Wendy Rubinstein, MD, PhD

FDA/CDRH/Office of In Vitro Diagnostics and Radiological Health

REAL WORLD DATA FOR IN VITRO DIAGNOSTICS

CLIAC MEETING

NOVEMBER 4, 2021

CLIAC meeting
November 4, 2021
Wendy Rubinstein

Disclosure Statement

I have no financial relationships to disclose and I will not discuss off- label or investigational use.

Disclaimer Statement

The views expressed during this presentation are those of the presenter and do not necessarily reflect finalized policy or position of the US FDA

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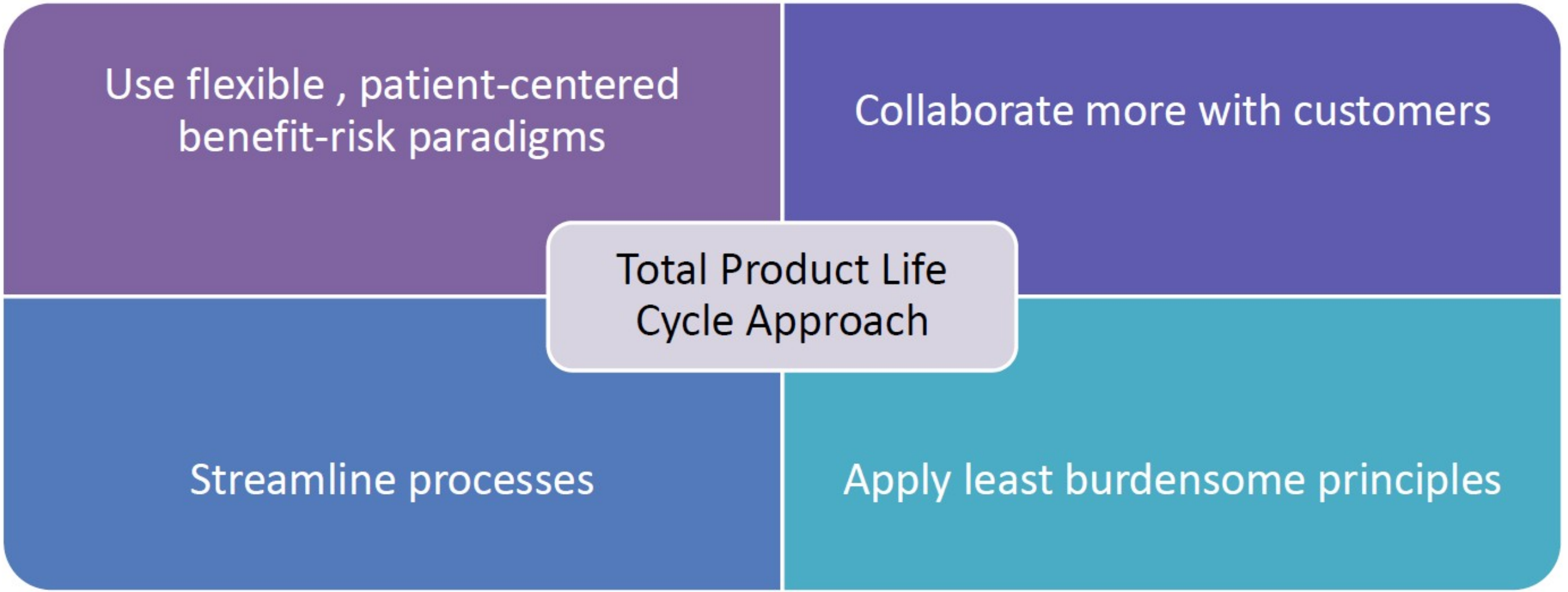
Outline

- CDRH Strategic Priorities
- Definitions and Background
- Regulatory context
- Examples of RWE use in Regulatory Decisions
  - General and IVD-specific
- Using RWE to convert Emergency Use Authorization to 510(k) (MDIC Open Hand)
- Conclusion and Questions

Take home points

- Real-world data represents device experiences outside the traditional study setting and provides valuable insights about device performance throughout the product's life cycle.
- Real-world evidence (RWE) has been leveraged in regulatory decisions spanning the total product life cycle.
- Relevance, reliability, and the role of RWE in addressing data requirements are important review considerations.
- RWE can be a stand-alone source of evidence for decision making, multiple sources can be combined, or it can be used in conjunction with traditional clinical trial data.
- There are helpful resources, including experts in OCEA, available to evaluate RWE.

