Semantic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD):

Building Reliable Infrastructure to Support Real-World Evidence (RWE) Use in Regulatory Decisions

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Finding Utility from 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)
Studies to Support IVD Clearance/Approval

**Analytical Studies:**
- Limit of Detection (LoD)
- Between Laboratory Reproducibility
- Within Laboratory Precision
- Linearity (*for quantitative assays only*)
- Reagent/Specimen Stability, Controls/Calibrators, etc.
- Inclusivity
- Cross-Reactivity
- Interference
- Matrix Equivalency
- Fresh vs Frozen

**Clinical Studies* (descending in relevance):**
1) Fresh prospectively collected specimens
2) Archived (e.g. frozen) prospectively collected specimens
3) Retrospective archived specimens
4) Contrived specimens in a clinical matrix
5) Contrived specimens in a non-clinical matrix

*Note: Clinical studies are conducted in comparison to a reference method (with some rare exceptions)
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Labeling Claims, Limitations, etc.

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Successful Pre/Post-Market Examples

*(partial summary from tracked submissions leveraging RWE)*

**RWE Use**
- New pre-market indications
- PMA approval *de novo* granting
- 510(k) clearance Pivotal trials
- Post-market surveillance
- Pre- and post-market controls indication expansion (primary and secondary) post-market studies evaluate labeling claims and secondary effectiveness outcomes
- HDE-to-PMA conversion
- Response to a final classification order
- Bayesian analysis with RWE

**RWE Data Sources**
- Electronic Health Records (EHRs)
- Sponsor registries National registries
- Hospitalization records Public databases
- CMS claims database OUS device data
- RWE Post-market study
- Remote-monitoring Retrospective studies
- OUS Clinical case summaries and chart data
- National Death Index
- Device-generated data Medical records
- Private databases Real-world Literature
- State-run routine screening programs
- International biobanks
Optimizing RWE Utility/Value

RWE Opportunity:
- There is a wealth of data siloed in data repositories (e.g., electronic health records - EHRs) that may be valuable in regulatory decisions.

Problems:
- Lack of interoperable infrastructure in data repositories is repeatedly cited as a significant impediment to accessing and using RWE.
- Insufficient resources exist to develop infrastructure.

Solutions:
- Improve interoperability by developing infrastructure that will enable RWE access.
- Development by a multi-stakeholder consensus forum, leveraging existing infrastructure.
- Focus efforts on building valuable infrastructure identified by stakeholders.
Building Valuable Infrastructure

- RWE Submission Tracking
- IVD Industry Feedback
- Multi-Stakeholder IVD Interoperability Meetings

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

• support regulatory decisions and sponsor actions throughout the Total Product Life Cycle (TPLC),

• reduce burdens to the healthcare ecosystem and

• promote development of innovative solutions to public health challenges.
Efforts Driving SHIELD Development

- 2013:
  - FDA engaged CDISC to advocate for LOINC inclusion in IVDs device

- 2014:
  - Assembly of multi-stakeholder consensus forum for lab data semantic interoperability
  - UDI for Class III devices

- 2015:
  - Draft Guidances: RWE, Interoperability, NGS Database
  - FDA/CDC/NLM/ONC/CMS Lab Data Interoperability Wkshp
  - LIVD Launch
  - UDI for Class II Devices

- 2016:
  - Final Guidances: RWE, Interoperability, NGS Database
  - Draft of HL7/FHIR implementation guide
  - Engage Lab US Realm
  - Submit PCORTF grants

- 2017:
  - Recognized Standards: LOINC, SNOMED-CT
  - Draft of LIVD

CDISC: Clinical Data Interchange Standards Consortium
LOINC: Logical Observations Identifiers Names and Codes
SNOMED: Systematized Nomenclature of Medicine-Clin Terms
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
PCORTF: Patient-Centered Outcome Research Trust Fund
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.
Semantic Interoperability Standards*

**LOINC®** – Logical Identifiers, Names and Codes

**SNOMED-CT** – Systematized Nomenclature of Medicine – Clinical Terms

**UCUM** – Unified Code for Units of Measure

**UDI** – Unique Device Identification

**LIVD** – Digital Format for Publication of LOINC Vendor IVD Test Results

**HL7/FHIR** – Health Level 7; Fast Healthcare Interchange Resource

*All internationally used (except LIVD) and aligned with several critical standards/nomenclatures (e.g., ISO; ANSI; GMDN)*
## SHIELD Infrastructure

