

# **An Overview of FDA Regulation: What the Canadian Biomedical Industry Needs to Know**

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# Agenda

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- I. Regulatory Approval
  - Pre-Market Product Testing
  - Access to the Market
- II. Manufacturing
- III. Marketing/Promotion
- IV. Post-Approval Reporting
- V. Imports into U.S.
- VI. Enforcement and Violation



# Regulatory Approval

# Regulatory Basics

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Person shall not adulterate or misbrand a product.

Nor may any person send or receive product which is adulterated (not in compliance with approval standards) or misbranded (false or misleading in any particular).

Illegal to introduce an unapproved product into interstate commerce if it does not comply with pre-marketing approval, manufacturing, marketing, reporting or import FDA regulatory requirements.

# Organizational Structure of FDA

Field Staff --  
(Office of Regulatory Affairs)

Enforce FDA regulatory policies and decisions; carry out site inspections; follow up on complaints; oversee implementation of recalls

Headquarters staff --

Make FDA regulatory policies and decisions

## Five Substantive HQ Centers

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Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

Center for Devices and Radiological Health (CDRH)

Center for Food Safety and Applied Nutrition (CFSAN)

Center for Veterinary Medicine (CVM)

CDER, CBER and CDRH govern the human biomedical industry.



# Drugs/Biologics

Regulatory Approval

# Drugs – CDER Regulates

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A drug is defined as:

- a) Article recognized in the official USP, HPUS or NF or any supplement to any of them,
- b) Article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals,
- c) Articles (other than food) intended to affect the structure or any function of the body of a man or other animals.

# Biologics – CBER Regulates

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Gene therapies

Cellular therapies

Allergen patch tests and allergenics

Antitoxins, antivenoms and venoms

Vaccines, including therapeutic vaccines

Toxoids and toxins intended for immunization

Blood, blood components, and related products

# Drugs – CDER Regulates

CDER regulates therapeutic biological products (transferred from CBER in 2003) including:

- Monoclonal antibodies for in vivo use.
- Most proteins for therapeutic use including:
  - cytokines (e.g. interferons)
  - enzymes (e.g. thrombolytics)
  - other novel proteins  
(growth factors but not vaccines and blood products)
- Immunomodulators – i.e., non-vaccine and non allergenic products intended to treat disease by inhibiting or down-regulating a pre-existing, pathological immune response
- CBER regulates other biologics

# Medical Device and Diagnostics – CDRH Regulates

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Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar related article, including any component, part or accessory.

- Intended for use in diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or other animals.
- Product must not achieve any of its principal intended purposes through chemical action within or on the body of man or other animal.
- Nor may it be dependent on being metabolized to achieve any of these purposes.

# Biotech Products Can Span Regulatory Categories

## **Biologics**

- Immunoglobulin
- Monoclonal antibodies

## **Drugs**

- Insulin
- Growth hormone

## **Medical Devices**

- Genotyping systems

# Category of Product Drives Essential Regulation

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## Market approval mechanisms

- Rx Drugs – Approvals
  - New Drug Application (NDA) -- Branded
  - Abbreviated New Drug Application (ANDA) -- Generic
- Over The Counter (OTC) -- Branded or Generic
- Biologics – Licensing (Biologics License Application (BLA))
- Medical devices and diagnostics – Approvals/clearances (Pre-Marketing Approval (PMA))/510(k)

# Drug/Biologic Regulatory Approval

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Rigorous scientific scrutiny to ensure that drug or biologic is safe and effective for its intended use.

## Average drug risk profile

- 1 in 350,000 discoveries approved
- Cost to approval - - \$800 million
- Time to approval - -15 years

# Drug Development and Approval Process

Discovery

Non-Clinical Animal Testing

Product and Process Development

- Chemistry, Manufacturing and Control (CMC)

Investigational New Drug Application (IND)

Clinical Trials (Phases 1, 2 and 3)

Good Clinical Practice (GCP) Regulations (21 C.F.R. . § 58)

- Protection of Human Subjects
- Financial Disclosures
- Institutional Review Board (IRB)
- Sponsor Responsibilities
- Clinical Investigator Responsibilities

New Drug (NDA) or Biologics License Application (BLA)

