Regulatory Pathways

Devices vs. Drugs
Are there roles for registries?

John Laschinger, MD
CDRH/ODE/DCD/SHDB
johnlaschinger@fda.hhs.gov

Disclosures and Disclaimer

John C. Laschinger, M.D.

I am a full time employee of the FDA. I have no financial conflicts of interest to report.

The views expressed in this presentation are those of the presenter and do not represent the official policies of the FDA.

Intersections

FDA Mission and the Regulatory Uses of Registry/EHR Data

Common Goals:

- **Protect the public health** - Ensure the safety, effectiveness, and quality of medical devices
- **Advance the public health** by speeding and enhancing innovation
- **Provide the public with accurate information** about regulated products throughout the total product life cycle

Common Pathway:

- **Acquisition of Scientific Evidence** needed to make informed decisions

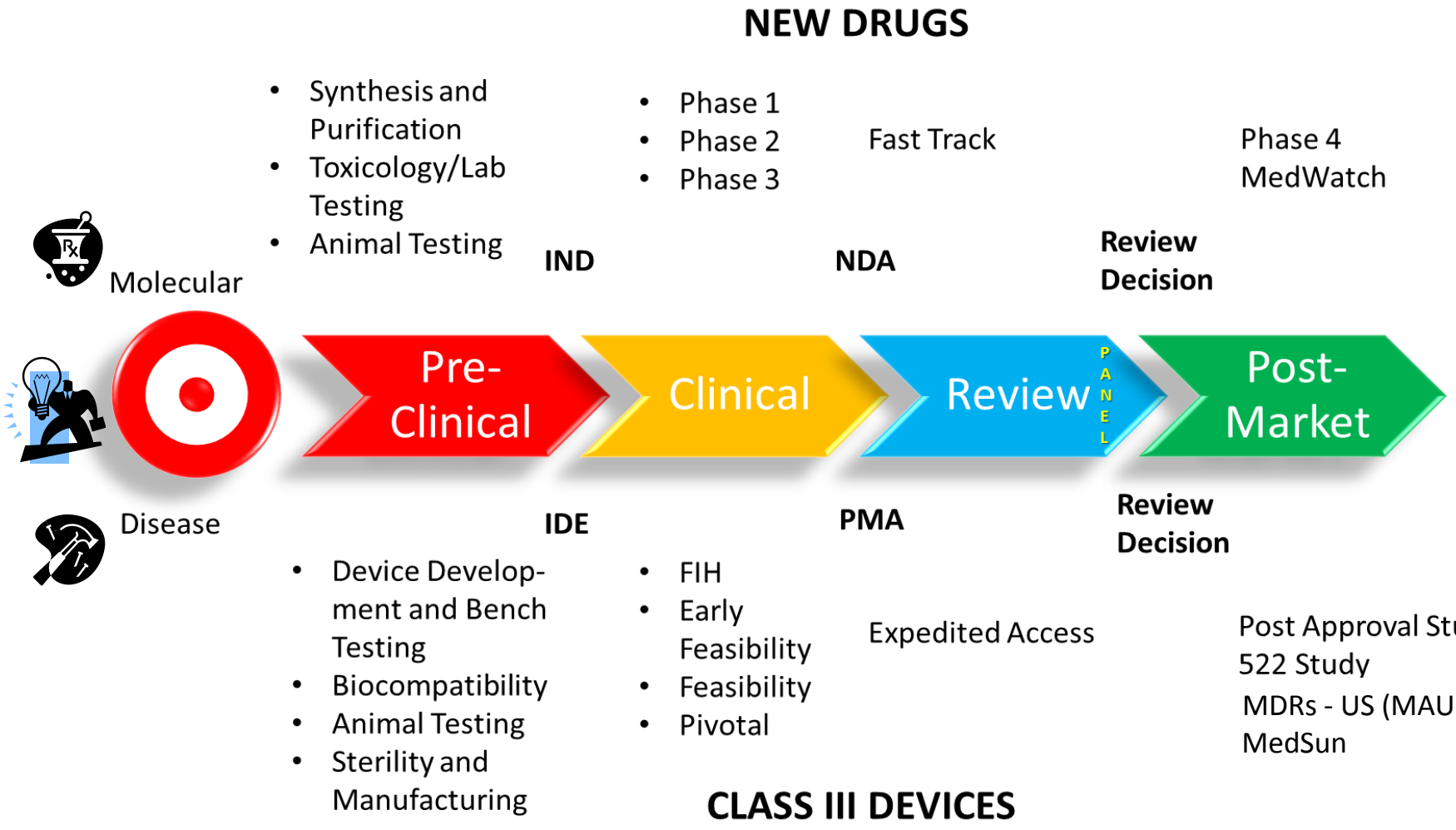
U.S. Drug and Device Development

Major Differences – Drug vs. Device Evaluation

Developmental Feature	Class III Device	New Drug
Rate of technology change	High	Low
Ease of in vitro assessment	High	Low
Pivotal studies required	1	2
Comparator	Varies	Concurrent Control (RCT)
Ability to blind treatments	Difficult	Easy
Study population size	Small/100's	Large/ 1000's
Influence of Physician technique	High	Low
Ability to visualize performance	High	Low
Total Product Lifecycle/Iterations	Months-Years	Years-Decades
Definition of "orphan"	4,000	200,000

U.S. Drug and Device Approval Paradigm

New Drugs and Class III Medical Devices



U.S. Drug and Device Approval Paradigm

Additional Pathways – Rely on Safety and Effectiveness of Existing Product

Devices - Substantial Equivalence to a Predicate Device

- **510(k)** – Pre-Market Notification
  - Similar Indications
  - Similar Technology
  - No new Questions of safety or effectiveness
  - Special Controls
- **DeNovo**
  - Device "types" that have never been marketed in the U.S., but whose safety profile and technology are now reasonably well understood

Device is as safe and effective, and performs at least as safely and effectively as the legally marketed device (Predicate)

Drugs – favorable BA and BE* to the Reference Listed Drug (Orange Book)

- **505(b)2** – Modifications of the RLD that allow partial reliance on existing clinical pharmacology and safety and efficacy data