CDRH Strategic Priorities:
Reduce Time and Cost of Clinical Evidence Generation

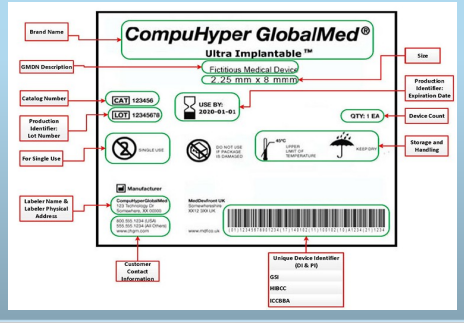


Definitions and Background

Real-World Data (RWD) Sources

Diagnostic Laboratory and Imaging

Device/Patient Registries



Device-Generated Data

Patient-Generated Data

Electronic Health Records

Medical Billing Claims

How does CDRH define Real-World Data and Real-World 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

Why Use RWE and RWD in Regulatory Decisions?

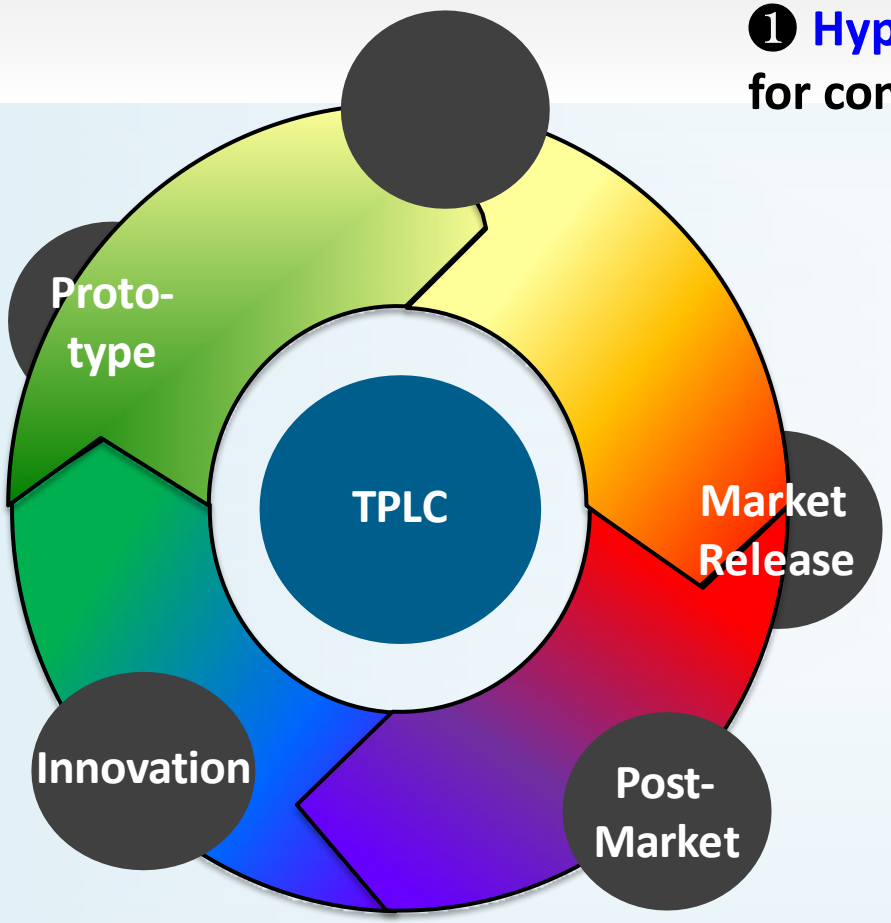
- **Traditional clinical trials**
  - Evaluate device performance in controlled setting
- **Benefits** include:
  - Control over the study design and protocol
  - Control for confounding
- **Limitations** include:
  - Usually expensive and time-consuming
  - May be difficult to collect rare outcomes
  - How generalizable are results?