Market Approval

Phase 4

# Product Approval Problems

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- Failure to comply with FDA regulatory requirements.
- Failure to show adequate safety
- Failure to show efficacy claimed
- Manufacturing changes/facility concerns
- Labeling issues

# Pre-Clinical Research

**DISCOVERY/SCREENING**

**SYNTHESIS  
AND PURIFICATION**

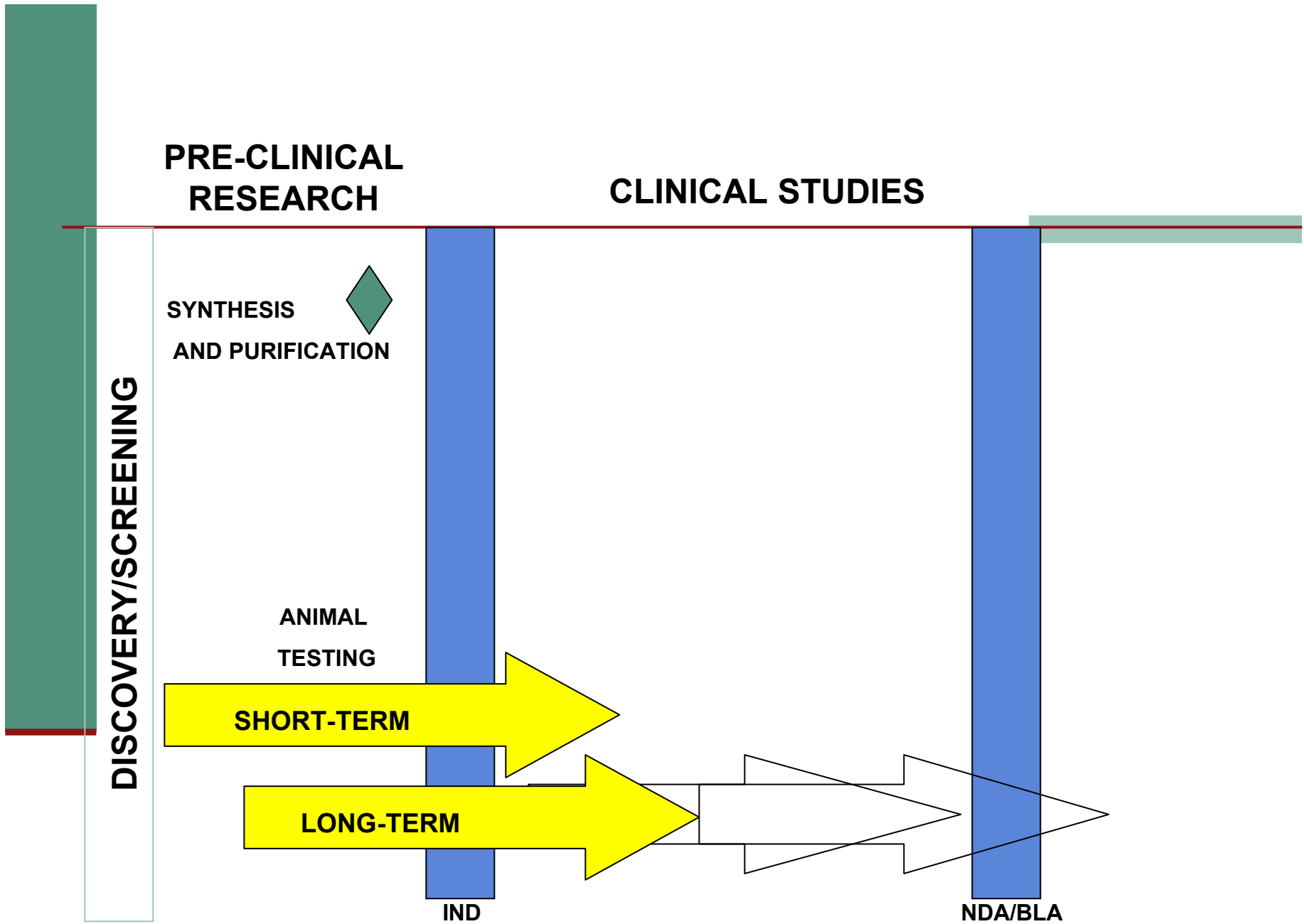


# Pre-Clinical Research

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This development stage completed by clinical investigators at manufacturers (or sponsors) or contract research organizations (CROs)

