Regulatory essentials of medical device and diagnostics development for clinical translation

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Outline

• Principles of medical device/diagnostics innovation
• The role of the FDA
• Principles of device regulation
• Current evolution
• Focus on differences for diagnostic products
The cycle of translational medical innovation

Discover mechanisms, biomarkers and targets

Recognize clinical need

Bedside-to-Bench

Development of new drugs, devices, biologics, diagnostics and procedures

Bench-to-Bedside

Translate to patients


Clinical need is the key driver for medical device development

Is the potential innovation different/better than available alternatives for problem (“standard of care”)?

Provable better outcomes
Identifies/treats specific patient groups (i.e., eliminates adverse effects, treats non-responders or high risk patients)

Disruptive treatment (minimally-invasive, new patients, new venue)

Permits early identification of disease
Lower cost

...
Clinical need is necessary but not sufficient!

*Is a medical device invention worth developing into a product?*

- What is the unmet need the technology addresses?
- Is it different/better than available alternatives for the problem ("standard of care")?
- Who is the customer?
- What is the value proposition?
- Can safety/efficacy be proven clinically?
- Is there a large, identifiable market and strong business plan?
- Can the product be manufactured/sold profitably?
- Will it be bought/adopted for clinical use?

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**Medical Device Innovation: The Path**

Learning from outcomes... successes and failures

*Image concept inspired by and modified from FDA documents*
Medical Device Development Lifecycle

Problems and Complications Can Arise at Any Stage

Solutions
- Re-develop
- Treat/Remove
- Manage

Technical Path and Business Processes are Integrated

TECHNICAL PATH
- Ideation
- Proof of... Concept, Feasibility, Value
- First-in-Human
- Clinical Trial
- Regulatory Approval
- General Clinical Use
- Standard of Care
Navigating Risk in Medical Device Development

FDA Responsibilities

• protect the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation
• approve medical products before commercialization.
• balance (sometimes competing) priorities:
  – provide *safe and efficacious* medical products supported by valid scientific evidence, with
  – ensure *timely access* to needed therapies and diagnostics.
Clinical/Translational Medical Product Innovation

For assessing human health and disease

Lab/OTC Diagnostics – Biomarker

For treating human disease

Implantable devices

Drugs

Biologics - Cells - Genomics

Medical devices and diagnostics are diverse

Mechanical heart valve

Tissue heart valve

Knee joint prosthesis

CT/MRI machines

Surgical robot

Hemodialysis machine

Laboratory diagnostic test

Pregnancy test (OTC)
Overview of Regulatory Framework - Key Definitions

<table>
<thead>
<tr>
<th>Safety</th>
<th>probable benefits outweigh probable risks</th>
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<tr>
<td>Effectiveness</td>
<td>valid scientific evidence suggests that, in a significant portion of the target population, the use of the device for its intended uses and conditions of use will provide clinically significant results</td>
</tr>
<tr>
<td>Valid Scientific Evidence</td>
<td>well-controlled investigations</td>
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What is a Medical Device?

“If a product is labeled, promoted or used in a manner that meets the following definition:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

– intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

– intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

it will be regulated by the Food and Drug Administration (FDA) as a medical device and is subject to premarketing and postmarketing regulatory controls.”

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance
Clinical/Translational Medical Product Innovation

For assessing human health and disease
- Lab/OTC Diagnostics – Biomarker
- Imaging devices

For treating human disease
- Drugs
- Implantable devices
- Biologics - Cells - Genomics

Regulated as medical devices

KEY US LAWS FOR REGULATING DRUGS AND DEVICES

Regulation of food and drugs
- 1906 Federal Food, Drug, and Cosmetic Act
  - Prohibited interstate commerce for misbranded or adulterated foods and drugs
  - Required that drugs meet standards of strength and purity
- 1912 Sherley Amendment
  - Prohibited labeling of drugs with false claims intended to defraud
- 1938 Federal Food, Drug, and Cosmetic Act
  - First time devices were regulated
  - Required that devices were not adulterated or misbranded
- 1968 Medical Device Amendment
  - Required postmarketing surveillance and adverse event reporting

