Reichman University

Class #3

Navigating the Regulatory Landscape

By Dr. Eyal Ballan

Reichman University

Why Regulation Matters for Entrepreneurs

Regulatory approval is critical for healthcare ventures because:

- It is mandatory for market entry and commercialization
- It significantly impacts development timelines (5-15 years)
- It drives capital requirements and investment decisions
- It affects market strategy and competitive positioning
- It determines reimbursement and market access
- Failure to comply results in severe penalties or market withdrawal

Overview of Global Regulatory Agencies

- **Major Regulatory Bodies Worldwide:**
- **FDA** (United States): Food and Drug Administration
- **EMA** (Europe): European Medicines Agency
- **PMDA** (Japan): Pharmaceuticals and Medical Devices Agency
- **NMPA** (China): National Medical Products Administration
- **TGA** (Australia): Therapeutic Goods Administration
- **Health Canada** (Canada)
- **MHRA** (United Kingdom): Medicines and Healthcare products Regulatory Agency

Israel

Ministry of Health (MOH): Pharmaceutical Administration
AMAR (Administration for Medical and Pharmaceutical Equipment Registration)

Reichman University

The FDA - Structure and Mission

U.S. Food and Drug Administration Mission: Protecting public health by ensuring safety, efficacy, and security of drugs, medical devices, biologics, food, and cosmetics.

CDER: Center for Drug Evaluation and Research
CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiological Health

Reichman University

FDA Regulatory Authority

Core regulatory powers include:

- Pre-market approval requirements
- Post-market surveillance and enforcement
- Manufacturing quality standards (GMP)
- Clinical trial oversight (IND applications)

Reichman University

The Reality of Post-Market Surveillance

1.7 million injuries and 83,000 deaths over 10 years potentially linked to medical devices

43% of AI device recalls occur within first 12 months of clearance

Companies may cut corners on testing to meet launch deadlines and financial targets

FDA's active surveillance system mandated in 2012, only launching pilot in 2024

Currently covers only 2 device types; 5-year expansion plan contingent on funding

Post-market surveillance remains largely passive (voluntary reporting)

Reichman University

The bottom line for entrepreneurs

Don't rely on FDA to catch problems. Build robust internal post-market surveillance systems from day one. Your reputation and patient safety depend on proactive monitoring, not reactive compliance.

Reichman University

Three Main Product Categories

1. Drugs (Small Molecules) Chemical compounds that diagnose, cure, mitigate, treat, or prevent disease. Regulated by CDER. Examples: aspirin, statins, antibiotics.

2. Biologics (Large Molecules) Products derived from living organisms including proteins, antibodies, vaccines, gene therapies. Regulated by CBER. Examples: insulin, monoclonal antibodies, CAR-T therapies.

3. Medical Devices Instruments, apparatus, or machines used to diagnose, prevent, or treat disease. Regulated by CDRH. Examples: pacemakers, glucose monitors, surgical robots.

Reichman University

FOCUS AREA: Wearables, sensors, apps

Discovery & Preclinical : Laboratory and animal studies

(3-6yr)

IND Application: Investigational New Drug application to FDA

Phase I Clinical Trials : Safety in 20-100 healthy volunteers

(1-2yr)

Phase II Clinical Trials: Efficacy and side effects in 100-300 patients

(2-3yr)

Phase III Clinical Trials: Efficacy in 1,000-3,000 patients

(2-4yr)

NDA: New Drug Application with complete data package

FDA Review : Standard or priority review

(6-10m)

Approval and Launch

Phase IV Post-Market Surveillance: Ongoing safety monitoring

Reichman University

The IND Application

Investigational New Drug (IND) Application Required before human clinical trials can begin.

Key Components:

- Animal pharmacology and toxicology studies
- Manufacturing information and composition
- Clinical protocols and investigator information
- Commitment to institutional review board (IRB) approval
- Informed consent procedures
- FDA has 30 days to review. If no clinical hold is issued, trials may proceed.