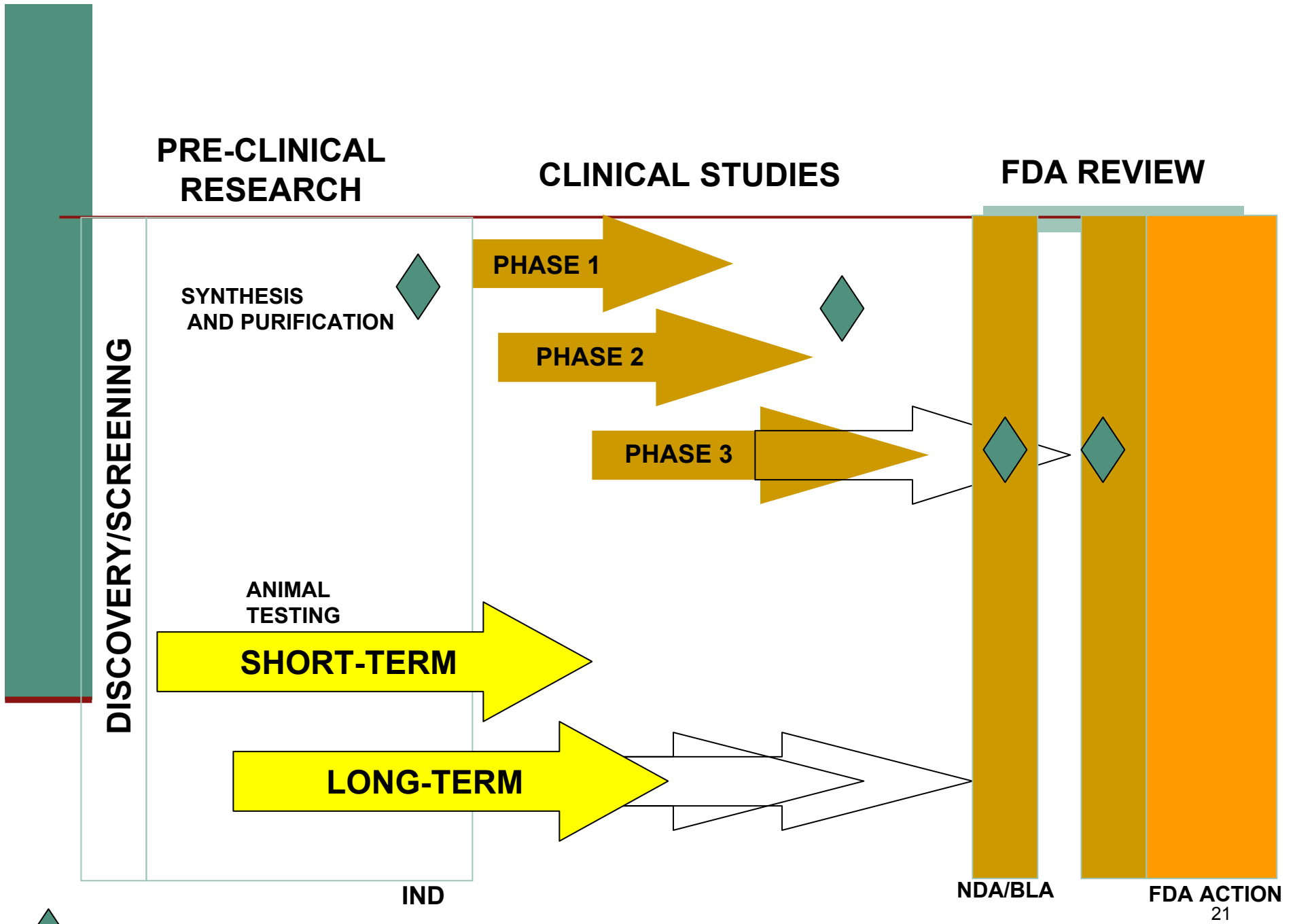
Discovery/screening – Identify a compound with desired effect but without toxicity



Sponsor/FDA Meetings Encouraged

# Pre-Clinical Research

- Study chemical properties of compound
- Develop steps for synthesis and purification
- Begin short and long term animal studies
  - Short term – How compound handled by body and acute toxicity issues
  - Long term – Issues of teratogenicity, carcinogenicity and genotoxicity
- FDA meeting with sponsor at pre-clinical stage if sponsor new to process or seeks “fast track” review status.