First substantial regulation of devices
- 1938 Federal Food, Drug, and Cosmetic Act

Postmarket surveillance and reporting
- 1976 Medical Device Amendment
  - Devices classified into 3 categories that defined approval process
- 1990 Safe Medical Devices Act
  - Required postmarketing surveillance for permanently implanted medical devices

Sweet BV et al – J Managed Care Pharm 17:40, 2011
1976 Medical Device Amendments to the 1938 Food, Drug and Cosmetic Act

“... established a risk-based regulatory framework for evaluating medical devices ... to be lawfully marketed ... with risk being assessed as the potential for the device to present harm to the patient, including in circumstances in which the device could malfunction or be used improperly.”


What are “Regulation” and “Approval” of Medical Devices?

• All manufacturers must be registered and all devices must be listed with FDA.

• Before marketing can occur, FDA must review and approve:
  • How the device is manufactured
  • How the device is tested
  • How the device is stored, labeled and distributed
  • How the device is “labeled”

• Labeling specifies how and under what medical circumstances (i.e., indications) a product is to be used.

• FDA does not approve “(bio)materials” per se.

• FDA does not regulate how physicians practice their art.
FDA Device Classification Panels

- FDA has classified and described over 1,700 distinct types of devices
- CDRH has 18 medical specialty "panels" such as Cardiovascular, Orthopedic or Neurological devices, and lab subspecialties.
- Panels make recommendations to the FDA Commissioner for approval/disapproval.
Regulatory classification of medical devices is risk-based

SAFETY and EFFECTIVENESS via VALID SCIENTIFIC EVIDENCE

For medical devices, safety depends on:
• Invasiveness
• Duration
• Risks – frequency, nature and outcomes

Medical devices vary in Invasiveness, Duration, Risks

Class I  LOW RISK
Include tongue depressors, arm slings, and stethoscopes (5%)

Class II  MEDIUM RISK
Include physiologic monitors, x-ray systems, gas analyzers, pumps, and surgical drapes (40%)

Class III  HIGH RISK
include pacemakers, replacement heart valves and total joint replacements (55%)

Source: Point-of-Care Center for Emerging Neuro Technologies (POC-CENT), U. Cincinnati
Pathways of FDA Approval for Medical Devices are based on risk

- **Exempt**
  Very low risk; register only

- **510(k) Clearance**
  New devices that are "substantially equivalent to devices that are already marketed legally for the same use"

- **Premarket approval (PMA)**
  New or high-risk medical devices

Increasing risk

Other Controls and Classifications

- Investigational Device Exemption for Clinical Trials (IDE)
- Design controls
- Risk/failure Mode Analysis analysis
- Manufacturer Inspections
- Postmarket studies
- Medical device reporting
- Tracking

Humanitarian Device Exemption (HDE)

Devices for orphan diseases

*Intended to benefit patients in diagnosis and/or treatment of disease or condition affecting fewer than 4,000 patients per year in the United States.*
Early Feasibility Studies (EFS) of Medical Devices

- Goal to streamline medical device development in US.
- Early first-in-human studies of complex devices are often done outside US.
- Used as first study where therapies are 1) otherwise not available, or 2) have novel safety or effectiveness concerns.
- For devices with limited experience in humans or for indication, i.e., complications may not be anticipated.
- Patients may gain early access to device.
- Patients are protected by careful selection, close monitoring and FDA oversight.
- EFS Require approval by the FDA.