  - new formulations
  - new molecular entities,
  - changed active ingredients
  - new drug combinations.
- **505(j)** - Abbreviated New Drug Applications
  - Generics

The new product must be as bioavailable and the release profile must be at least as favorable as that of the RLD

*BA=Bioavailability, BE=Bioequivalence

New Drug Approvals: Pre-Market Registry Use

Can Registry Data be Considered Evidence?

New Drugs

21 CFR 314.126

Reports of **adequate and well-controlled investigations** provide the primary basis for determining whether there is **"substantial evidence"** to support the claims of **effectiveness** for new drugs….

An adequate and well-controlled study consists of the following:

- The study uses a design that permits a **valid comparison with a control** to provide a quantitative assessment of drug **effect**
  - Placebo concurrent control
  - Dose-comparison concurrent control
  - Active treatment concurrent control
  - No treatment Concurrent control
- Historical control designs are usually reserved for special circumstances
- **Uncontrolled studies or partially controlled studies are not acceptable** as the sole basis for the approval of claims of effectiveness.

New Device Approvals: Pre-Market Registry Use

Can Registry Data be Considered Evidence?

New Devices

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, and **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. The **evidence required may vary** according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use."

NDA and PMA Goals

Providing The Evidence Needed to Reach Key Decisions

Common Key Regulatory Decisions for Approval:

- ❑ Is the drug/device **safe and effective in its proposed use(s)**, and do the drug/device **benefits outweigh the risks**
- ❑ What should the label should contain? Is the **proposed labeling (package insert) appropriate** for the drug/device,

} **Requires Pre-Clinical and Clinical Evidence**

- ❑ Are the **methods used in manufacturing** the drug/device and the **controls** used to maintain the drug's/device's quality adequate to preserve the identity, strength, quality, and purity of the drug or the durability, performance, sterility and biocompatibility of the device