◆ Sponsor/FDA Meetings Encouraged

# Pre-Clinical Research

## Investigational New Drug (IND) Application

- Enables investigators to ship and handle unapproved drugs
- Contains pre-clinical data and proposed plans for human study
- FDA must review IND within 30 days
- Human clinical trials may not begin until IND granted
- FDA has significant oversight of clinical trials
- Trials can be abroad but must comply with FDA protections

# Pre-Clinical Research

## PHASE 1

First in Man

Safety and  
Tolerability

Pharmacokinetics

Time: 2-3 years

80% proceed to  
Phase 2

## PHASE 2

Proof of Concept

Dose Ranging

Safety/PK in Special  
Populations and Risk  
Factors

Time: Months-2  
years

Less than 40%  
proceed to Phase 3

## PHASE 3

Large, Multicentered

Usually Placebo-  
Controlled

Usually replicated

Primary data to  
support marketing  
approval in  
NDA/BLA

Time: 1-4 years

Less than 20% file for  
market approval

# Pre-Clinical Research

## Phase 1 Failures

- Animal models  $\neq$  human experience
- Inadequate pre-clinical data
- Change in drug formation
- Poor study design
- Toxicity too high

## Phase 2 and 3 Failures

- Drug – drug interactions
- Drug – disease interactions
- Genetic
- Insufficient effectiveness
- Economic reasons

# Expanded Access Schemes

Treatment IND – Allows patients with serious or life-threatening conditions to begin to use compound before formal FDA approval where no comparable or alternative therapy.

Parallel track program – Designed for individuals with AIDS whose condition prevented them from participating in clinical trials

Accelerated approval (Fast Track) – Specialized program for accelerated approval based on “surrogate endpoints” – such as a laboratory findings or physical signs that predict meaningful, therapeutic benefit.

- Serious or life threatening disease
- Potential to address unmet medical needs

## Emergency Use

- Serious disease with no time for IND submission
- Can be done by phone; generally followed by IND submission

# New Drug Application (NDA) or Biologic License Application (BLA)

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Contains the following:

- Pre-clinical studies
- Human clinical studies
- Manufacturing details
- Labeling
- Additional information

# One NDA



# Legal Protection of Approved Products (Exclusivities)

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Orphan Drug (7 years) -- Genzyme

New Chemical Entity (5 years)

New Clinical Study/New Indication (3 years)

Pediatric (6 months)

Patent protection



# Medical Device/Diagnostics

Regulatory Approval

## 3 Device Classifications

Class I – Devices for which general statutory controls are sufficient for safety and effectiveness

General controls include:

- Seizure or enjoining distribution
- Registration requirements
- Reporting obligations

Most Class I devices are exempt from pre-marketing notifications

Examples of Class I devices: tongue depressors, elastic bandage and certain “general purpose” instruments

## 3 Device Classifications

Class II – Devices for which general statutory controls are not sufficient to ensure safety and effectiveness but for which there is sufficient information to provide assurance through special controls

Special controls –

- Post-market surveillance
- Development and dissemination of guidelines (including guidelines for submission of clinical data and pre-marketing notification submission)
- Other administrative controls
- Performance and labeling standards

Examples of Class II devices – Syringes, bone plates, hearing aids and resuscitation devices

# 3 Device Classifications

Class III – Devices that cannot be adequately regulated under Class I or Class II

General controls not sufficient

Not enough known about device to craft adequate special controls

Products pose potential unreasonable risk of injury

Class III devices therefore subject to pre-market approval (PMA) application containing valid scientific evidence of safety and effectiveness

Examples of Class III devices: Pacemakers and artificial hearts

# Device Approval Process

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Illegal to distribute an unapproved device

Two paths to approval:

- 510(k) for lower risk devices (analog to ANDA)
- PMA for higher risk devices (analog to NDA/BLA)

# 510(k) Submission for Some Class I, Most Class II, and Very Few Class III Products

## Substantial Equivalence (SE)

Goal of 510(k) is to show SE to a device already legally marketed; name from Section 510(k) of Food Drug and Cosmetic Act (FDCA)

Done through 90-day pre-market notification

510(k) process compares the legally marketed device (predicate device) to the device to be introduced to the market