FDA Breakthrough Devices Program

- A voluntary program yielding priority for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions

- Available for products with a greater extent of uncertainty of the benefit-risk profile, which is sufficiently balanced by other factors, such as probable benefits for patients to have earlier access to the device (e.g., a device that treats a life-threatening disease when no alternative treatments are available) and adequate postmarket controls
Post-market surveillance is crucial to identify device failures

Class III devices, including CV, Neurology, Obstetrics/Gynecology, and Orthopedics


Metal-on-Metal Hip Replacement – FDA Approved via 510k Path

Medical Device Reporting

• Since 1984, the FDA Medical Device Reporting (MDR) regulations have required firms who have received complaints of device malfunctions, serious injuries or deaths associated with medical devices to notify FDA of the incident.

• The Safe Medical Devices Act (SMDA) of 1990 provided FDA with two additional postmarketing activities:
  ✓ Postmarket Surveillance for the monitoring of products after their clearance to market
  ✓ Tracking for maintaining traceability of certain devices to the user level

• Initial reporting responsibility lies primarily with the discover of problem, usually a provider.

Ongoing/Future Innovation in Medical Devices

• Miniaturization
• Fabrication using 3D printing (personalized)
• Products for consumer use and/or in low-resource environments
• Minimally-invasive/natural orifice implantation
• Multifunctionality (e.g., diagnosis/therapy, HIT and devices)
• Combination products
• Cell-based therapies and devices
• Intelligent/dynamic
• Nano-technology/MEMS/microfluidics
• Resorbable materials and devices
• Regenerative approaches
• Sophisticated diagnostics
**Implantable Cancer Vaccine**
A small implant that recruits and reprograms a patient's own immune cells "on site" to kill cancer cells

![Image of implantable cancer vaccine](image)

*David Mooney et al*

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**Personalized Medical Devices**

(3D printed bioabsorbable airway splint for tracheo-bronchomalacia in an infant)

![Images of personalized medical devices](images)

**Evolution of Pacemaker Technology**

- **1956**
  - Weight: 12.4g
  - Size: 35cc
- **1991**
  - Weight: 55g
  - Size: 25cc
- **1995**
  - Weight: 14g
  - Size: 6cc
- **2009**
  - Weight: 20g
  - Size: 12.8cc
- **2013**
  - Weight: 2g
  - Size: 1cc

The evolution of pacemaker technology shows significant miniaturization over time, with the latest models being much smaller and lighter than early models.

**Micra(TM) Transcatheter Pacing System (TPS), Medtronic**

**Evolution of Diabetes Management**

- **1956**
  - Method: Insulin injections
- **1991**
  - Method: Insulin pens
- **2009**
  - Method: Continuous glucose monitoring systems
- **2013**
  - Method: Wearable insulin pumps

The evolution of diabetes management has seen a transition from manual insulin injection to more automated systems, improving the quality of life for diabetics.

**Medtronic MiniMed 670G system**

Continuous glucose monitoring systems and insulin pumps have become more prevalent, offering better control over blood glucose levels.
Drug Development Process

Drug Discovery  Pre-Clinical  Clinical Trials  FDA Approval

10,000 Compounds

Phases of Clinical Trials

1 2 3 4 Cpd

First in Human (FIH)  Proof of Concept (POC)  Definitive, Registration Pathway Trial  Translation to Clinical Practice and Populations

Modified from Elliott Antman, MD

Drugs vs Medical Devices – Other Key Differences...

Drugs have:
• Limited effect duration (half-life)
• Reversible adverse effects
• Ability to make therapeutic change

Device design
Materials
Manufacture

Post-op care
Adjunctive therapy
Patient factors

Implant
Surgeon - Interventionalist
Patient

Biomaterials-Tissue Interactions
Evolving/Emerging Diagnostic Technologies

- Germline genetics
- Cancer genetics
- Infectious disease genetics
- Epigenetics
- Molecular imaging
- Quantitative metabolomics (mass spectroscopy
- Single cell gene expression analysis
- Microwell arrays for single-molecule detection
- Circulating cell-free DNA/RNA, etc. (liquid biopsy)
- Circulating tumor cells
- Immunoassays
- Histocompatibility
- …

