Harnessing Real-World Data (RWD) for and from \textit{in vitro} Diagnostics (IVDs)

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Center for Devices and Radiologic Health (CDRH)
Food and Drug Administration (FDA)

\textit{ISPOR – Baltimore, MD 5/23/2018}
Context for RWE Guidance

- FDA Reauthorization Act (FDARA) including MDUFA IV commitment to use of real-world evidence to support device pre/postmarket decisions
- National Evaluation System for health Technology (NEST)
- 2016-2017 CDRH Strategic Priorities
- Guidance issued to clarify how RWE may be used to support regulatory decisions
Context for RWE Guidance

- FDA Reauthorization Act (FDARA) including MDUFA IV commitment to use of real-world evidence to support device pre/postmarket decisions
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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.

• Each individual device is ‘who’s asking.’
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).
Evidence for Regulatory Decisions

Traditional Regulatory Pathway

Primary purpose of information collection is for research activity – generate Clinical Evidence

Pre-Clinical Testing \(\rightarrow\) (IDE) \(\rightarrow\) Clinical Studies \(\rightarrow\) Pre-Market Application \(\rightarrow\) Post-Market

New Hypotheses Device Innovation
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Pre-Clinical Testing → (IDE) → Clinical Studies → Pre-Market Application → Post-Market

New Hypotheses
Device Innovation

Informed Clinical Decision Making

Real-World Device Use
Physician and Patient Experience

Healthcare Information

- Claims Databases
- Pharmacy Data
- Social Media
- Laboratory Tests
- Patient Experience
- Registries
- Electronic Health Records
- Hospital Visits

Real-World Data/Evidence
Retrospective Analysis

Design → Conduct → Analysis

Pre-Clinical Testing (IDE) → Clinical Studies → Pre-Market Application → Post-Market

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Analysis ← Selection ← Data Generation
Data Quality

‘Fit for Purpose’
Data must be complete, consistent, accurate, and contain all critical data elements needed to evaluate a medical device and its claims.

Relevant & Reliable

Benefit

Risk

Safety
...probable benefits to health from use of the device outweigh any probable risks [21 CFR 860.7(d)(1)]

Effectiveness
...use of the device in the target population will provide clinically significant results [21 CFR 860.7(e)(1)]
Embedded Clinical Study

Pre-Clinical Testing → (IDE) → Clinical Studies → Pre-Market Application → Post-Market

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Patient Protections

- 21 CFR 812  Investigational Device Exemptions
- 21 CFR 50  Protection of Human Subjects (Informed Consent)
- 21 CFR 54  Financial Disclosure of Investigators
- 21 CFR 56  Institutional Review Boards (IRBs)
- 45 CFR 46  "Common Rule"
- Health Insurance Portability and Accountability Act (HIPAA)
- Other federal and local regulations

- RWE Guidance does not address all issues related to patient protection - focus is on the IDE process.
Patient Protections

Traditional Regulatory Pathway – 21 CFR 50, 54, 56, 812 Apply

Pre-Clinical Testing → (IDE) → Clinical Studies → Pre-Market Application → Post-Market

New Hypotheses

Device Innovation

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Healthcare Information

Claims Databases
Pharmacy Data
Social Media
Electronic Health Records
Laboratory Tests
Patient Experience
Registries
Hospital Visits

Real-World Device Use
Physician and Patient Experience

HIPAA Privacy Rule
Research on Information

Pre-Clinical Testing → (IDE) → Clinical Studies → Pre-Market Application → Post-Market

New Hypotheses → Device Innovation

Informed Clinical Decision Making

Healthcare Information:
- Claims Databases
- Pharmacy Data
- Social Media
- Electronic Health Records
- Laboratory Tests
- Patient Experience
- Registries
- Hospital Visits

Access and Use – Research Under Common Rule

Real-World Device Use → Physician and Patient Experience

21 CFR 50, 56
# Example Case Studies

<table>
<thead>
<tr>
<th></th>
<th>Device (Submission)</th>
<th>Data Source</th>
<th>Used</th>
<th>Action</th>
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<tbody>
<tr>
<td>1</td>
<td>Wearable (PMA/S)</td>
<td>Wearable Device &amp; Patient Reports</td>
<td>Modification of claims from adjunctive to non-adjunctive to use diagnostic for treatment decisions</td>
<td>Indication Expansion</td>
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<tr>
<td>2</td>
<td>Computer assisted triage software (De Novo)</td>
<td>Literature</td>
<td>Peer reviewed literature Meta-analysis.</td>
<td>New Indications</td>
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<tr>
<td>3</td>
<td>Sequencing assay (510(k))</td>
<td>Public NGS database</td>
<td>Publicly-maintained database support clinical validity of the test in lieu of clinical trials</td>
<td>Indication Expansion</td>
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<tr>
<td>4</td>
<td>Screening assay (De Novo)</td>
<td>State lab &amp; surveillance databases</td>
<td>Pivotal clinical trial was embedded in routine clinical practice (under an IDE) in lieu of a traditional pivotal trial.</td>
<td>New Indications</td>
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<tr>
<td>5</td>
<td>Implantable Cardioverter-Defibrillator (PAS)</td>
<td>Multiple RWD data sources</td>
<td>Monitor multiple aspects of real-world device safety and performance using data collected in routine care.</td>
<td>Condition of Approval</td>
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LOINC is used throughout electronic healthcare messaging, from ordering to reporting.