Qs – Same intended use

No new technological characteristics or questions of safety and effectiveness

Data demonstrates equivalence

# PMA Process

PMA required for most Class III devices to establish as safe and effective

PMA filing includes:

- Animal studies
- Clinical studies
- Indications for use
- Contraindications, warnings and adverse events
- Manufacturing information
- Proposed labeling

# Investigational Device Exemption (IDE)

## IDE regulations:

- Enable legal shipment of devices for clinical testing prior to market approval
- Protect human subjects
- Produce useful clinical information

IDE must be approved before PMA studies start

Site Institutional Review Board (IRB) must be approved

Financial conflicts must be disclosed

# Investigational Device Exemption

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Sponsor must monitor study

Reporting obligation

IDE results part of PMA

FDA inspect, both sponsor and study sites

- FDA Form 483s/warning letters issued to study sites and physicians



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# Drugs/Biologics and Medical Devices/Diagnostics

Manufacturing Regulation

# Manufacturing Regulation

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Producers of drugs and devices must register

Foreign producers must register their establishment and list their products

- FDCA § 510(i)
- 21 C.F.R. § 207.40

# Manufacturing Regulation

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Drugs – Good manufacturing practices (GMP) for drugs  
21 C.F.R. Parts 210 and 211

Biologics – GMP for biologics  
21 C.F.R. Part 600 et. seq.

Medical devices and diagnostics – Quality system review (QSR)  
21 C.F.R. Part 820

# Manufacturing (QSR and GMP)

## QSR: Quality System Regulation

Management must review suitability and effectiveness of Quality System at defined intervals and sufficiently frequently to ensure integrity of system

- Comply with FDA QSR Regulations
- Comply Quality Policy and Objectives

Failure to follow company's own policy can be QSR violation even if not required by FDA regulation

# GMP/QSR

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Design controls

Document controls

Purchasing controls

Identification and traceability

Production and process controls

Acceptance activities

Non-conforming product

Corrective and preventative action

Labeling and packaging controls

Handling, storage, distribution and installation

Records

Servicing

# GMP/QSR Inspections

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FDA always focuses on GMP/QSR compliance

No patience for systemic or repeated problems

FDA demand “state of control”

Severe consequences for non-compliance

# Reason for Inspection

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Routine (FDA Form 482)

For Cause

Follow up to complaints or FDA enforcement action

Recall effectiveness check

Start-up

Pre-approval

# Results of Inspection

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FDA Form 483

Responses to Form 483



# Marketing/Promotion

# Marketing/Promotion

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FDA regulates advertising of prescription drugs

Federal Trade Commission (FTC) regulates advertising of OTC drugs

Securities and Exchange Commission (SEC) regulates statements in connection with securities documents

# FDA Regulations of Marketing/Promotion

## Key issues:

Uses promoted must be “intended uses”

Promotion may make no unapproved claims regarding safety or efficiency, comparative claims or cost effectiveness claims, nor make any false or misleading statements

