GInAS/GSRS Meeting

CDER Informatics Initiatives and the IDMP

Mary Ann Slack
Director
Office of Strategic Programs (OSP)
Center for Drug Evaluation and Research (CDER)

November 16, 2018

FDA DISCLAIMER

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Selected CDER Standardization Topic Areas

- Product Quality/Chemistry & Manufacturing Controls (PQ/CMC)
- Real-world evidence (RWE)
- IDMP implementation
- E2B IND Safety Reports

PQ/CMC INITIATIVE

PQ/CMC

- The PQ/CMC project is aimed at developing and implementing structured data standards for quality/CMC submissions to marketing applications
  - Benefits: Consistent high-quality computable data requiring no human interpretation; hi-tech quality assessments; and Improved crisis response
  - Involves CDER, CBER and CVM
  - Includes IDMP harmonization (where feasible)
  - Topic informally broached in ICH with interest expressed
  - This first phase includes over 150 data elements within eCTD Module 3 (CMC), analyzed and defined, with new controlled terms proposed where appropriate

PQ/CMC Public Meeting

- Public Meeting on PQ/CMC standardized data conducted on Oct 19
  - Objectives: to share progress on the standardization effort, provide perspective on FRN comments (over 480), and solicit stakeholder inputs
- Next steps
  - Development & testing of appropriate combination of technologies (e.g. FHIR)
  - Proof of concept using Quality Specification to inform next steps for the full scope
  - Development of draft guidance

REAL-WORLD EVIDENCE (RWE)