U.S. Drug and Device Approval Paradigm

Data vs. Evidence – Implications for Regulatory Approvals

- **Data**

  Raw Measurement

  Facts and statistics collected together for reference or analysis
  Meaningless by themselves, yet foundational
  - Accurate, reliable and timely
  - Auditing, monitoring , adjudication, core labs

- **Information**

  Addition of critical context

  Gives meaning to data - What is being measured and why
  Allows knowledge communicated or received concerning a set of facts

- **Evidence**

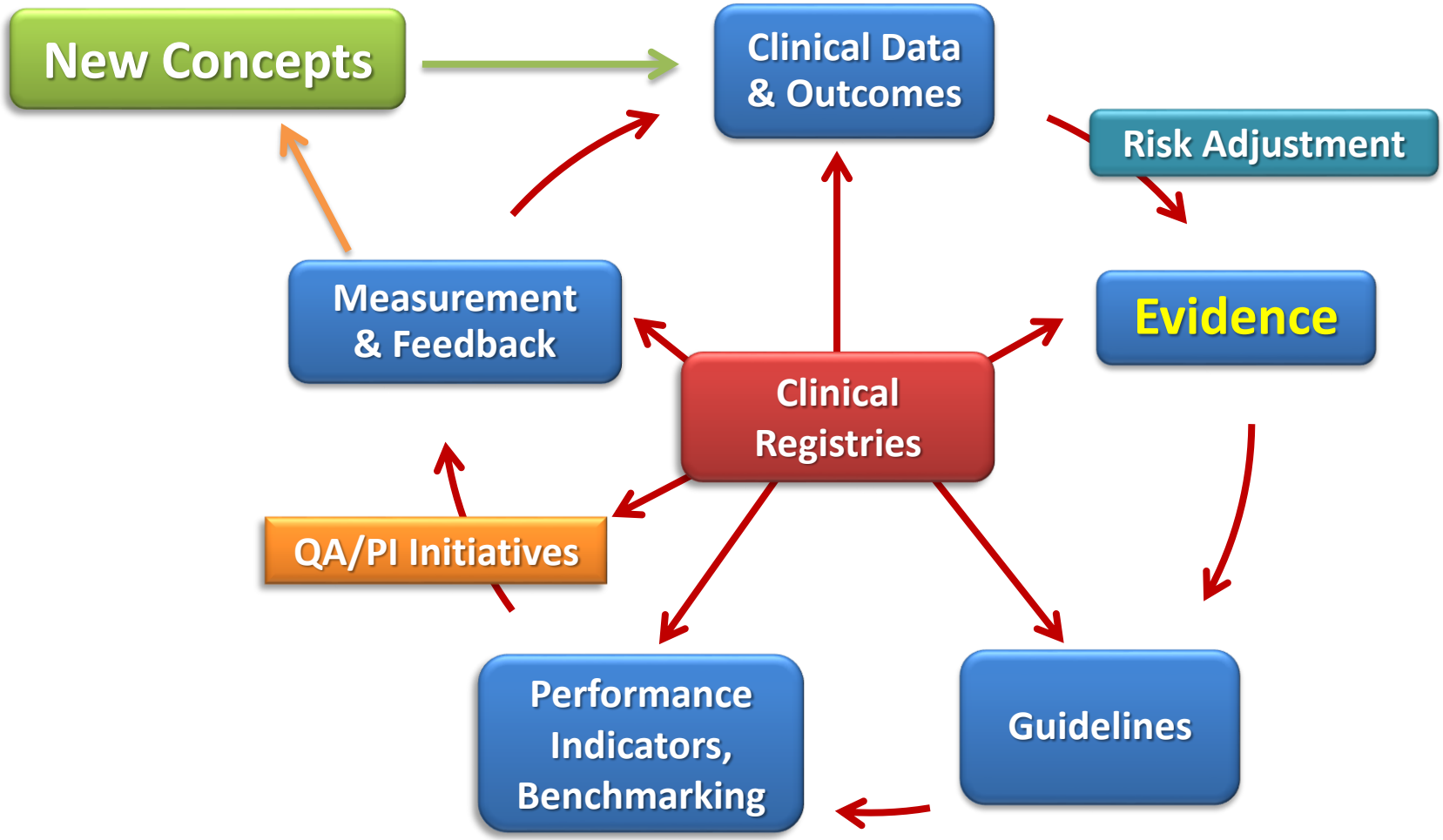
  Combination and analysis of information and facts

