U.S. FOOD & DRUG ADMINISTRATION

Enhancing Laboratory Data Infrastructure to Access Real-World Evidence (RWE) for *in vitro* Diagnostics (IVDs):

Three Models for RWE Use

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MDEpiNet Annual Meeting
Thursday, October 19th, 2017

SHIELD Mission

(Systemic Harmonization & Interoperability Enhancement for Lab Data)

Support efforts to harness non-traditional *in vitro* diagnostic (IVD) data sources to:

- support regulatory decisions for IVDs and more throughout the Total Product Life Cycle (TPLC),
- reduce burdens to the healthcare ecosystem and
- promote development of innovative solutions to public health challenges.

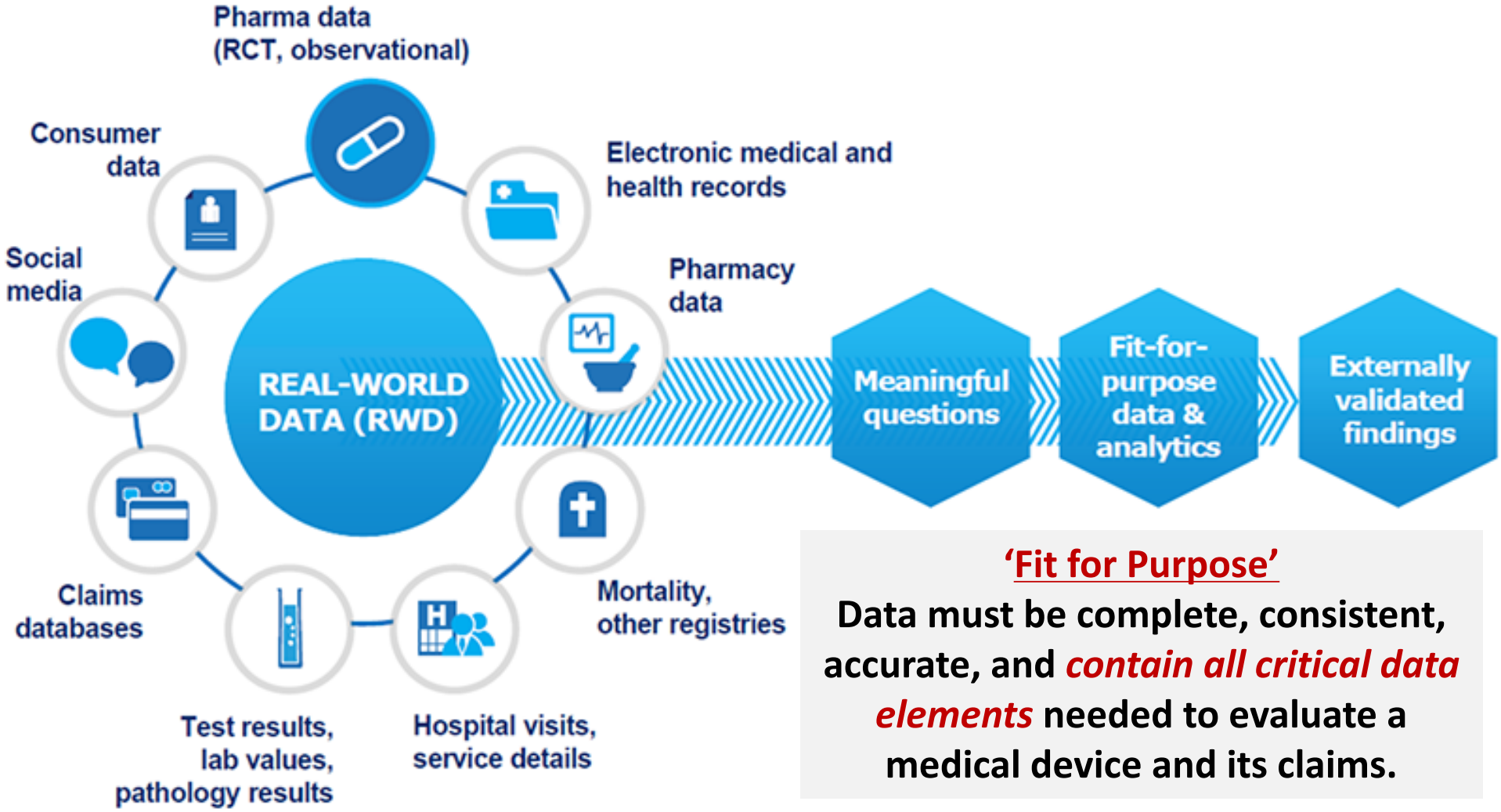
What IVDs Do?

