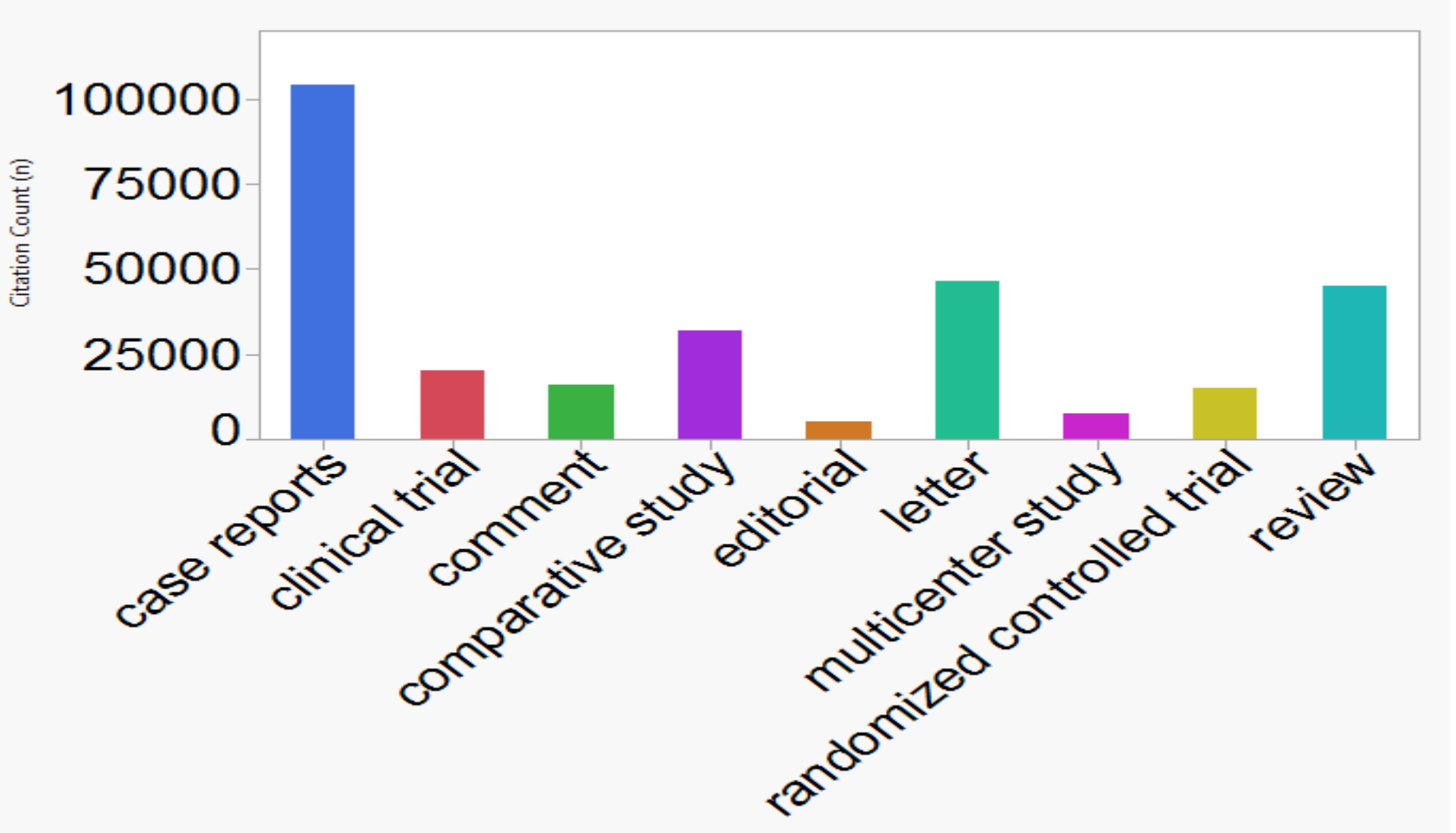


Drug Class Level



Time Course Graph

PEARL detects drug-adverse event safety signals from diverse scientific literature