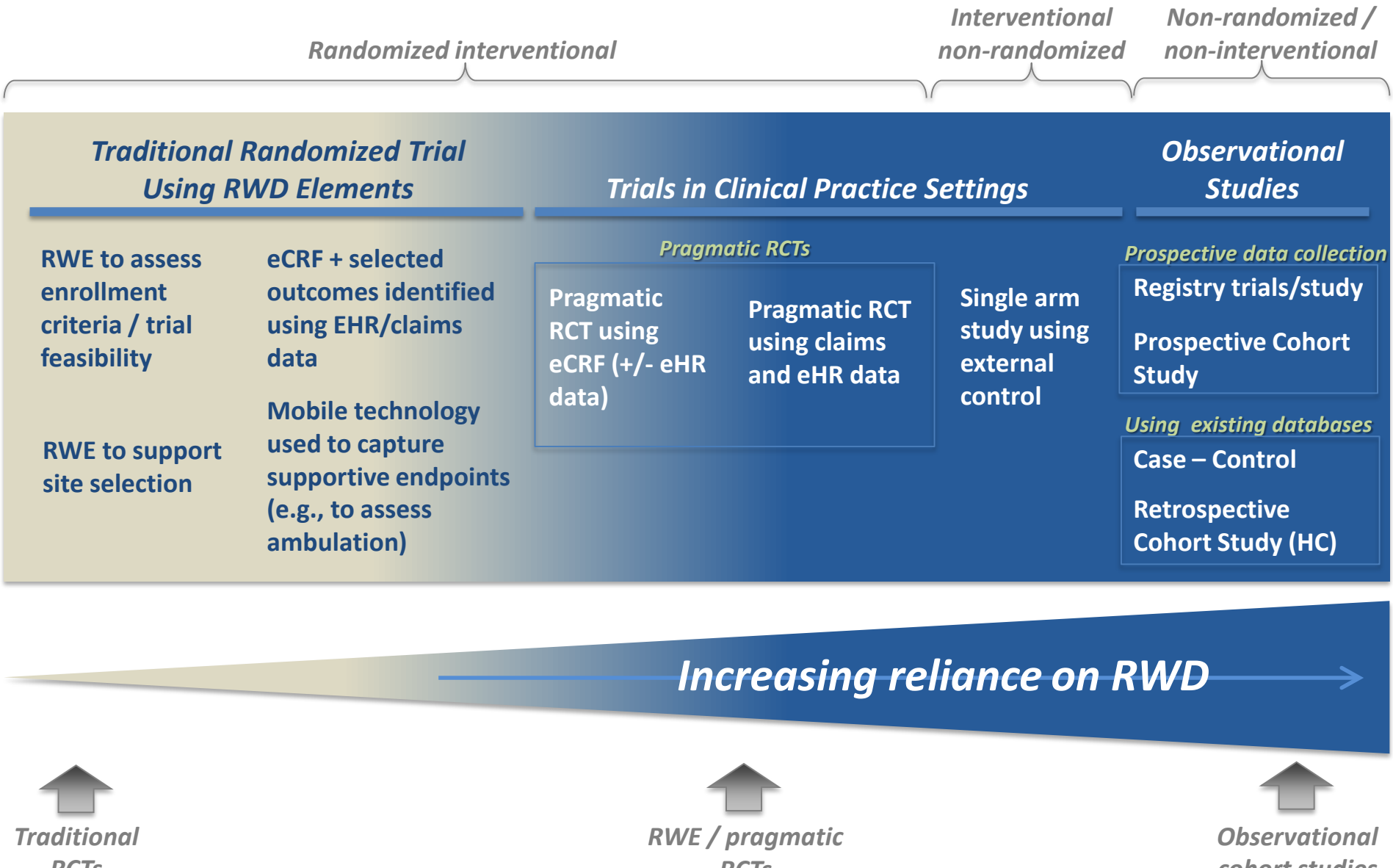
FDA CDER Definitions

- **Real World Data are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.**
- **Real World Evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.**

RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices.