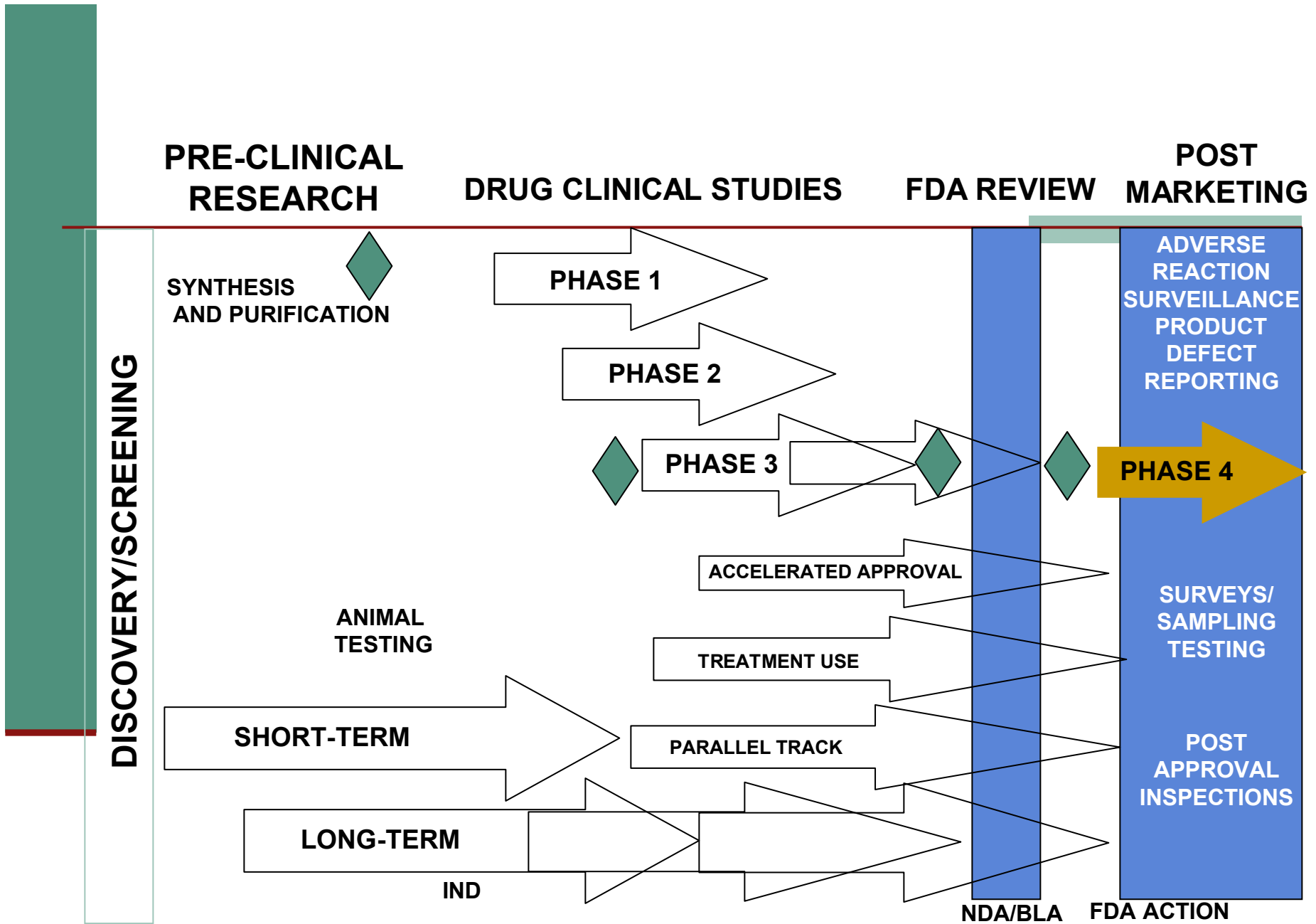
FDA does regulate Internet websites through its labeling regulations

If promoted off-label, a product may be found to be “misbranded” or “adulterated”

But FDA does not regulate the practice of medicine



# Post-Approval Reporting



Sponsor/FDA Meetings Encouraged

# Drugs

## Potential Regulatory Action for Postmarketing Safety Issues

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- Labeling change
- Scientific publication
- “Dear Doctor” letter (for specific warnings)
- Restricted use
- Restricted distribution
- Patient medication guide
- Product withdrawal

# Device Reporting

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Must report any correction or removal from market of a device taken to:

- Reduce risk to health
- Remedy a violation of FDCA caused by device that might present a risk to health



Imports into U.S.