  Makes data useful - Indicates whether a belief or proposition is true or valid
  Answers clinical or scientific questions - guides decision-making
  Evidence Requirements for Regulatory Decisions:
  - Different for Drugs and Devices
  - Implications for use of registry data

http://blogs.fda.gov/fdavoice/index.php/2015/12/what-we-mean-when-we-talk-about-data

Clinical Registries

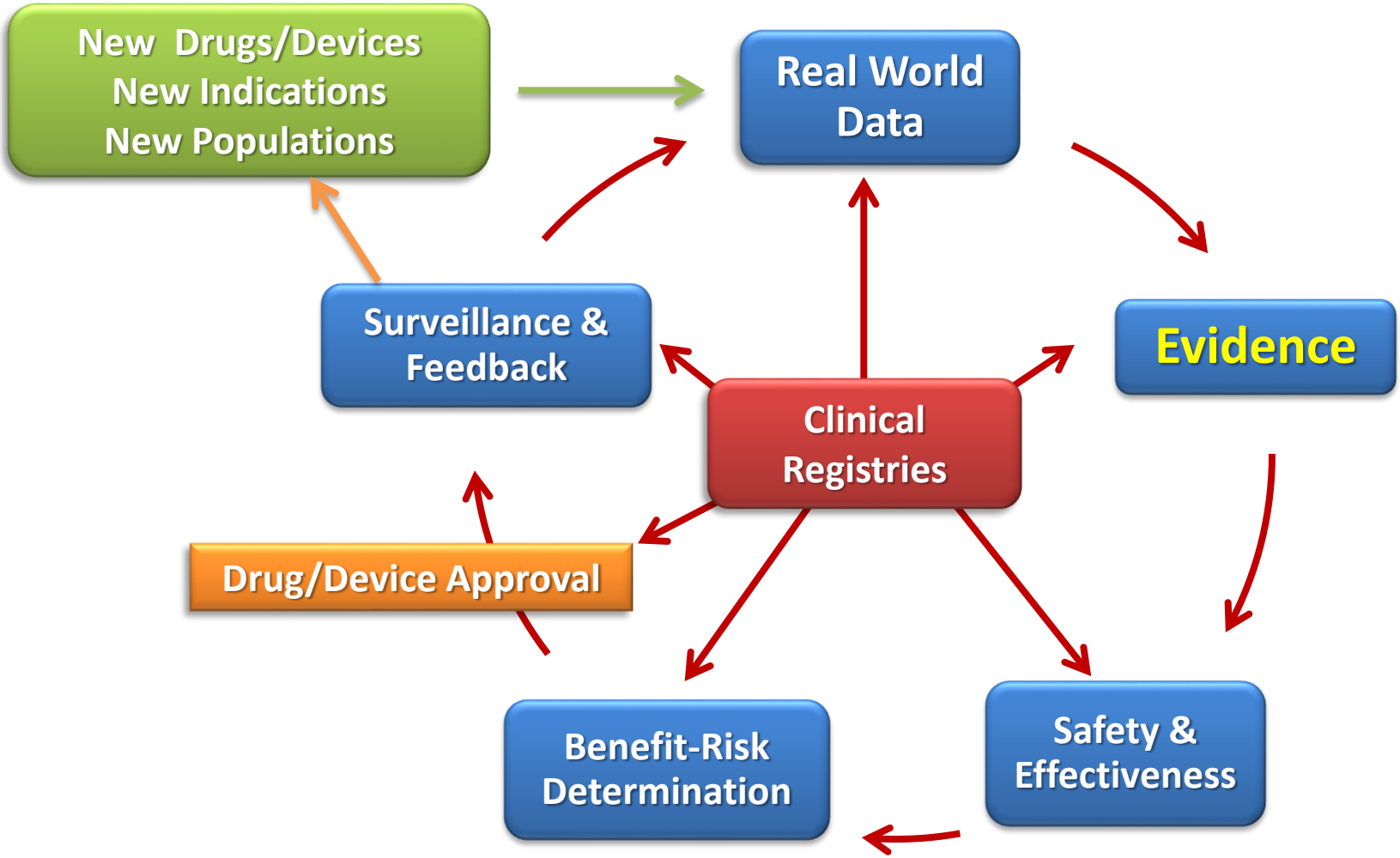
Proven Role in the Cycle of Quality



Adapted from: Califf et al. JACC 2002;40:1895–901
Bhatt et al. JACC 2015;68:2230-2245

Clinical Registries

Is There a Role in New Drug/Device Development



Judging the Quality of Registry Data

Retrospective Registry Data - Quality and Fitness of Purpose

- ✓ Accrual
- ✓ Accuracy
- ✓ Assurance

Reliable

- ❑ Purpose (why)
- ❑ People
- ❑ Processes
- ❑ Data Checks
- ❑ Monitoring/auditing
- ❑ Patient Protections
- ❑ Common Definitional and Temporal Framework

Is it Good Data?

- ✓ Aggregation
- ✓ Acceptability

Robust (medical community determination)

- ❑ Validated Predictive Risk Modeling
- ❑ Benchmarking and Quality Assurance
- ❑ Performance improvement
- ❑ High Penetrance (sustainable)
- ❑ Post-market surveillance
- ❑ Informs Practice Guidelines
- ❑ Generates Peer reviewed publications

Does the data generate Useful Information?

If Yes….

- ✓ Adequacy
- ✓ Analysis

Relevant

- ❑ Applies to question at hand
- ❑ Amenable to sound analysis
- ❑ Interpretable using Informed Clinical Judgment

Is Relevant Evidence produced?

Judging the Quality of Registry Data

Acquiring Prospective Data Within a Registry

Prospective interventional clinical trials provide:

- Control of bias, confounding and variability
- A basis for causal inference (randomization)
- Generalizability?

Key Questions Drugs and Devices:

- Can a prospective Randomized Control Trial be embedded within an existing Registry
  - Is evidence from real-world data appropriate to assess safety and infer causal inference for effectiveness
  - Can Modular data sets, core-labs, monitoring and adjudication be added
- Data governance, access, sequestration, etc.

Data Quality and Fitness of Purpose

New Registry Development

Nuts and Bolts – Begin with the End in Mind

- Define and answer relevant questions
  - Baseline dataset and Standard modular add-ons
- Develop uniform definitions and CRFs
  - Common definitional and temporal framework
  - Linkages to other datasets
- Establish quality by design
- Ensure data quality
  - Ability of registry to withstand audit
- Address relevant informed consent issues
  - QA/PI vs. Research
- Develop incentives and utility for routine use
  - Risk prediction and adjustment
  - Sustainability

Research Uses of Registry Data

Additional Monitoring Requirements

Critical Roles of the Office of Scientific Investigations and the Office of Compliance

Registry and Clinical Site Monitoring:

- **People**
  - Registry Infrastructure and Support
  - Site support and training
    - Who is collecting/abstracting data - appropriate knowledge base
    - Personnel trained in data definitions and their consistent application
- **Processes**
  - Auditing/monitoring processes
    - Data integrity and accuracy
      - all patients are being entered
      - all essential data is being entered accurately – source verification
    - Protocol Integrity
      - Minimize missing data, protocol deviations and lost follow-up
- **Patient Protections**
  - Appropriate and necessary patient protections in place (Informed Consent)

Who is Responsible?

Thank You!

John Laschinger, MD

Medical Officer, SHDB

301.796.1210

john.laschinger@fda.hhs.gov