- *In vitro* diagnostics (IVDs) products are… intended for use in diagnosis of disease or other conditions... [21 CFR 809.3]

- Fundamentally, IVDs 'ask' a question of a specimen taken from a human body.

- The result that follows is the 'answer' to that question.

Registries/EHRs: Accessing RWE

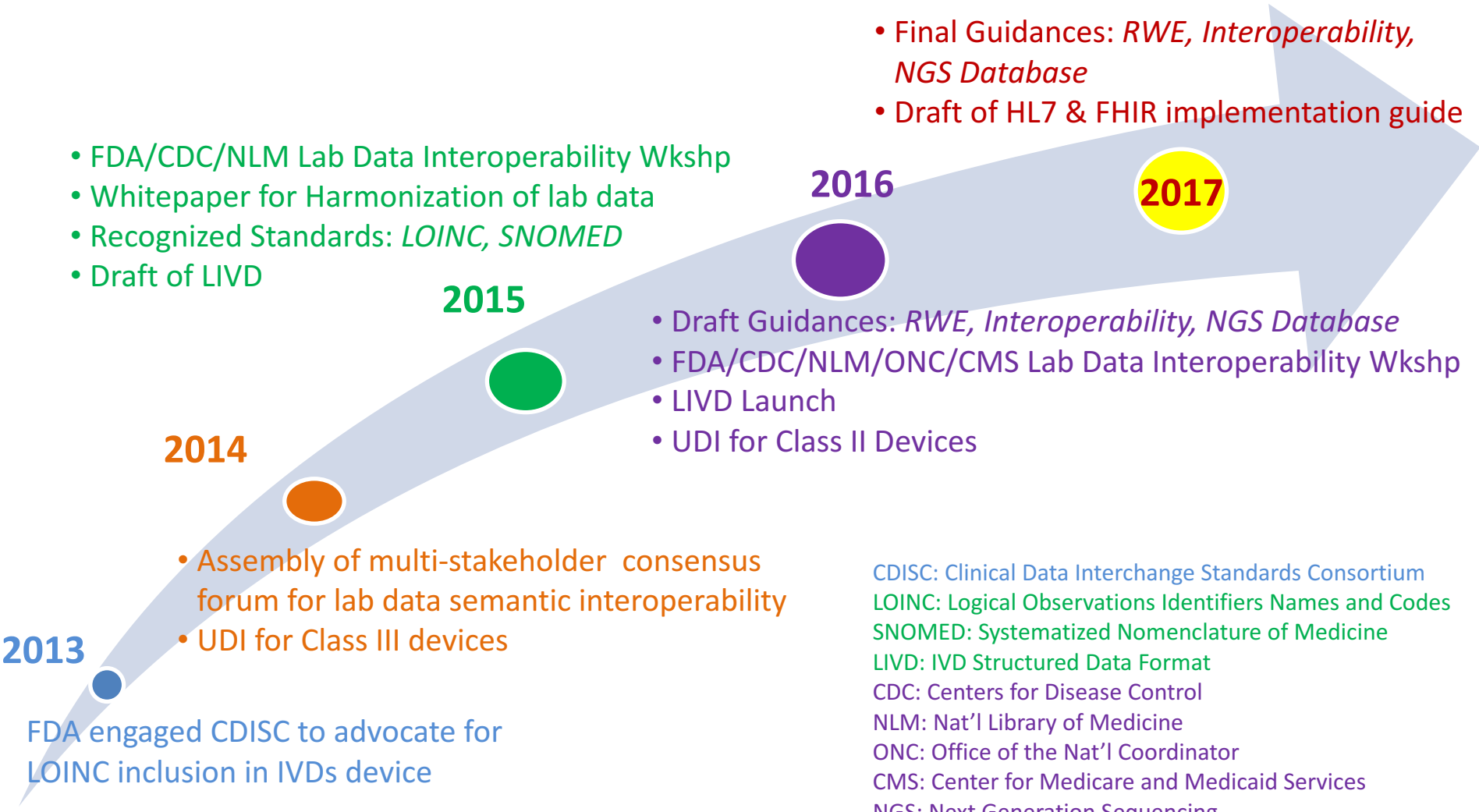


'Fit for Purpose'

Data must be complete, consistent, accurate, and *contain all critical data elements* needed to evaluate a medical device and its claims.