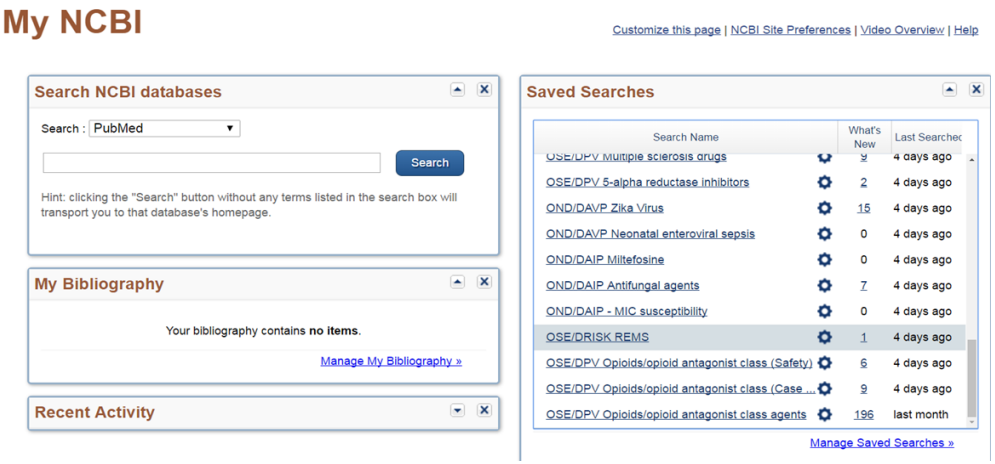


Weekly PubMed Literature 'Alerts'

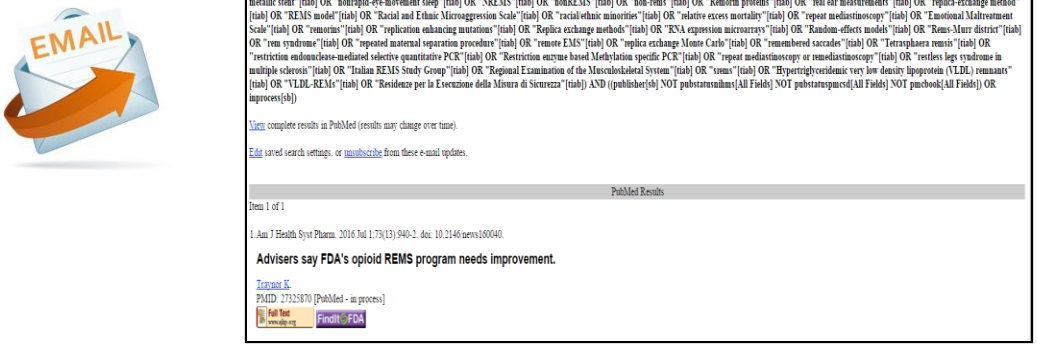
- Aim: to detect safety and efficacy issues that are newly emerging and not known prior to the search
- Leverages existing search functionality in PubMed (MyNCBI)
- Focus on the most recently deposited PubMed/MEDLINE citations that have not yet been MeSH indexed