RWE can be generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Wide Spectrum of Potential Uses of RWD/RWE in Clinical Studies



21st Century Cures: Expectations

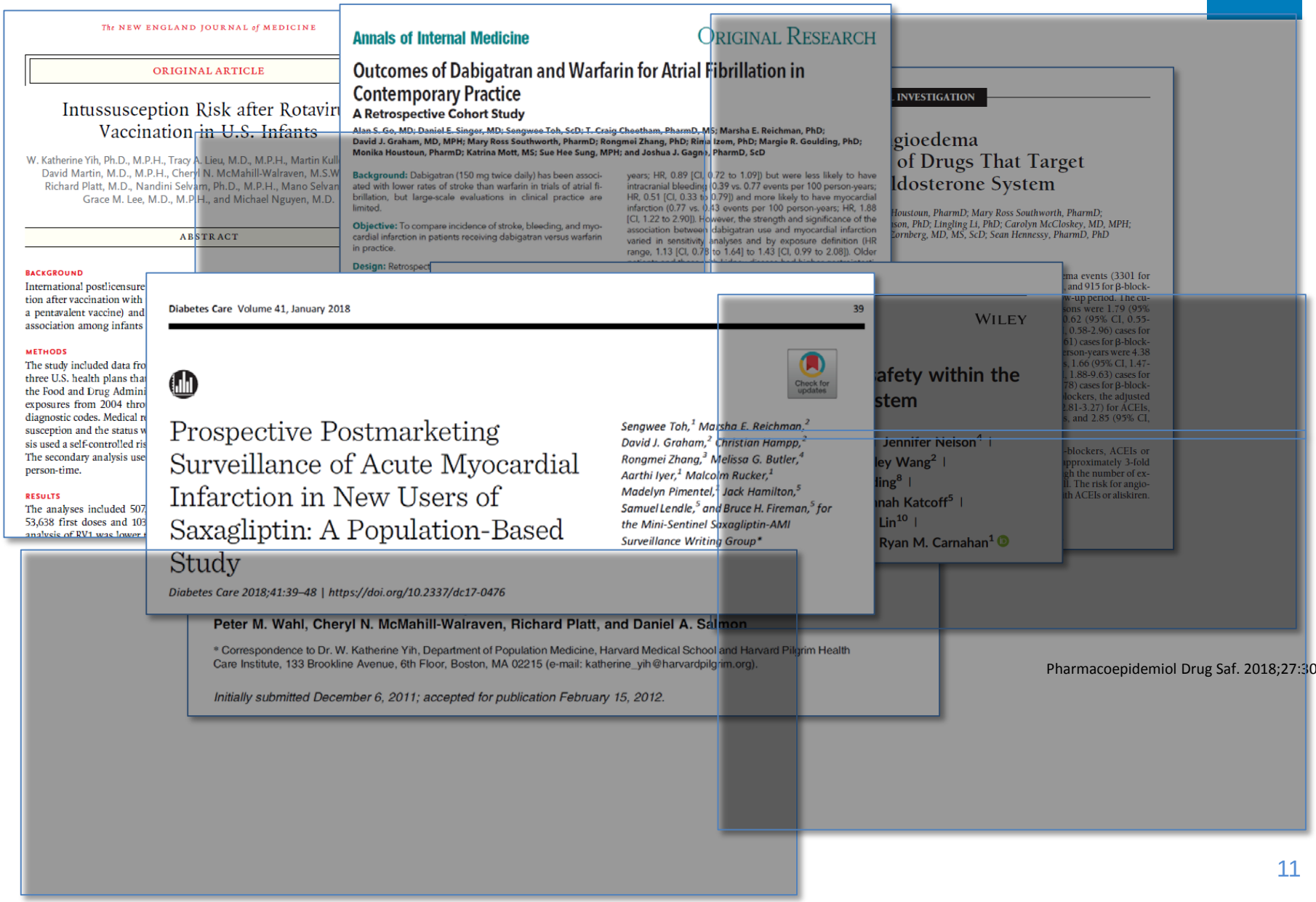
Section 3022 of the Cures Act states:

- **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**
- **Program will be based on a framework that:**
  - **Categorizes sources of RWE and gaps in data collection**
  - **Identifies standards and methodologies for collection and analysis**
  - **Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address**

Framework for program implementation will be developed in consultation with stakeholders.

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*

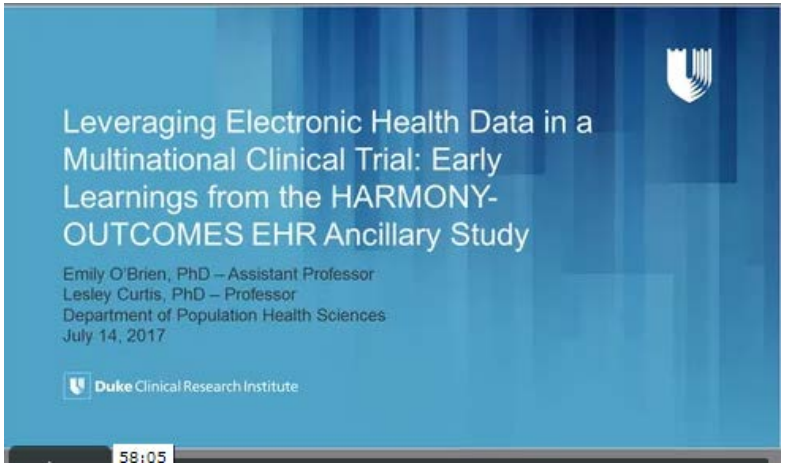
FDA has Embraced RWE for Safety



Pharmacoepidemiol Drug Saf. 2018;27:30–37

Demonstration Projects: Assessing Data Fitness

- **Collaboration between Duke Clinical Research Institute and GlaxoSmithKline**
- **Supported by FDA**
- **Assessing EHR ability to:**
  - **Facilitate recruitment**
  - **Populate baseline characteristics**
  - **Identify clinical endpoints**