Reichman University

Clinical Trial Phases Explained

Phase I (Safety): 20-100 healthy volunteers, 1-2 years. Tests safety, dosage range, side effects. ~70% advance.

Phase II (Efficacy): 100-300 patients with disease, 2-3 years. Tests effectiveness and optimal dosing. ~33% advance.

Phase III (Confirmation): 1,000-3,000 patients, 2-4 years. Confirms efficacy, monitors adverse reactions, compares to existing treatments. ~25-30% approved.

Phase IV (Post-Market): Ongoing monitoring after approval. Safety surveillance, new indications, long-term effects.

Reichman University

The NDA Submission

New Drug Application (NDA) Comprehensive submission requesting FDA approval to market a new drug.

Required Contents:

- Complete chemistry, manufacturing, and controls (CMC) data
- Non-clinical pharmacology and toxicology results
- Human pharmacokinetics and bioavailability data
- Clinical trial data from all phases
- Safety update reports
- Proposed labeling and patient information
- Patent information

Reichman University

Accelerated Approval Pathways

Why These Pathways Exist?

For serious/life-threatening diseases with unmet medical needs, waiting 10-15 years for traditional approval means patients die while effective treatments sit in development. FDA created these pathways to balance speed with safety.

Rare diseases affecting fewer than 200,000

Over 7,000 rare diseases exist

Reichman University

Accelerated Approval Pathways

Bottom Line:

These pathways are game-changers for biotech startups treating serious diseases. They can:

- Cut development time nearly in half
- Reduce costs by hundreds of millions
- Get life-saving therapies to patients faster
- Make development economically feasible for smaller companies

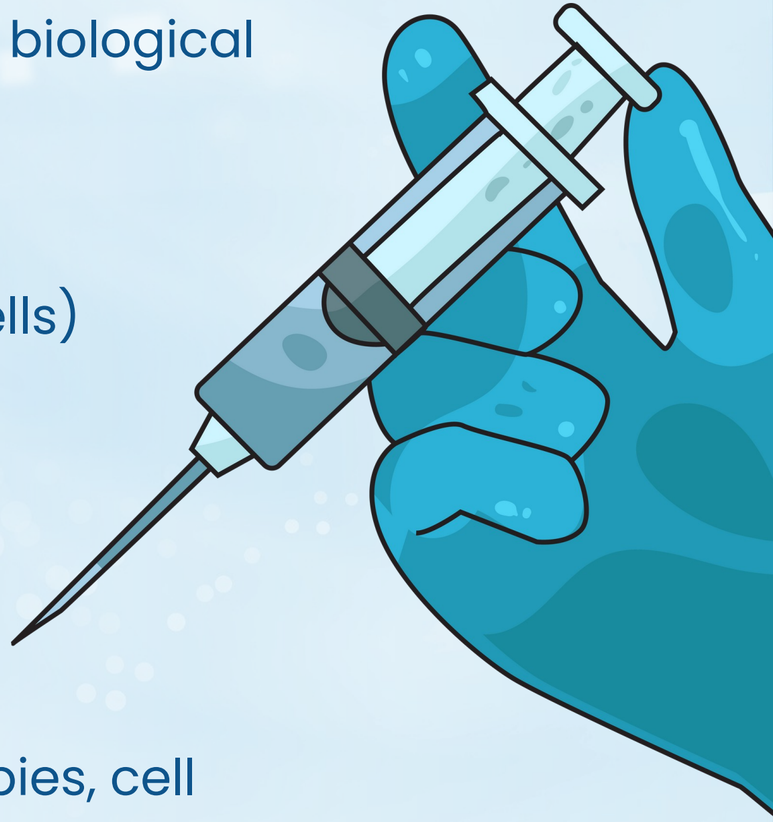
Reichman University

Biologics Regulatory Pathway

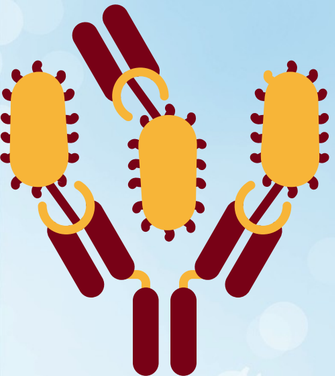
Biologics License Application (BLA) Similar to NDA but for biological products. Regulated by CBER.