Why Use RWE and RWD in Regulatory Decisions?

Potential benefits of real-world data sources include:

- Understand device performance in real-world environment to inform benefit-risk
- Collect outcomes not always feasible in traditional trials
- Opportunities to partner w/patients in new ways
- Reduced time/cost to answer important questions
- Inform future device modifications and new technology development
- Better align evidence generation with innovation cycles

Potential Uses of RWE for Total Product Life Cycle Device Evaluation



❶ Hypothesis generation (e.g., treatment effect estimation for comparative studies)

❷ Inform prospective trial design

❸ RWE as a control arm for a clinical trial

❹ Real-world data source as a platform to support a clinical trial (data collection / randomization)

❺ Data collection framework for postmarket evidence generation (e.g., post-approval studies)

❻ Public health surveillance

❼ Generate evidence to support indication expansions and future innovation

Regulatory Context for RWD/RWE

- MDUFA IV Commitment and FDA Reauthorization Act for RWE framework and pilot projects – Starting 2016
- National Evaluation System for health Technology (NEST) as one of CDRH 2016-2017 Strategic Priorities – July 2017
- Guidance issued to clarify how RWE may be used to support regulatory decisions – August 2017
- Publication of RWE examples on FDA.gov – March 2021

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.

What is Acceptable?

- 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.

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)]*

IVD Real World Evidence

Framework Released August 24, 2020

https://mdic.org/resource/ivd-rwe-framework/

Use of RWE for Regulatory Decisions: Illustrative Examples

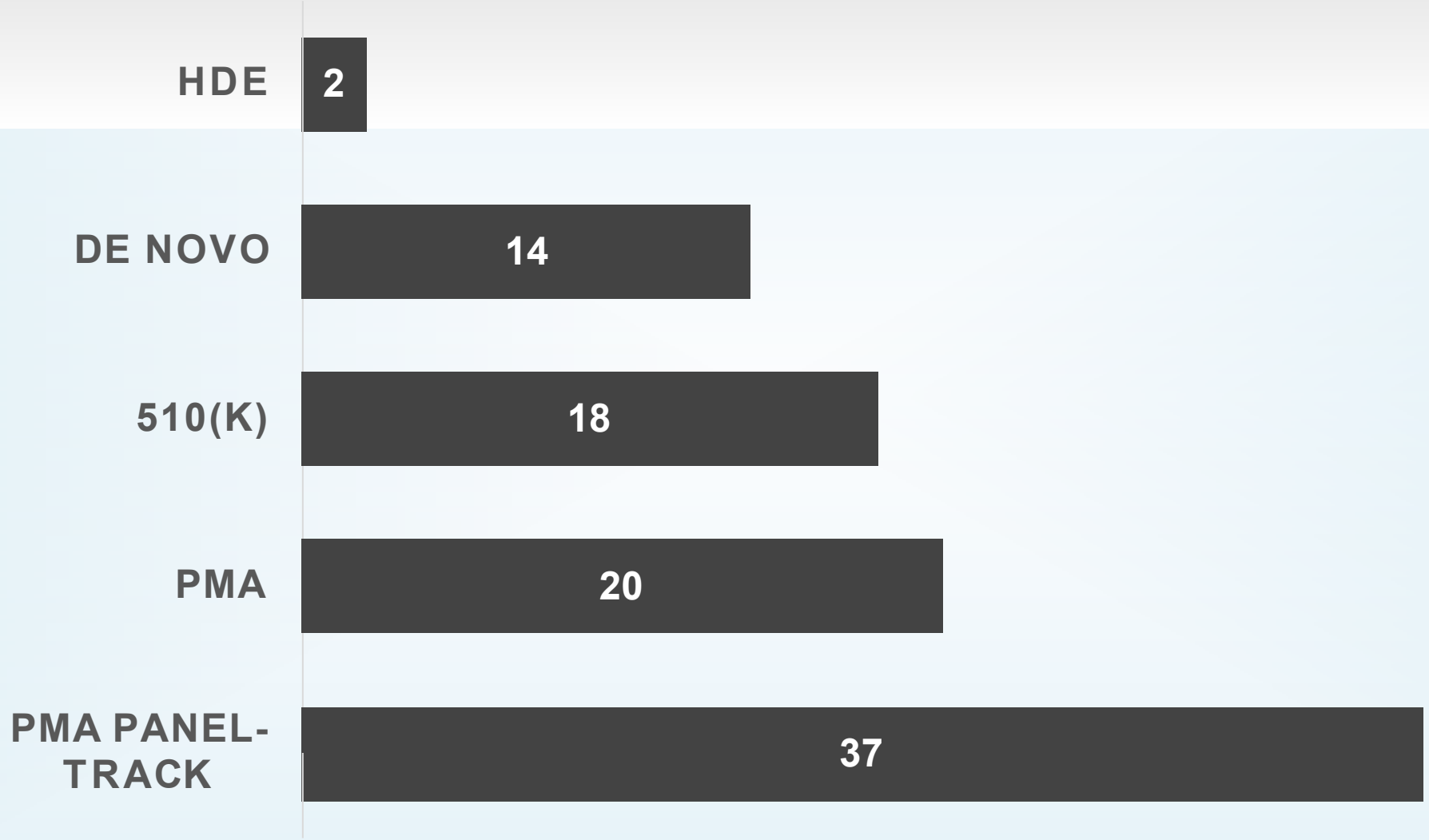
Use of RWE in Regulatory Decision Making