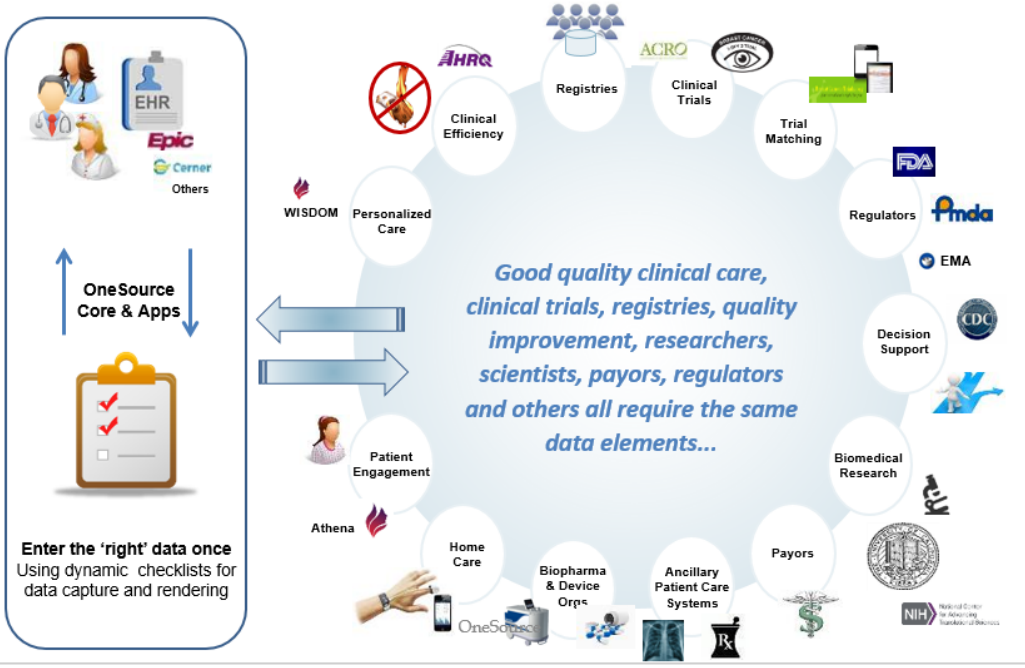
July 14, 2017: Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-Outcomes EHR Ancillary Study

http://www.rethinkingclinicaltrials.org/grand-rounds-7-14-17/

Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus – NCT02465515

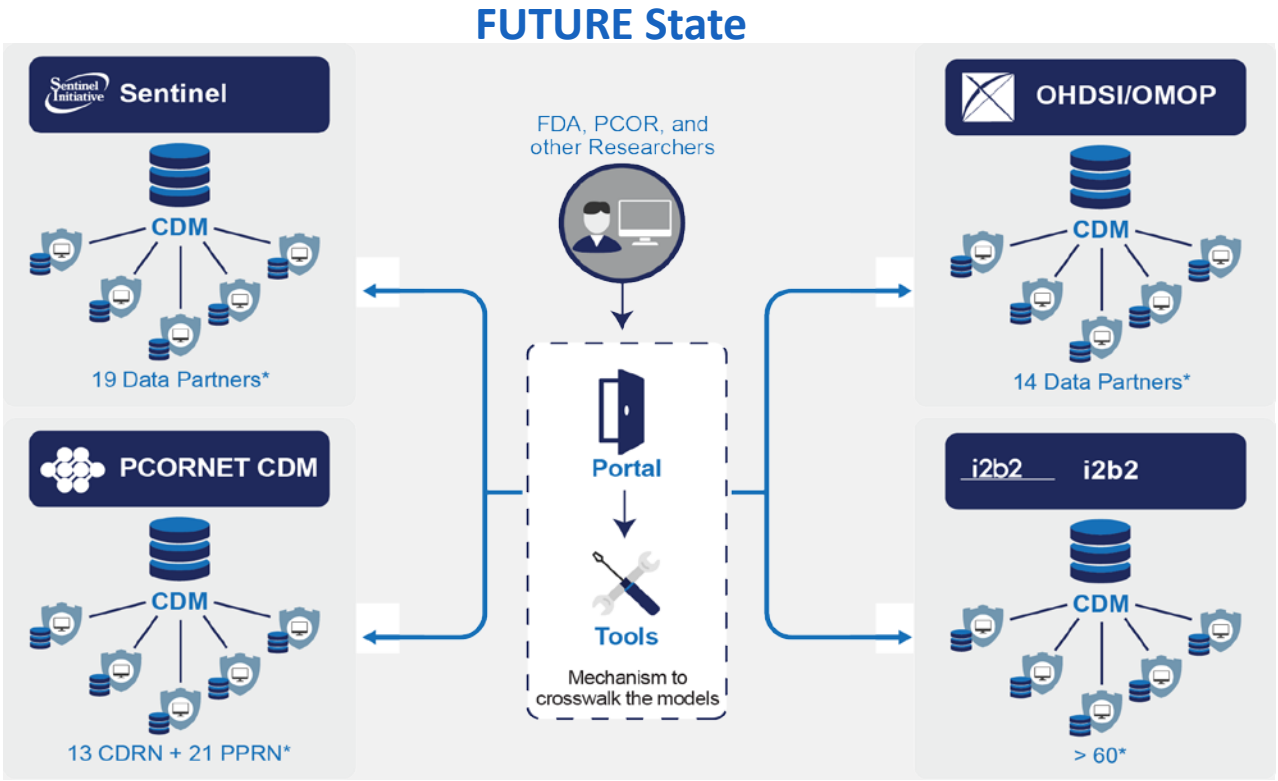
Demonstration Projects: Assessing Data Fitness / Standards