Key Differences:

- Manufacturing is more complex and critical (living cells)
- Batch-to-batch variability must be controlled
- Immunogenicity testing required
- Biosimilars (not generics) for follow-on products
- Stricter facility inspections



Examples: Vaccines, monoclonal antibodies, gene therapies, cell therapies, blood products.



Reichman University

Gene and Cell Therapy Regulations

Special Considerations:

Regenerative Medicine Advanced Therapy (RMAT) designation available

Individualized patient treatments vs. standardized products

Long-term follow-up requirements (up to 15 years)

Vector characterization and potency assays

Unique manufacturing and quality control challenges

Recent approvals: CAR-T therapies, gene therapies for inherited diseases.

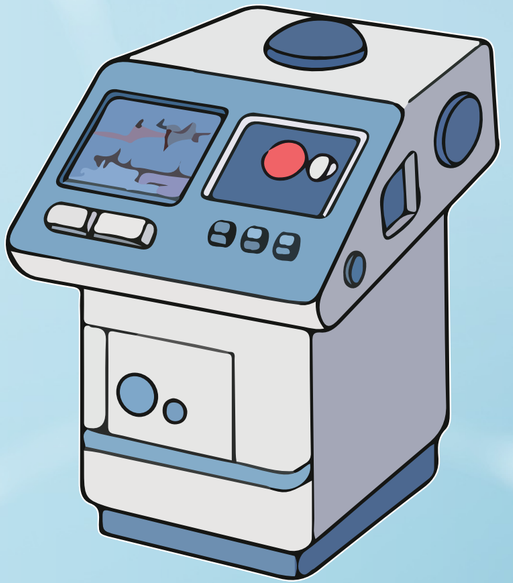
Medical Device Classification

Devices are classified by risk level:

Class I (Low Risk): General controls only. Examples: bandages, tongue depressors. Often exempt from pre-market notification.

Class II (Moderate Risk): General + special controls. 510(k) clearance required. Examples: powered wheelchairs, pregnancy tests, surgical gloves.

Class III (High Risk): Life-sustaining/supporting or high risk. PMA (Pre-Market Approval) required. Examples: pacemakers, heart valves, implantable defibrillators.



Students: Find example in the web

Reichman University

What Is 510(k) Clearance?

Core Concept: You prove your device is "substantially equivalent" to a device already legally on the market (called a "predicate device").

Key point: It's called "clearance" not "approval"

- FDA doesn't approve 510(k)s - they "clear" them
- Lower standard than PMA (Pre-Market Approval)
- You're not proving safety and efficacy from scratch
- You're proving equivalence to something already allowed

Reichman University

510(k) Vs PMA

Feature	510(k) Clearance	PMA Approval
Device class	Class II (mostly)	Class III
Standard	Substantially equivalent	Safe and effective
Clinical trials	Usually not required	Required
Timeline	3-12 months	1-3 years
Cost	$50K-300K	$1M-10M+
Success rate	~85%	~50%
FDA scrutiny	Moderate	Intense
Examples	Glucose meter, wheelchairs	Pacemaker, heart valve

PMA - Pre-Market Approval

Requirements:

Complete device description and manufacturing

Non-clinical laboratory studies

Clinical trial data demonstrating safety and effectiveness

Proposed labeling and instructions

Quality system regulation (QSR) compliance

Reichman University

PMA - Pre-Market Approval

Requirements:

Complete device description and manufacturing

Non-clinical laboratory studies

Clinical trial data demonstrating safety and effectiveness

Proposed labeling and instructions

Quality system regulation (QSR) compliance

Reichman University

De Novo Classification

Pathway for Novel, Low-to-Moderate Risk Devices When no predicate device exists but risk is not high enough for Class III.