Considerations for diagnostics

When reviewing tests, the FDA assesses:
- Whether a test can accurately and reliably measure what it claims to measure (analytical validity);
- Whether the measurement is predictive of a certain state of health (clinical validity); and
- What a company says about their test and how well it works (claims).
Some direct-to-consumer tests (DTCs) are reviewed by the FDA while others are not. In general, direct-to-consumer tests for non-medical, general wellness, or low risk medical purposes are not reviewed by the FDA before they are offered. Direct-to-consumer tests for moderate to high risk medical purposes, which may have a higher impact on medical care, are generally reviewed by the FDA to determine the validity of test claims.

Regulatory Pathways of Direct-to-Consumer Tests are stratified to risk

- **Carrier Screening Tests** ([21 CFR 866.5940](https://www.hhs.gov)) - exempt from FDA premarket review, but need to follow specific requirements.
- **Genetic Health Risk Tests** ([21 CFR 866.5950](https://www.hhs.gov)) - Companies that offer DTC GHR tests are required to obtain FDA clearance prior to offering their first test; then offer most additional tests without FDA premarket review.
- **Pharmacogenetics Tests** ([21 CFR 862.3364](https://www.hhs.gov)) → require premarket review and clearance. (FDA has not authorized any DTC pharmacogenetic tests that predict whether an individual is likely to respond to or have adverse reactions from any specific therapeutic drug).
- **Cancer Predisposition Tests** ([CFR 21 866.6090](https://www.hhs.gov)): considered moderate to high risk → premarket review and clearance.
- **Low Risk General Wellness Tests**: FDA generally [does not review](https://www.hhs.gov).
- **Ancestry Tests**: FDA [does not review](https://www.hhs.gov).


**Laboratory Developed Test (LDT)**

- *In vitro* diagnostic test that is **designed, manufactured, and used within a single laboratory**
- Offered to patients only when prescribed by a health care provider.
- Typically do not have the FDA’s independent assurance of the analytical validity, clinical validity, or clear communication of test results.
- In recent years, FDA has attempted to more actively regulate LDTs.

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**Essential evaluation parameters for a new diagnostic test**

<table>
<thead>
<tr>
<th>Scientific validity</th>
<th>Is the test associated with the condition of interest?</th>
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<tbody>
<tr>
<td>Analytical performance</td>
<td>Is the test precise, reproducible, specific and sensitive?</td>
</tr>
<tr>
<td>Clinical performance</td>
<td>Does the test have clinical value/impact (i.e., improve outcomes) in patients: consider target condition, threshold, triage vs confirmation, consequences of true and false positive or negative results</td>
</tr>
</tbody>
</table>

... and cost-effectiveness and effects on society

*Leeflang MMG, Allerberger F – Clin Micro Infect 25: 54, 2019*
Clinical Laboratory Improvement Amendments (CLIA)

- **CLIA regulate laboratory testing** and require clinical laboratories to be certificated by their state as well as the Center for Medicare and Medicaid Services (CMS) before they can accept **human samples** for diagnostic testing.

- Assures **test validation, quality assurance, proficiency of personnel**

- **Three federal agencies** are responsible for CLIA: The Food and Drug Administration (FDA), Center for Medicaid Services (CMS) and the Center for Disease Control (CDC).

**Companion diagnostic**

- **A companion diagnostic** is a diagnostic test used as a companion to a therapeutic drug to determine its applicability to a specific person.

- Companion diagnostics are co-developed with drugs **co-developed with drugs** to aid in selecting or excluding patient groups for treatment with that drug based on biological characteristics that determine responders and non-responders.

- **Companion diagnostics** are developed based on biomarkers that prospectively **help predict likely response or severe toxicity**.
Use of Companion Diagnostics to Optimize Patient-Specific Therapy

Regulatory Science

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

http://gencurix.com/engcodingfiles/science03.html