- **OneSource: "enter the right clinical data once, use many times"**
- **FDA collaboration with Dr. Laura Esserman, UCSF**
- **Integration of standards based tools into the EHR to bring together health care and research**
- **Demonstration in breast cancer clinical trials**



Courtesy of Dr. Laura Esserman and Susan Dubman

Demonstration Projects: Harmonization of Common Data Models

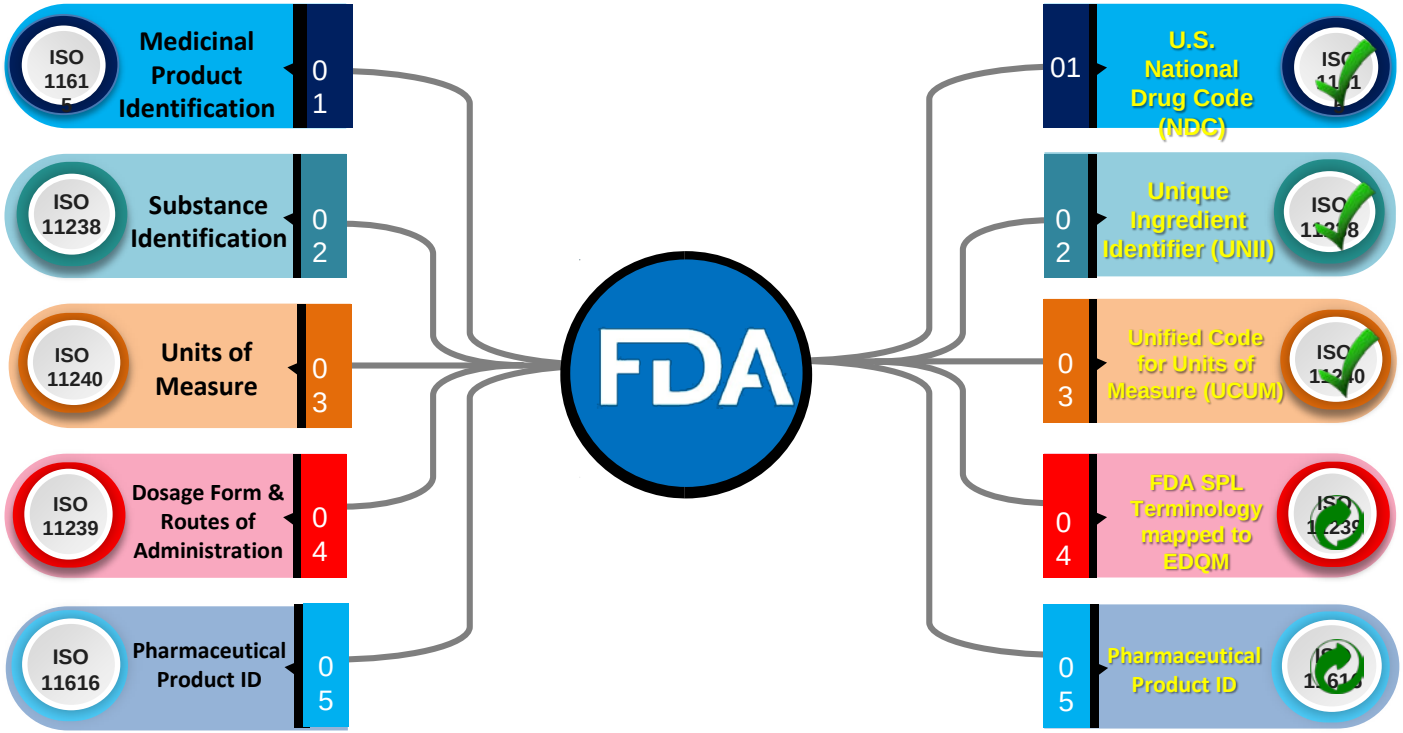


Observational Studies and Effectiveness

- **Using RWD analyses for Effectiveness Research**
  - **Brigham and Women's Hospital (Dr. Schneeweiss) and Harvard Medical School collaboration**
    - **Using a scalable analytics platform with Medicare and commercial claims databases, investigators will try to use RWD to replicate the findings of phase 3 or 4 randomized controlled trials relevant to regulatory science.**

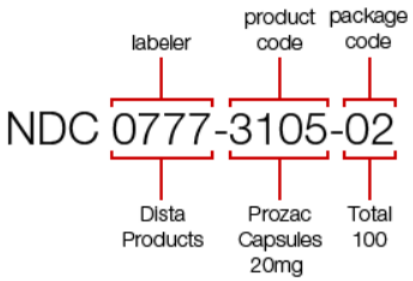
FDA'S APPROACH TO IDMP

FDA's Approach to ISO IDMP Standards



ISO 11615 Medicinal Product Identification (MPID)

- **MPID Description**
  - Data elements and structures for unique identification and exchange of regulated medicinal product information
- **U.S. National Drug Code (NDC)** is FDA's regional MPID
  - First two segments of the NDC code will be used to represent MPID
  - The full NDC will be used to represent the medicinal product at the package level (known as the PCID)
    - **Example:**



Regional Identifiers

Medicinal Product Identification (MPID)

- **MPID Exchange Standard (ISO/TS20443)**
  - FDA uses SPL (HL7 v3 message) for labeling and drug listing and registration submissions, and does not currently have plans to change
    - FDA determined that the MPID required components are captured in the SPL label
    - Indication will be captured prospectively via regulatory submissions
  - FDA is collaborating with EMA to develop and test HL7 Fast Healthcare Interoperability Resource (FHIR) for information exchange
    - Test will ensure adherence to the ISO (TS20443) technical specification, *and*
    - FDA will evaluate and determine steps necessary to accept FHIR messages as well as SPL

ISO 11238 Substance Identification (SubID)

- **SubID Description**
  - Data elements and structures for unique identification and exchange of regulated information on substances
- ***Unique Ingredient Identifier (UNII)*, ISO 11238 compatible, used by FDA for many years to uniquely and unambiguously identify substances**
- The Open Source Global Substance Registration System (GSRS) has been developed and is available at https://tripod.nih.gov/ginas/#/
  - **FDA-GSRS is in production** (approx. 150,000 entries)

ISO 11238 Substance Identification (SubID)

- Collaboration to make GSRS a much richer system
  - EMA co-developing GSRS in their environment
  - Ensure that the systems remain synchronized as a global effort

- **Substance ID Exchange Standard**
  - Testing of a FHIR Substance Registration resource is planned for HL7 Connectathon in May 2019
  - Exploring the capability for Sponsors to register their own substances