In Vitro Diagnostic Devices (IVDs)

Diagnostics Regulated by CDRH Tests performed on samples (blood, urine, tissue) to detect disease, conditions, or infections.

Reichman University

Digital Health and Software Regulation

FDA's Risk-Based Approach:

- High risk: Clinical decision support affecting treatment = regulated
- Moderate risk: Disease monitoring, general wellness = lighter oversight
- Low risk: Administrative functions, general health information = may be exempt

Reichman University

Quality Management Systems

Good Manufacturing Practices (GMP) FDA requires manufacturers to follow quality standards:

For Drugs: cGMP (current Good Manufacturing Practice)

- 21 CFR Part 210 & 211
- Process validation, quality control, documentation

For Devices: Quality System Regulation (QSR)

- 21 CFR Part 820
- Design controls, production controls, corrective actions

CFR = Code of Federal Regulations

Reichman University

Good Clinical Practice (GCP)

Standards for Clinical Trial Conduct Ethical and scientific quality standards for designing, conducting, recording, and reporting trials.

Key GCP Principles:

- Institutional Review Board (IRB) approval required
- Informed consent from all participants
- Investigator qualifications and responsibilities
- Protocol adherence and documentation
- Data integrity and quality assurance
- Safety reporting (adverse events)
- Regulatory inspection readiness

Reichman University

Good Clinical Practice (GCP)

Standards for Clinical Trial Conduct Ethical and scientific quality standards for designing, conducting, recording, and reporting trials.

Key GCP Principles:

- Institutional Review Board (IRB) approval required
- Informed consent from all participants
- Investigator qualifications and responsibilities
- Protocol adherence and documentation
- Data integrity and quality assurance
- Safety reporting (adverse events)
- Regulatory inspection readiness

Reichman University

Regulatory Strategy for Startups

Developing Your Regulatory Roadmap:

1. Early Planning: Identify regulatory pathway in concept phase
1. Pre-Submission Meetings: Request FDA feedback before major studies
1. Regulatory Affairs Expertise: Hire or consult with regulatory professionals
1. Quality by Design: Build quality and compliance into development
1. Documentation: Maintain thorough, inspection-ready records
1. Parallel Paths: Consider multiple geographic markets simultaneously
1. Risk Management: Identify and mitigate regulatory risks early

Regulatory strategy should drive development timelines and funding needs.

Reichman University

Key Takeaways

- Regulatory approval is mandatory, lengthy, and expensive
- Different pathways exist for drugs, biologics, and devices
- Early FDA engagement improves success probability
- Quality systems and documentation are critical
- Regulatory strategy should guide business planning

Vioxx - The $4.85 Billion Recall
• The Blockbuster That Killed (1999-2004)

- **The Drug:**
- Vioxx (rofecoxib) - COX-2 inhibitor for arthritis pain
- Merck's blockbuster: $2.5 billion/year in sales
- Heavily marketed ("Ask your doctor about Vioxx")
- FDA Approval:
- Approved 1999 with standard review
- Showed effective pain relief
- **What Went Wrong:**
- Post-market data showed increased heart attacks and strokes
- Study (VIGOR trial) showed 2-4x increased cardiovascular risk
- Merck knew about risks but downplayed them
- FDA pressured by internal reviewer Dr. David Graham

Reichman University

Vioxx – The $4.85 Billion Recall
The Blockbuster That Killed (1999-2004)

The Withdrawal:

- September 2004: Merck voluntarily withdrew Vioxx
- Estimated 88,000-139,000 heart attacks in US alone
- Estimated 38,000-55,000 deaths
- Merck faced 27,000+ lawsuits

Cost:

- Merck settled for $4.85 billion
- Criminal investigation (no charges)
- Congressional hearings exposed FDA failures