Featured Functionalities

Managed customized literature search queries



Sample literature 'Alert' email

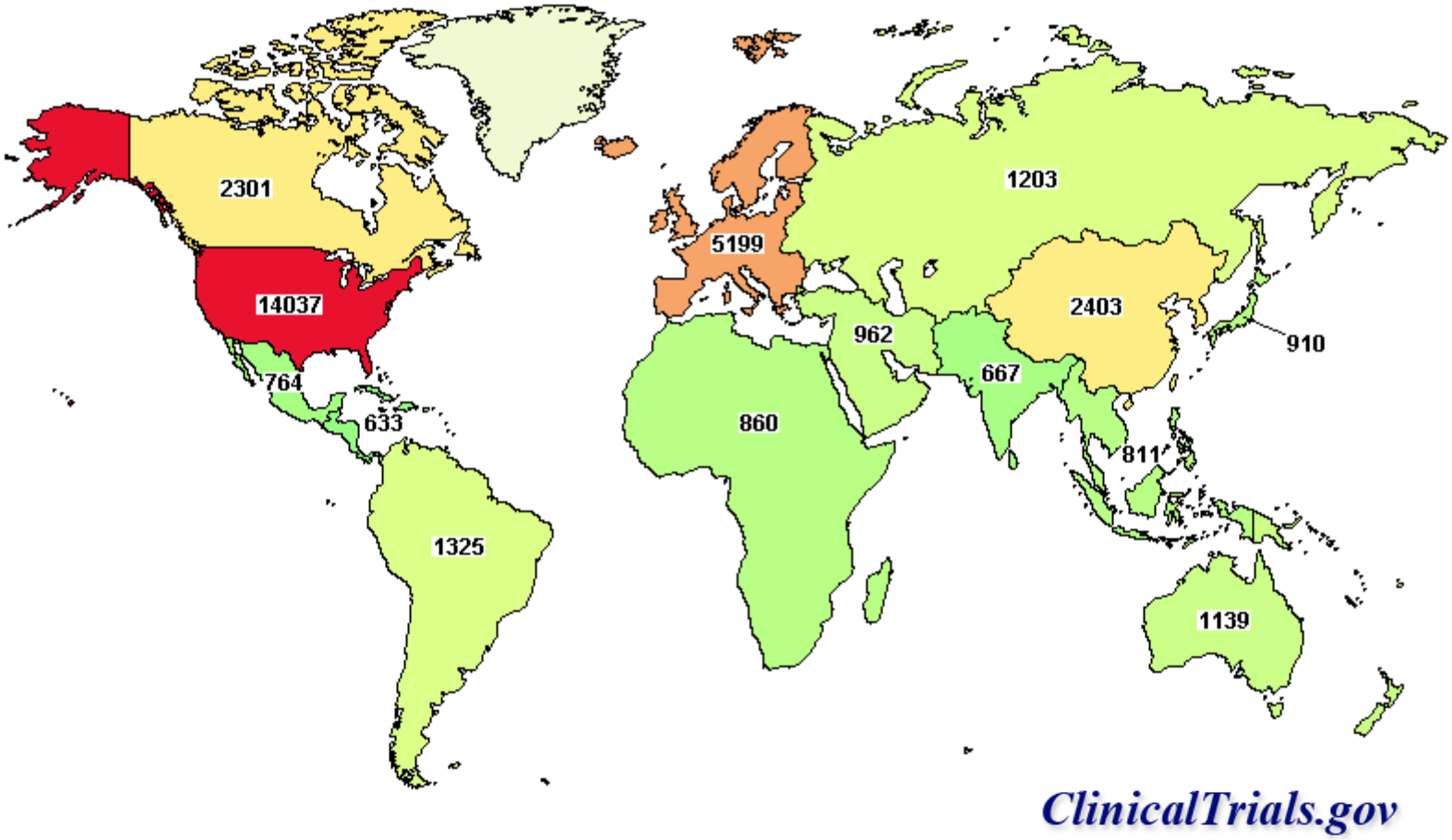


ClinicalTrials.gov

- A registry and database of clinical trials established as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA).
- Expanded in 2007 under the Food and Drug Administration Amendments Act (FDAAA) to require the reporting of summary results, including adverse events, for certain trials

ClinicalTrials.gov

ClinicalTrials.gov



A total of 22,546 completed studies with results through June 2017.

Electronic Health Records

- Preliminary work designed to establish a block chain-mediated connection between a group of selected USCIIT participating hospitals and FDA
- Identify influenza cases using patient level data for case reporting and patient outcome evaluation
- Ensure removal or anonymize PII/PHI data
- Use FHIR accelerator to onboard hospitals
- Operations and analytics to be conducted in secure data broker and FDA GovCloud

PII = personally identifiable information; PHI = protected health information
USCIIT = US Critical Illness and Injury Trials Group

RAPID Summary

- Bidirectional mobile platform to collect information and analyze it in real-time, and provide information/response back within 24 hours
- Enhance efficiency and speed of response to urgent public health needs
- Flexible data and analytic cloud platform
- Enhances product safety surveillance activities
- Use cases oriented to medical countermeasures in response to emerging infectious disease threats (pandemic influenza), CBRN agents, REMS, and medication errors

CBRN = chemical, biological, radiological, or nuclear;
REMS = risk evaluation and mitigation strategy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