ISO 11239

Dosage Form (DF) & Route of Administration (RoA)

- **DF & RoA Description**
  - Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
- European Directorate for the Quality of Medicines (EDQM) terminology identified as the ISO 11239 compliant terminology set and maintenance organization
- FDA Terminology for SPL (SPL) is used in electronic content of labeling, and drug registration and listing; also used in CDISC Controlled Terminology
  - National Cancer Institute / Enterprise Vocabulary Service (NCI /EVS) curates the SPL terminology as part of the larger NCI terminology

ISO 11239

Dosage Form (DF) & Route of Administration (RoA)

- EDQM terminology is hierarchical and more granular
  - For example, 166 SPL DF terms vs ~536 EDQM BDF & PDF terms
- NCI / EVS added the entire EDQM terminology to the NCI terminology
- NCI / EVS and FDA mapped SPL to EDQM Terminology for DF and RoA
  - Currently, FDA and NCI/EVS are reviewing the mapping and gaps to determine next steps

Update: FDA is reviewing the standard for a potential higher level interpretation that would enable FDA terminology for SPL to become compliant; else no plans to transition for content of labeling at this time.

Note: Drug product nomenclature (i.e. container labels, carton labeling and prescribing information) will continue to use USP terminology as per FD&C Act.

ISO 11240

Units of Measurement

- **Units of Measurement Definition**
  - Data elements and structures for unique identification and exchange of units of measurement

- The ***Unified Code for Units of Measure*** (**UCUM**) was selected as the ISO 11240 compliant standard
  - UCUM is a system intended to include all units of measures being contemporarily used in international science, engineering, and business
  - Currently, FDA receives submissions that use the UCUM syntax standard for dosage strength in both content of product labeling and drug establishment registration and drug listing.

ISO 11616

Pharmaceutical Product Identification (PhPID)

- **PhPID Description -** *PhPID is a code generated by an algorithm that can be used to determine pharmaceutical equivalence of products*

- FDA is currently testing the generation of regional PhPIDs
- In May 2018, WHO/ UMC presented a conceptual proposal for validation and maintenance of global PhPIDs.
- Planning to participate at a technical and policy working group meeting in 4Q 2018.

PhPID_SUB_L1 → Substance Term(s)

PhPID_SUB_L2 → Substance Term(s) + Strength + reference strength

PhPID_SUB_L3 → Substance Term(s) + Administrable Dose Form

PhPID_SUB_L4 → Substance Term(s) + Strength + reference strength + Administrable Dose Form

25

IDMP on FHIR

- In January, the EU endorsed using FHIR as the basis for the API for the Product Management Service
  - Makes FHIR the data standard that supports the exchange of information about medicinal products, substances, and related reference data in the EU
- HL7's BR&R workgroup presently sponsors the development of ISO IDMP 11238 (Substance Specification) and IDMP 11615 (Medicinal Product) resources
  - Medicinal Product resource development takes place in collaboration with HL7's Pharmacy work group
  - The goal is to harmonize IDMP and the existing product resources reflecting Pharmacy use cases
  - Initial work (ready for ballot) is expected to be completed for January 2019 HL7 WG meeting
  - IDMP resources are expected to be balloted for May 2019 meeting

E2B IND SAFETY REPORT

E2B IND Safety Report

- Primary Objective
  - Implement a digital framework for the electronic submission, review, and tracking of IND safety reports to improve FDA's ability to detect, track, and act upon safety signals that occur during the conduct of clinical trials.
- IND sponsors are required to report serious adverse reactions
  - Current process for submission and review of IND safety reports submitted as PDF files or on paper is inefficient, labor intensive, and poses significant challenges for safety signal detection and tracking
- CDER is conducting a pilot, with six participating sponsors, to created a digital framework for the electronic submission of IND safety reports using ICH E2B data standards
- CDER expects to implement the new digital framework and issues guidance in late FY2019
  - Need to identify and assign unique substance ID (UNII) during IND phase

Thank you