# Importation

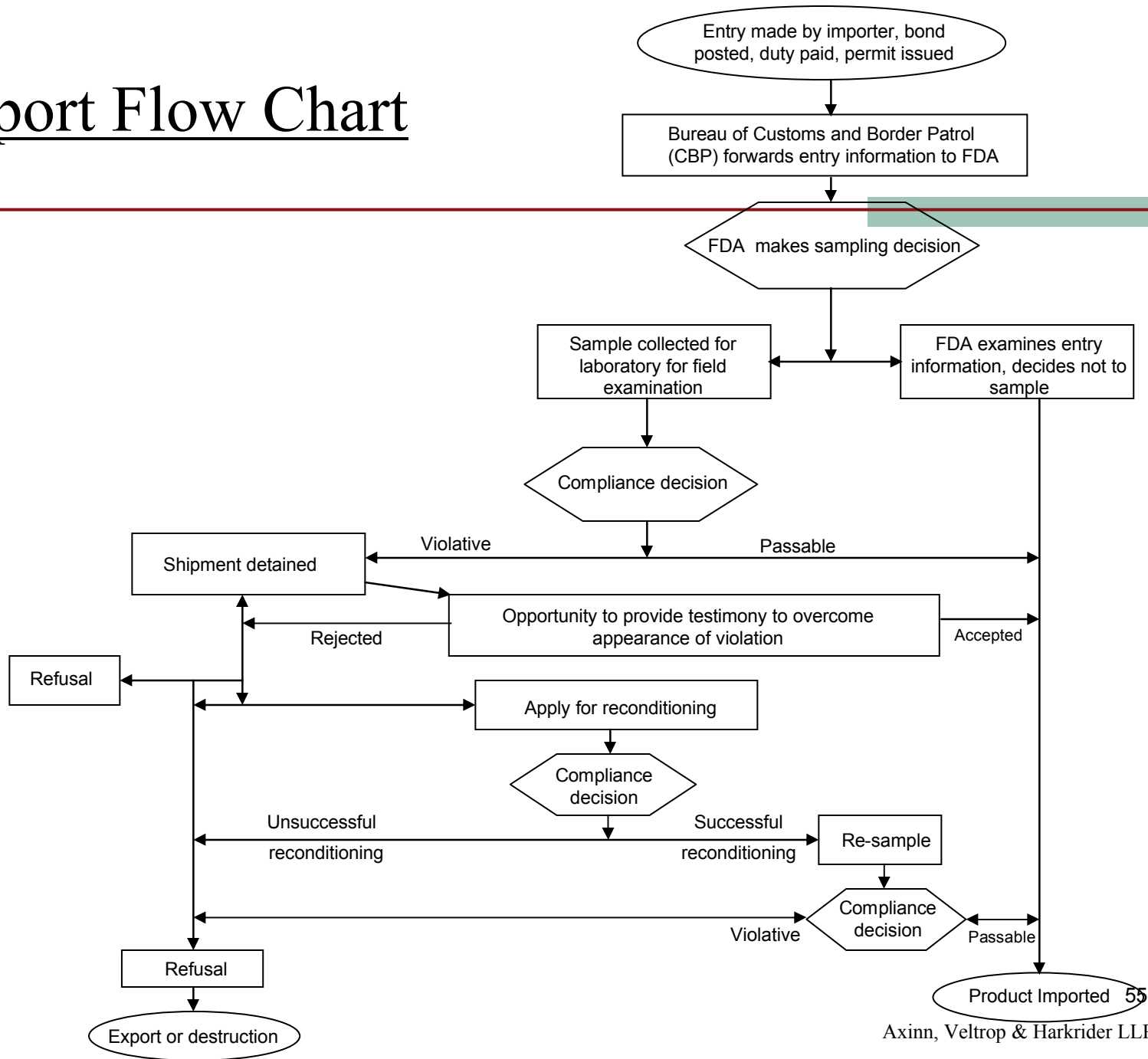
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FDA powers apply to any drugs/biologics or devices imported into U.S.

FDA can insist on inspections at foreign establishments in order to satisfy that product is neither adulterated or misbranded

Interaction between FDA and Homeland Security

# Import Flow Chart





# Enforcement and Violations

# Enforcement and Violations

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Violation of FDA regulatory requirements can result in FDA enforcement of its regulations and lead to civil and/or criminal violations

# Enforcement and Violations

## Statutory Enforcement Tools

- Seizure
- Injunction (continuous FDA oversight of operations)
- Civil penalties (up to \$1 million)
- Equitable disgorgement of profits
  - Schering-Plough (\$500 million; drugs)
  - Abbott (\$199 million; devices and diagnostics)
- Criminal prosecution
  - No criminal intent needed for most cases (Park Doctrine)
  - 1 year imprisonment plus fines for first-time offenders
  - 3 years imprisonment plus fines for repeat offenders
  - When actual harm to patients, pattern of non-compliance, evidence of intent, or need to set example

# Enforcement and Violations

## Non-Statutory Enforcement Tools

- FDA Form 483 (75% of inspections)
- Untitled letter  
(action within 30 days)
- Warning letter (10%-20% of 483s)  
(principal enforcement mechanism)  
(action within 15 days)
- Publicity by FDA
- Recall (not uncommon)  
(for devices mandatory, for drugs “voluntary”)
- Revocation or suspension of approvals