KEY: Coordination/Harmonization (Interoperability)

Multi-Stakeholder IVD Semantic Interoperability Efforts



CDISC: Clinical Data Interchange Standards Consortium
LOINC: Logical Observations Identifiers Names and Codes
SNOMED: Systematized Nomenclature of Medicine
LIVD: IVD Structured Data Format
CDC: Centers for Disease Control
NLM: Nat'l Library of Medicine
ONC: Office of the Nat'l Coordinator
CMS: Center for Medicare and Medicaid Services
NGS: Next Generation Sequencing
HL7: Health-Level 7
FHIR: Fast Healthcare Interchange Resource

SHIELD Infrastructure

Function	*Candidate Coding*	*Elements (partial list)*	*Transmission Format*
Describe IVD device/method type	LOINC (Logical Observations Identifiers Names and Codes)	Component Property Time System Scale Method	Structured Data Format -LIVD
Describe IVD device/method result	SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms)	Detected Not Detected Inconclusive Test Not Completed	Structured Data Format –LIVD II
	UCUM (Unified Code for Units of Measure)	Units of Measures (e.g. grams, etc.)	Structured Data Format –LIVD II
Unique Device Identification	UDI (FDA Unique Device Identification System)	Device Identifier Elements of UDI	Structured Data Format -LIVD

Associated data populated into Laboratory Information Systems (LISs) can be queried. Fast Healthcare Interchange Resource (FHIR) implementation guide is near completion.

Ongoing SHIELD Efforts

1. Developing tools for the application of semantic standards in structured data formats through:
   - step-by-step manual defining how to map LOINC to IVD devices
   - Government/Industry/Laboratory Clinical IVD Semantic Interoperability Meeting – Value Sets (LIVD II)

2. FDA is developing regulatory guidance and inter-Office/Center infrastructure to determine how/when regulatory grade Real-World Evidence (RWE) can be leveraged in regulatory decisions.

Involved Stakeholders:

FDA (CDRH, CDER, CBER), CDC, NIH, ONC, CMS, IVD Manufacturers, EHR Vendors, Laboratories, CAP, Standards Developers, Academia

Some Nuances Unique to IVDs

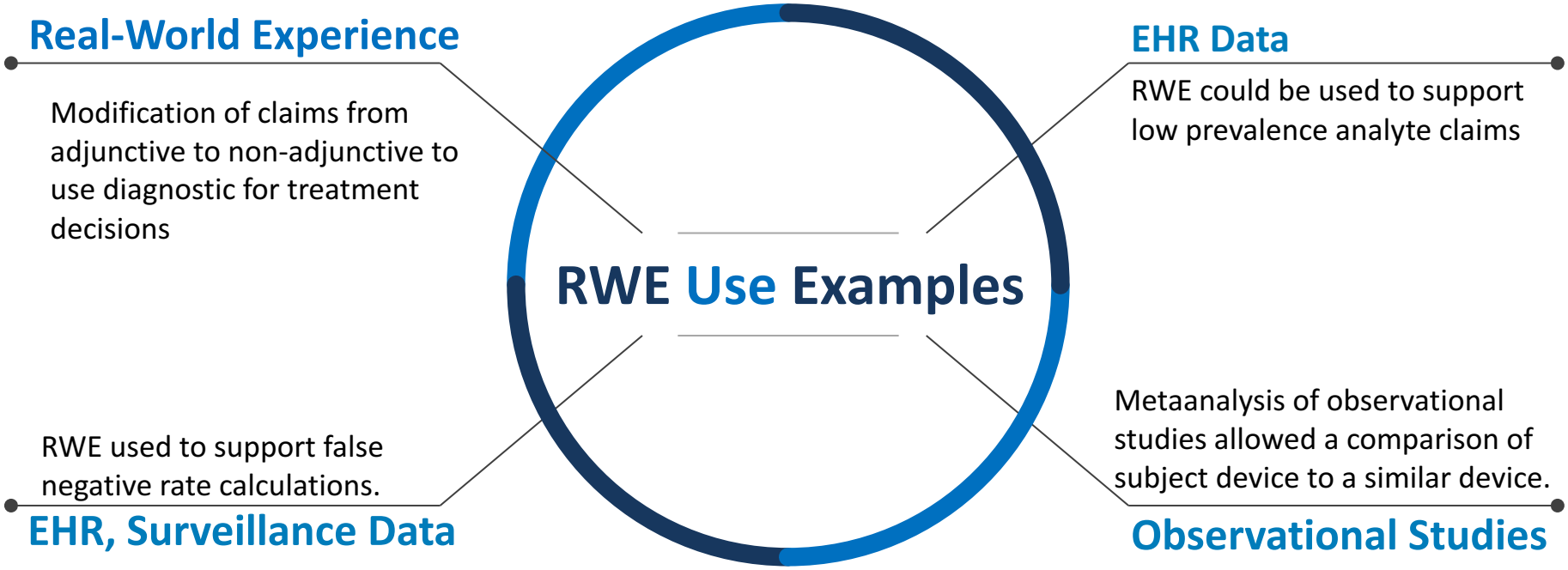
- Labs operate under the Clinical Laboratory Improvement Amendments (CLIA) regulations
- CMS oversees labs through the College of American Pathologists (CAP) lab accreditation program Labs regularly conduct proficiency testing of CAP panels and submit results to CAP (for most tests)
- Labs conform to Good Laboratory Practices (GLP; 21 CFR 58 & 42 CFR 493)
- Labs have to validate off-label use and Laboratory Developed Tests (LDTs)