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<thead>
<tr>
<th>LOINC</th>
<th>Use</th>
<th>Answer Sets</th>
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<tbody>
<tr>
<td>UDI</td>
<td>who’s asking</td>
<td>UCUM values</td>
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<td>UDI</td>
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<tr>
<td>Production Identifier</td>
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<tr>
<td></td>
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<td></td>
<td>Timing</td>
<td>Point in Time</td>
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<td></td>
<td>System</td>
<td>Cerebral Spinal Fluid</td>
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<tr>
<td></td>
<td>Scale</td>
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<td>Method</td>
<td>Manual Count</td>
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SHIELD: Empowering Tools for Lab Data

Systemic Harmonization and Interoperability Enhancement for Lab Data
Projected Return On Investment (ROI)

GOAL: IVD Manufacturers Intend to Map and Send Codes for:

- Question (e.g., LOINC)
- Answer (e.g., SNOMED-CT)
- Who’s Asking (e.g., UDI)

Transmission (i.e., LIVD) → Clinical Information Sharing System (i.e., HL7 v2/FHIR) → Laboratory Information Systems (LIS)

RWD/RWE through TPLC
- Reliable/robust quality pre/postmarket RWD
- Access to meaningful RWE

Tracking
- Infectious disease outbreak monitoring
- Real-time epidemiology
- Public health reporting
- Signal detection

Savings
- Lab savings
- Reduced RWD costs

Patient Protection
- Adverse event reduction
- Clinical Decision Support (CDS)
- Healthcare research

SHIELD Stakeholders:

FDA, CDC, NIH, ONC, CMS, Industry, Labs, EHR Vendors, Standards Developers, more.

Get involved. Contact: Michael.Waters@fda.hhs.gov

Systemic Harmonization and Interoperability Enhancement for Lab Data
Case Example: Leveraging RWE in a Pre-Market De Novo Application

FDA approved an indication expansion:

**from:** *adjunctive* use followed by an invasive monitoring procedure

**to:** *non-adjunctive* use—where Continuous Glucose Monitor CGM information can be used directly to make diabetes treatment decisions.

**Patient & Healthcare Provider Experience; Wearable Device Data Logs:**

- Panelist clinical experience *w/* 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.
- Data was generated both by the device (through event logs) and by the patients (through a log of their experience).
- Additional safety endpoints around symptomatic (subject reported) or asymptomatic (device derived) hypoglycemia as well as severe hypoglycemic episodes were reported.

FDA granted a De Novo for computer-assisted triage and notification software intended to notify an on-call neurosurgeon specialist of a potential stroke in their patients.

**Traditional Multi-Reader Multi-Case (MRMC) Study:** MRMC study with hundreds of patient cases and 20 to 30 readers in multiple reading sessions (with and without device).

https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf
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**Traditional Multi-Reader Multi-Case (MRMC) Study:** MRMC study with hundreds of patient cases and 20 to 30 readers in multiple reading sessions (with and without device).

**Study with RWE**— Published studies comparing the standard of care with and without computer-assisted triage software was used to supplement stand alone testing.

- Meta-analysis from peer reviewed literature recording the time to notification for an on-call neurosurgeon.
- Stand alone testing to estimate the performance of the subject device to a test data set with known ground truth for sensitivity and specificity analysis.

[https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf)
Case Example: Leveraging a RWD Database to Enable Pre-Market Claims

FDA cleared two 510(k)s for sequencing assays for variant/variant combinations associated with cystic fibrosis using a public next-generation sequencing (NGS) database.

**Traditional Studies:** Full clinical trials/summary of information available in peer-reviewed literature to provide evidence of the test’s clinical validity.

https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf
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**Study Using Public Database** – An established publicly-maintained database hosted by the academic institution was used to support clinical validity of the test in lieu of clinical trials.

- Database used as a source of valid scientific evidence to establish which variants/variant combinations were causal for the target disease.
- Additional relevant patient information, e.g. sweat chloride, lung function, pancreatic status, and *Pseudomonas* infection rate, associated with each variant/variant combination were included in the evaluation.

https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf
Case Example: Embedded Pivotal Trial in a RWD Source for a Pre-Market De Novo Application

FDA granted a De Novo for a newborn screening assay for enzymes associated with lysosomal storage disorder from dried blood spots.

**Traditional Pivotal Trial**: Full traditional pivotal trial to capture each of the endpoints that were captured in the embedded pivotal trial.

https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150035.pdf; Advisory panel meeting, 8/10/16
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**Traditional Pivotal Trial**: Full traditional pivotal trial to capture each of the endpoints that were captured in the embedded pivotal trial.

**Collection from RWD source** – In lieu of a traditional pivotal trial, a pivotal clinical trial was embedded in routine clinical practice.

- Pivotal trial evaluated performance on all samples submitted to a state lab for routine screening in lieu of banked bio-specimens artificially enriched with known positives.
- Used a department of health surveillance program to check for false negatives reported to the state’s contracted metabolic centers.
- This study was conducted under an Investigational Device Exemption (IDE).

[https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150035.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150035.pdf); Advisory panel meeting, 8/10/16