<table>
<thead>
<tr>
<th>Function</th>
<th>Candidate Coding</th>
<th>Elements (partial list)</th>
<th>Transmission Format</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Describe IVD device/method type</strong></td>
<td>LOINC (Logical Observations Identifiers Names and Codes)</td>
<td>Component Property Time System Scale Method</td>
<td>Structured Data Format -LIVD</td>
</tr>
<tr>
<td><strong>Describe IVD device/method result</strong></td>
<td>SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms)</td>
<td>Detected Not Detected Inconclusive Test Not Completed</td>
<td>Structured Data Format –LIVD II</td>
</tr>
<tr>
<td></td>
<td>UCUM (Unified Code for Units of Measure)</td>
<td>Units of Measures (e.g. grams, etc.)</td>
<td>Structured Data Format –LIVD II</td>
</tr>
<tr>
<td><strong>Unique Device Identification</strong></td>
<td>UDI (FDA Unique Device Identification System)</td>
<td>Device Identifier Elements of UDI</td>
<td>Structured Data Format -LIVD</td>
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Associated data populated into Laboratory Information Systems (LISs) can be queried. Fast Healthcare Interchange Resource (FHIR) implementation guide is near completion.
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<tr>
<td>Describe IVD device/method type Question</td>
<td>LOINC (Logical Observations Identifiers Names and Codes)</td>
<td>Component, Property, Time, System, Scale, Method</td>
<td>Structured Data Format -LIVD</td>
</tr>
<tr>
<td>Describe IVD device/method result Answer</td>
<td>SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms)</td>
<td>Detected, Not Detected, Inconclusive, Test Not Completed</td>
<td>Structured Data Format –LIVD II</td>
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Building Valuable Infrastructure

Systemic Harmonization and Interoperability for Laboratory Data (SHIELD)
Network of Experts

Infrastructure Development

Preferred Terms IVD Mapping Tools
LIVD Structured Data Format
HL7 Implementation Guides

IVD Manufacturers Map and Send Codes for:
- IVD Question (e.g., LOINC)
- IVD Answer (e.g., SNOMED-CT)

Implementers (e.g., Laboratories)
**Lab Data Interoperability/RWE/TPLC**

**SHIELD Aims to:**

Improve decision support, real-time epidemiology, healthcare cost savings, access Real-World Evidence (RWE) throughout the Total Product Life Cycle (TPLC) and more...

**OIR is currently:**

- Engaging in cross-center multi-stakeholder consensus efforts to aid the adoption of semantic interoperability and structured data format standards into lab workflow.
  - Unambiguous step-by-step manual defining how to map LOINC to IVD devices
  - Clinical IVD Semantic Interoperability Meeting – Value Sets (*Jan. 22-23, 2018*)
  - Actively writing grants to support laboratory data interoperability efforts

- Providing guidance on how to leverage RWE and safely disseminate data harmonization information to increase access to meaningful RWE.

**Critical Involved Stakeholders:**

FDA (CDRH, CDER, CBER), CDC, NIH, ONC, CMS, IVD Manufacturers, EHR Vendors, Laboratories, Standards Developers, Academia
Objective:
Collaborate with stakeholders in the development of an *unambiguous step-by-step manual defining how to map LOINC to IVD devices* intended to identify and evaluate infectious disease agents.

Proposal:
- Develop a standardized document/manual to include:
  - processes, examples of all types of Microbiology IVDs, tools for LOINC adoption in microbiology
  - Mechanisms to solicit new LOINC codes
- Pilot manual clinical laboratories
- Coordinate with key stakeholders to attain input (Industry, EHR vendors, CDC, ONC, CMS, etc.).
- Post manual feedback, revision, implementation, support
Logical Observation Identifiers Names and Codes (LOINC®)

Guide for Using LOINC Microbiology Terms
Components:
• Background/ Appendix
• Microscopic Examination
• Cultures
• Susceptibility Testing
• Resistance Testing
• Antigen Tests
• Nucleic Acid Tests
• Serology Testing

Features:
• Mapping Examples
• Examples in the manual
• Link to externally populated
• How to deal with:
  • Qualitative/ Quantitative Assays
  • Multiplex Assays
• Mapping Validation
Help Us to Help You

To focus efforts pragmatically, please let us how we can support your efforts to leverage RWE by:

• Sending a *pre-submission* describing how you would like to leverage RWE in a regulatory submission.

• Get involved in multi-stakeholder efforts to adopt/develop and pilot data harmonization standards.

**Questions/Comments?**
Contact: Michael.Waters@FDA.hhs.gov