Three RWE Use Cases for IVDs *

- Low prevalence analytes/patient population subgroups/rare endpoints/long-term outcomes *(e.g., patient/healthcare provider experience)*
- Bringing off-label use on-label and under a Quality System *(leveraging EHR data; Observational Studies)*
- Leveraging data generated external to the United States *(leveraging OUS data that is fit for US)*

* Existing examples and models for future…

RWE Examples



RWE Example 1

Background/Claim

- A diagnostic device was approved based on traditional clinical trials and analytical studies.
- Sponsor sought shift
  from: *adjunctive* use followed by an invasive monitoring procedure
  to: *non-adjunctive* use—where CGM information can be used directly to make diabetes treatment decisions.

RWE

- Panelist's clinical experience with current off-label non-adjunctive use of the marketed device.
- Direct comments from current users regarding their experience with off-label non-adjunctive use of the marketed device including:
  - public comments from patients, caregivers and other members of the community impacted by the disease.
- Pragmatic Clinical Trial with patients using the adjunctive and non-adjunctive methods.

Real-World Experience

Modification of claims from adjunctive to non-adjunctive to use diagnostic for treatment decisions

RWE Example 2

RWE used to support false negative rate calculations.

EHR, Surveillance Data

Background/Claim

- Laboratories developed and conducted screening tests in the absence of any FDA cleared or approved assay.
- Some states mandate disease screening tests due to the high disease mortality rate.
- Sponsor sought *de novo* screening claim to aid in the diagnosis of disease.

RWE

- A traditional pivotal study was conducted with the new device in comparison to the routine laboratory screening to determine true positives.
- It was impractical to perform confirmatory testing (or other suitable follow-up) on all negative patients.
- The ***false negative*** result rate was calculated based on the clinical status of all patients who tested negative. Public health labs worked with diagnostic centers to collect surveillance information to follow up on all patients in the clinical study that were diagnosed with any of the screened conditions and participated (false negatives). There were no false negatives.

RWE Example 3

Metaanalysis of observational studies allowed a comparison of subject device to a similar device.

Observational Studies

Background/Claim

- Traditional analytical studies were conducted along with studies to demonstrate user comprehension of the labeling and test results.
- Sponsor sought *de novo* claim assess the probability that a patient is at risk of developing a series of different diseases.

RWE

- Clinical performance for this test was assessed using published data. Meta-analyses of published studies of a wide range of patient populations for several diseases were conducted to calculate likelihood ratios (an estimate of how the test result affects the chances of a condition).

RWE Mock Example

Background/Claim

- Traditional clinical trials show that genes to identify an infectious organism can be detected, but genes to infer antibiotic resistance are too low prevalence.
- Low prevalence analytes/ patient population subgroups/ rare endpoints/ long-term outcomes can all be difficult claims to attain and dramatically increase the size of a clinical trial.

RWE could be used to support low prevalence analyte claims

RWE

- For some assays, there is routine clinical follow-up regardless of the results of the test.
- It may be possible to release the device to market with a well-qualified presumptive claim for the detection of resistance genes based on analytical studies and minimal clinical information collected in trials.
- post-market susceptibility/resistance data for all detected organisms could be collected along with the obligate reference method to be submitted in a second application to remove the presumptive qualifications.

EHR Data

Potential Use Case Collaborations

Title: *"Adding Lightning Speed to Clinical Laboratory Data Assessment Tools - Implementation of Add-On Tools that will Generate Semantic Interoperable Laboratory Data Outputs from Clinical Trials (CTs) and Electronic Health Records (EHRs) to expedite analytical processes using Acute Kidney Injury (AKI) as a Case Study"*

Lead: FDA/CDER

Title: *"Emergency Medicine Opioid Data Infrastructure: Key Venue to Address Opioid Morbidity and Mortality"*

Lead: NIH/NIDA

Conclusions/Requests

- SHIELD implementation can unlock RWE siloed in data repositories which may be leveraged in regulatory decisions.
- OIR is engaging in cross-center and multi-stakeholder efforts to assist in the adoption of semantic interoperability standards and structured data formats.
- Collaboration and support is critical to realizing the benefits of these efforts.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