Regulatory Pathways

Devices vs. Drugs
Are there roles for registries?

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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

<table>
<thead>
<tr>
<th>Developmental Feature</th>
<th>Class III Device</th>
<th>New Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of technology change</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ease of in vitro assessment</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Pivotal studies required</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Comparator</td>
<td>Varies</td>
<td>Concurrent Control (RCT)</td>
</tr>
<tr>
<td>Ability to blind treatments</td>
<td>Difficult</td>
<td>Easy</td>
</tr>
<tr>
<td>Study population size</td>
<td>Small/100’s</td>
<td>Large/ 1000’s</td>
</tr>
<tr>
<td>Influence of Physician technique</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ability to visualize performance</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Total Product Lifecycle/Iterations</td>
<td>Months-Years</td>
<td>Years-Decades</td>
</tr>
<tr>
<td>Definition of “orphan”</td>
<td>4,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>
U.S. Drug and Device Approval Paradigm

New Drugs and Class III Medical Devices

NEW DRUGS

• Synthesis and Purification
• Toxicology/Lab Testing
• Animal Testing

Phase 1
• Phase 2
• Phase 3

Fast Track

Phase 4

MedWatch

Review Decision

Post-Approval Study
522 Study
MDRs - US (MAUDE)
MedSun

Pre-Clinical

Molecular

Disease

IND

IND

NDA

IDE

Pre-Clinical

Clinical

Review

PMA

Review Decision

_CLASS III DEVICES

• Device Development and Bench Testing
• Biocompatibility
• Animal Testing
• Sterility and Manufacturing

• FIH
• Early Feasibility
• Feasibility
• Pivotal

Expedited Access
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

**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

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

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
  - Active treatment concurrent control
  - Dose-comparison 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,

- 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

Requires Pre-Clinical and Clinical Evidence
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

Clinical Registries
Proven Role in the Cycle of Quality

New Concepts
Clinical Data & Outcomes
Risk Adjustment
Evidence
Clinical Registries
Measurement & Feedback
QA/PI Initiatives
Performance Indicators, Benchmarking
Guidelines

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

- New Drugs/Devices
  - New Indications
  - New Populations

- Real World Data

- Surveillance & Feedback

- Evidence

- Drug/Device Approval

- Clinical Registries

- Benefit-Risk Determination

- Safety & Effectiveness
Judging the Quality of Registry Data

Retrospective Registry Data - Quality and Fitness of Purpose

- ☑ Accrual
- ☑ Accuracy
- ☑ Assurance

Reliable
- Purpose (why)
- People
- Processes
- Common Definitional and Temporal Framework

Is it Good Data?

Robust (medical community determination)
- Validated Predictive Risk Modeling
- Benchmarking and Quality Assurance
- Performance improvement
- High Penetration (sustainable)
- Post-market surveillance
- Informs Practice Guidelines
- Generates Peer reviewed publications

Does the data generate Useful Information?

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

Is Relevant Evidence produced?

If Yes....

- ☑ Aggregation
- ☑ Acceptability

- ☑ Adequacy
- ☑ Analysis
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!

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