- RWE has been used for regulatory purposes for years, consistent with the definition of valid scientific evidence for medical devices.

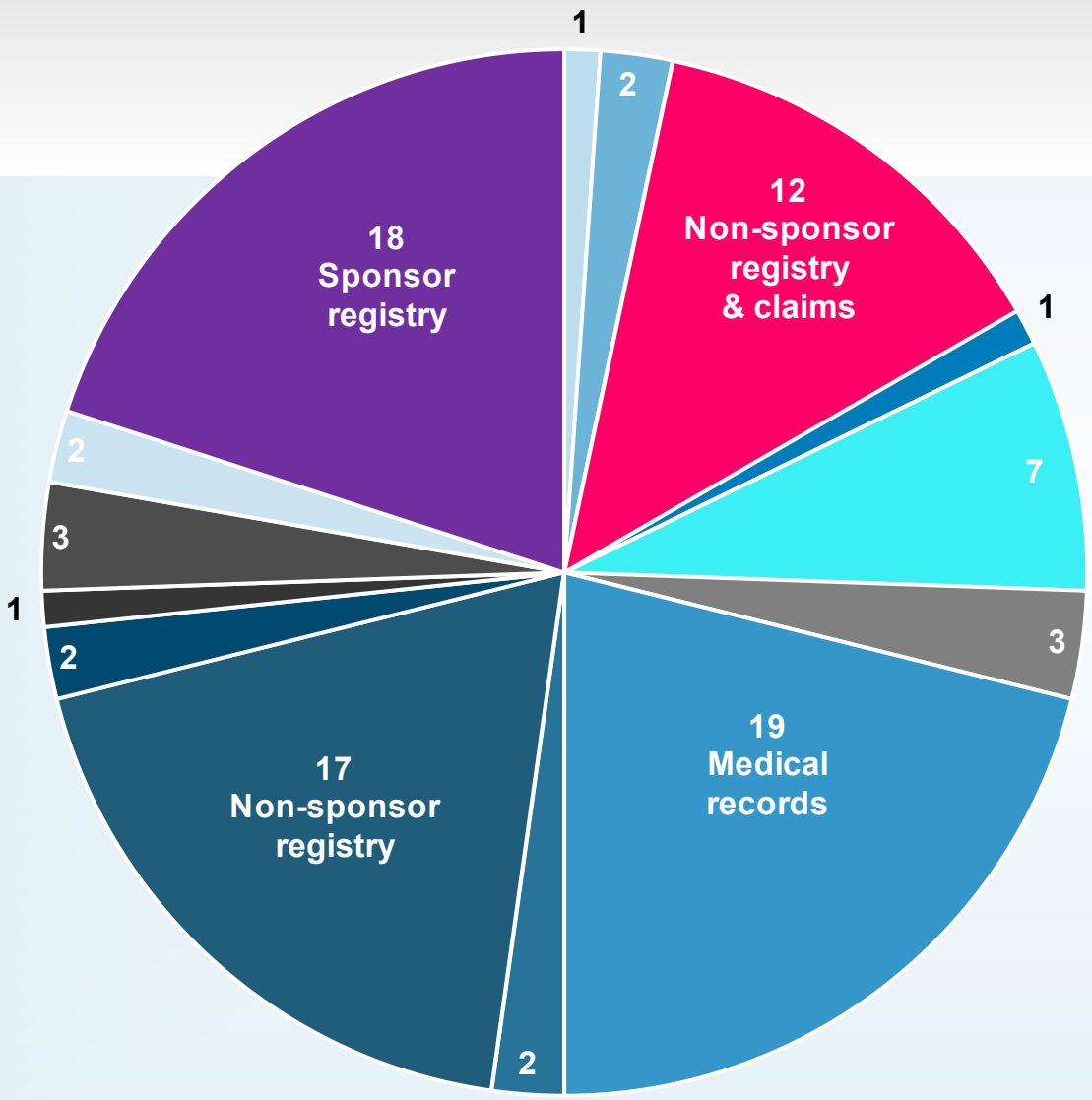
- On March 16, 2021, CDRH published examples of RWE usage for regulatory purposes from FY 2012 to FY 2019.

