Real-World Evidence (RWE): Context for Supporting Regulatory Decisions

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Office of In Vitro Diagnostics and Radiological Health (OIR)
Center for Devices and Radiologic Health (CDRH)
Food and Drug Administration (FDA)
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)
- 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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Turning Data into Evidence

Real-World Data (RWD)
“Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”

Real-World Evidence (RWE)
“Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD”

Guidance Addresses issues related processes of:
• Generation and collection of RWD
• Analysis of RWD
• When results might be considered valid scientific evidence
Traditional and Real-World Evidence

- Pre-Clinical Testing
- Pre-Market Application
- Post-Market Application
- Analysis
- Selection
- Data Generation

- New Hypotheses
- Device Innovation
- Informed Clinical Decision Making

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

- Real-World Device Use
- Physician and Patient Experience

Real-World Data/Evidence
RWE must be understood and reliable to be useful.
Valid Scientific Evidence

• 21CFR 860.7(c)(1)
  – Although the manufacturer *may submit any form of evidence* to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon *only valid scientific evidence* to determine whether there is reasonable assurance that the device is safe and effective.
• 21 CFR 860.7(c)(2)

Valid scientific evidence is evidence from
– Well-controlled investigations,
– Partially controlled studies,
– Studies and objective trials without matched controls,
– Well-documented case histories conducted by qualified experts,
– Reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.
What is **Not** Acceptable?

- 21 CFR 860.7(c)(2) continued

  ...Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are **not regarded as valid scientific evidence to show safety or effectiveness**. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.
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

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

Risk

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

Informed Clinical
Decision Making

Healthcare Information

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

Claims Databases → Pharmacy Data → Social Media → Electronic Health Records → Hospital Visits

Laboratory Tests → Patient Experience → Registries

Healthcare Information

Real-World Device Use
Physician and Patient Experience

Access and Use – Research Under Common Rule

21 CFR 50, 56
# RWE Example Case Studies

<table>
<thead>
<tr>
<th>#</th>
<th>Device (Submission)</th>
<th>Data Source</th>
<th>Used</th>
<th>Action</th>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>
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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**Traditional Studies:** Full clinical trials/summary of information available in peer-reviewed literature to provide evidence of the test’s clinical validity.

**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
Need RWE help for medical devices?

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There are Public-Private Partnerships (PPP) in FDA to enable access to high-quality RWE.

GET INVOLVED – LEARN MORE

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THANK YOU!