https://www.fda.gov/media/146258/download

RWE Examples by Submission Types



RWE Examples by Data Sources



- Administrative claims data
- Annotated biospecimens
- Both non-sponsor registry & administrative claims data
- Curated database
- Device-generated data
- Literature
- Medical records (EHR, EMR, or chart review)
- Next-generation sequencing
- Non-sponsor registry
- OUS commercial use
- OUS compassionate use
- OUS postmarket surveillance
- Patient-generated data
- Sponsor registry

Use of RWE in regulatory decision-making is not all or none!

A RWD source does not always have to stand on its own.

RWD sources can be combined with:

- Other RWD sources
- Other external data such as historical trial data
- A traditional prospective clinical trial
- Multiple sources of RWE can be combined, or used to supplement traditional clinical data

Key Characteristics of RWD

Relevance

- Device Use
- Outcomes of Interest
- Study Population
- Relevant Variables
- Follow-up Information

Reliability

- Data Accrual
- Data Assurance/Quality Control

Common RWE Considerations

Relevance	Reliability
The data captured are generalizable to a wider, relevant target population	Bias and missing data are minimized via statistical methods for study design and analysis
The sample size is sufficient to power a study, adjusting for variability and confounders	There is adequate information for review, regarding data collection/extraction procedures, analytical methods, and linkage technology
	Hypothesis testing, success criteria, analysis plan, study protocol, data elements, and data dictionary are appropriate for the specified regulatory question

RWE in In Vitro Diagnostics Submissions

https://www.fda.gov/media/146258/download

Appendix Section VI. Examples of Real-World Evidence Use for In Vitro Diagnostics

Guide to Examples of Real-World Evidence Use for In Vitro Diagnostics

	File	Sponsor	Device	Real-World Data (RWD) Source(s)	RWE Use	Key Tags
83	K132750	Illumina, Inc.	Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay	CFTR2 Database	**Premarket:** Information from the CFTR2 Database, a publicly-maintained Next Generation Sequencing database, was used as the sole source of evidence supporting this 510(k) for a cystic fibrosis indication for the subject IVD.	Next-generation sequencing; RWE as a primary source of clinical evidence;
84	K124006	Illumina, Inc.	Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay	CFTR2 Database	**Premarket:** Clinical evidence from the CFTR2 Database, a publicly-maintained Next Generation Sequencing database, was used as the sole source of evidence supporting this 510(k) for a cystic fibrosis variant assay.	Next-generation sequencing; RWE as a primary source of clinical evidence;
85	DEN150035	Baebies, Inc.	SEEKER System	Missouri State Public Health Laboratory and Missouri Department of Health and Senior Services (MDHSS) Surveillance Program	**Premarket:** This de novo classification request was solely supported by a pivotal trial embedded in a state-run routine screening program testing newborn dried blood samples and actively surveilling for false negatives.	Pediatric RWE; RWE as a primary source of clinical evidence;
86	DEN140010	Wallac Oy	EnLite Neonatal TREC Kit	Danish Newborn Screening Biobank Danish medical records	**Premarket:** This de novo classification request was primarily supported by a pivotal trial that analyzed and linked samples from an international biobank to data from medical records systems.	Medical records (EHR, EMR or chart review); Pediatric RWE; RWE as a primary source of clinical evidence;

https://www.fda.gov/media/146258/download
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87	DEN160026	23andMe	23andMe Personal Genome Service (PGS)	Real-world literature	**Premarket:** To support this de novo classification request, peer-reviewed real-world literature was submitted for each of the 10 conditions included in the Genetic Health Risk tests.	RWE as a primary source of clinical evidence;
88	DEN170058	Memorial Sloan-Kettering Cancer Center	MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)	Retrospective review of medical records from one (1) US site	**Premarket:** This is a next generation sequencing based tumor profiling test. RWE extracted from a retrospective review of medical records was used to estimate somatic mutation prevalence, to validate a cut-off, and to support evaluation of a claim for this De Novo classification request.	Medical records (EHR, EMR or chart review); Next-generation sequencing; RWE as a primary source of clinical evidence;
89	P140020	Myriad Genetic Laboratories	BRACAnalysis CDx	Sponsor database	**Postmarket:** As a condition-of-approval, the sponsor is required to collect data on all IVD results during commercial use.	
90	P160052	QIAGEN, Inc.	PartoSure Test	Observational clinical study with follow-up data collected from medical records	**Premarket:** To support this PMA, the primary clinical evidence submitted was an observational study of pregnant patients tested with the subject device to detect preterm delivery, with follow-up data on pregnancy and delivery outcomes collected from the patients' medical records. **Postmarket:** As a condition-of-approval, the sponsor agreed to conduct a confirmatory study to collect additional data from medical records of pregnant women presenting with signs and symptoms of preterm labor, with the sponsor following up with study participants up to 39 weeks of gestation to collect outcome data.	Medical records (EHR, EMR or chart review); RWE as a primary source of clinical evidence; Total-Product Lifecycle Example;

https://www.fda.gov/media/146258/download
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Detecting Genetic Changes Associated with Cystic Fibrosis

- The November 19, 2013 marketing authorization of the Illumina MiSeqDx cystic fibrosis (CF) products used RWE to support clinical validation. The device is used to detect DNA changes in the *CFTR* gene, which can result in CF.

- Data about which DNA changes are associated with symptoms of CF were obtained from the CFTR2 database. This multi-site, multinational database included genetic information collected in routine clinical practice from patients diagnosed with CF. Recent efforts focused on ascertaining which mutations were disease liabilities through the Clinical and Functional Translation in the CFTR project.

https://mdic.org/resource/ivd-rwe-framework/
https://www.fda.gov/media/146258/download

Classification of a Newborn Screening IVD Using Clinical Evidence from a Pivotal Trial Leveraging RWD Collection in a State Public Health Laboratory

- Key elements or endpoints from RWE source included total presumed affected, true positives, presumptive false positive and false negative rates, and other data

https://mdic.org/resource/ivd-rwe-framework/
https://www.fda.gov/media/146258/download

Classification of an IVD Using Clinical Evidence from a Pivotal Trial Leveraging RWD Collection from an International Biobank and Medical Records

- Invalid test rate, presumptive positive rate, normal rate

https://mdic.org/resource/ivd-rwe-framework/
https://www.fda.gov/media/146258/download

Memorial Sloan-Kettering Cancer Center MSK-IMPACT IVD Regulatory Assessment Using RWE

- Sponsor-submitted RWE played a role in the November 15, 2015 marketing authorization of the MSK-IMPACT, a NGS based tumor profiling test through the De Novo classification process. This single-site assay is an IVD that uses targeted NGS of tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi-gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability. MSK- IMPACT used a clinical evidence curation resource (OncoKB) to facilitate the clinical interpretation of detected mutations.
- As part of this marketing authorization, the FDA published a groundbreaking pathway, in the form of an FDA Fact Sheet: CDRH'S Approach to Tumor Profiling Next Generation Sequencing Tests, for use of accepted clinical evidence.

https://mdic.org/resource/ivd-rwe-framework/
https://www.fda.gov/media/146258/download

FDA recognizes Memorial Sloan-Kettering database of molecular tumor marker information

On October 7, 2021, the Food and Drug Administration granted recognition to a partial listing of the Memorial Sloan Kettering Cancer Center's Oncology Knowledge Base (OncoKB) as the first tumor mutation database to be included in the Public Human Genetic Variant Databases.

FDA recognized a portion of the OncoKB as a source of valid scientific evidence for Level 2 (clinical significance) and Level 3 (potential clinical significance) biomarkers. Under the FDA's database recognition program, test developers can use these data to support the clinical validity of tumor profiling tests in premarket submissions.

Determining the mutation profile of a tumor using DNA sequencing enables the use of targeted therapies and investigational treatment options.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-recognizes-memorial-sloan-kettering-database-molecular-tumor-marker-information

Database Recognition Program

Final Guidance:
Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics
Published April 13, 2018

Scope: publicly accessible databases of genetic variants
Recommendations for administrators of databases to demonstrate that the database can be considered a source of "valid scientific evidence"
Voluntary database recognition pathway (similar to standards recognition)
Evidence from databases could support the clinical validity of NGS- based tests

Using RWE to convert Emergency Use Authorization to 510(k)

The 'Open Hand' process:
Applying principles of the framework in a novel process to pave a pathway for using IVD RWE in regulatory submissions

Goals of Open Hand

- Provide a transparent process to evaluate new technology and methods
- Capture the ‘how’ to share with broader community while staying in precompetitive space and protecting proprietary information
- Create educational modules on application
- Capture learnings in peer-reviewed publication

Process for Open Hand

- Sponsor that has a diagnostic EUA for COVID-19 sends a pre-submission to discuss conversion to full 510(k) or De Novo premarket submission
- MDIC participates in pre-submission meetings to capture learnings
- Educational modules created (blinded and proprietary information removed)
- Shared authorship on peer-reviewed publication on learnings from exercise.

Open Hand Learnings

- What constitutes RWD?
- Fit for purpose
- Relevance and reliability of RWD
- Missingness
- Instrument family
- Data generated with third-party control

Conclusion

OCEA's Expertise in RWE Review

OCEA is here to provide high-quality and consistent support

CDRHClinicalEvidence@fda.hhs.gov

- Policy and program support for clinical evidence and human subject protection.
- Regulatory oversight of clinical investigations.
- Biostatistical and epidemiologic analyses, including development of data infrastructure and expertise on clinical investigations and RWE.
- Outreach and collaboration with hospitals and other external stakeholders.

Available Resources

RWE FDA Guidance

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff (fda.gov)

FDA Voices

Leveraging Real World Evidence in Regulatory Submissions of Medical Devices | FDA

Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions

Framework for FDA's RWE Program (applies to other medical products) https://www.fda.gov/media/120060/download

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Thank you!

Any questions?

Wendy.Rubinstein@fda.hhs.gov