

# FDA 101

Presented

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by

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# Presentation Outline

- Introduction
- History
- Regulatory Classification
- Development Process
- cGMP
- DMF
- ICH and Harmonization
- Important Organizations & Websites
- Summary



# What do these products have in common besides being block buster products?



Endeavor® Sprint

ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM

Biocompatible polymer  
for rapid, complete,  
and functional vessel healing

LEARN MORE ▶



We earn our stripes



For US Healthcare Professionals

# Before they could be sold, marketing approval had to be granted from FDA



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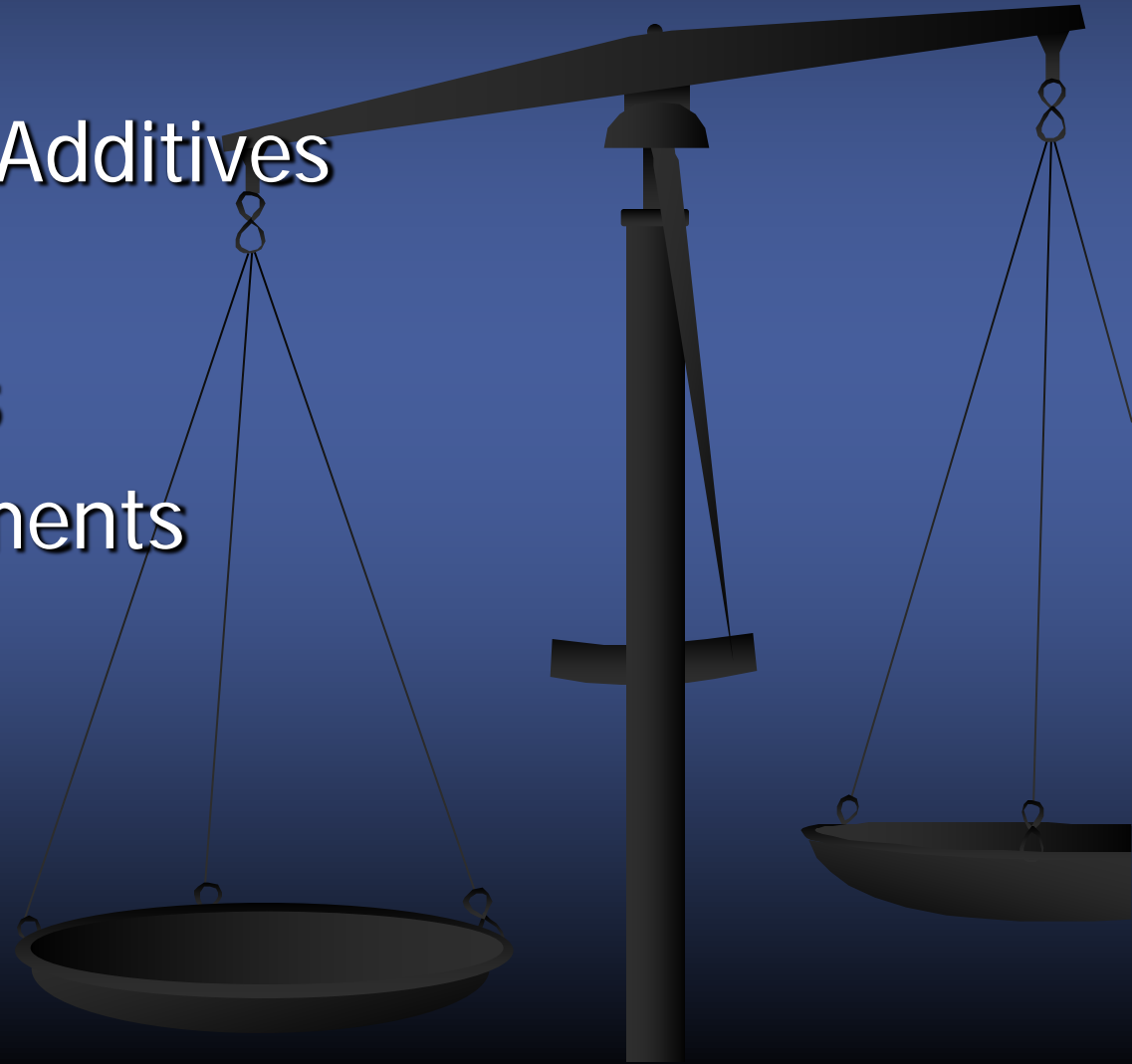
We earn our stripes



For US Healthcare Professionals

# What Products does the FDA Regulate

- Biologics
- Food and Food Additives
- Drugs
- Medical Devices
- Dietary Supplements
- Medical Foods
- Cosmetics
- Tobacco



# HISTORY

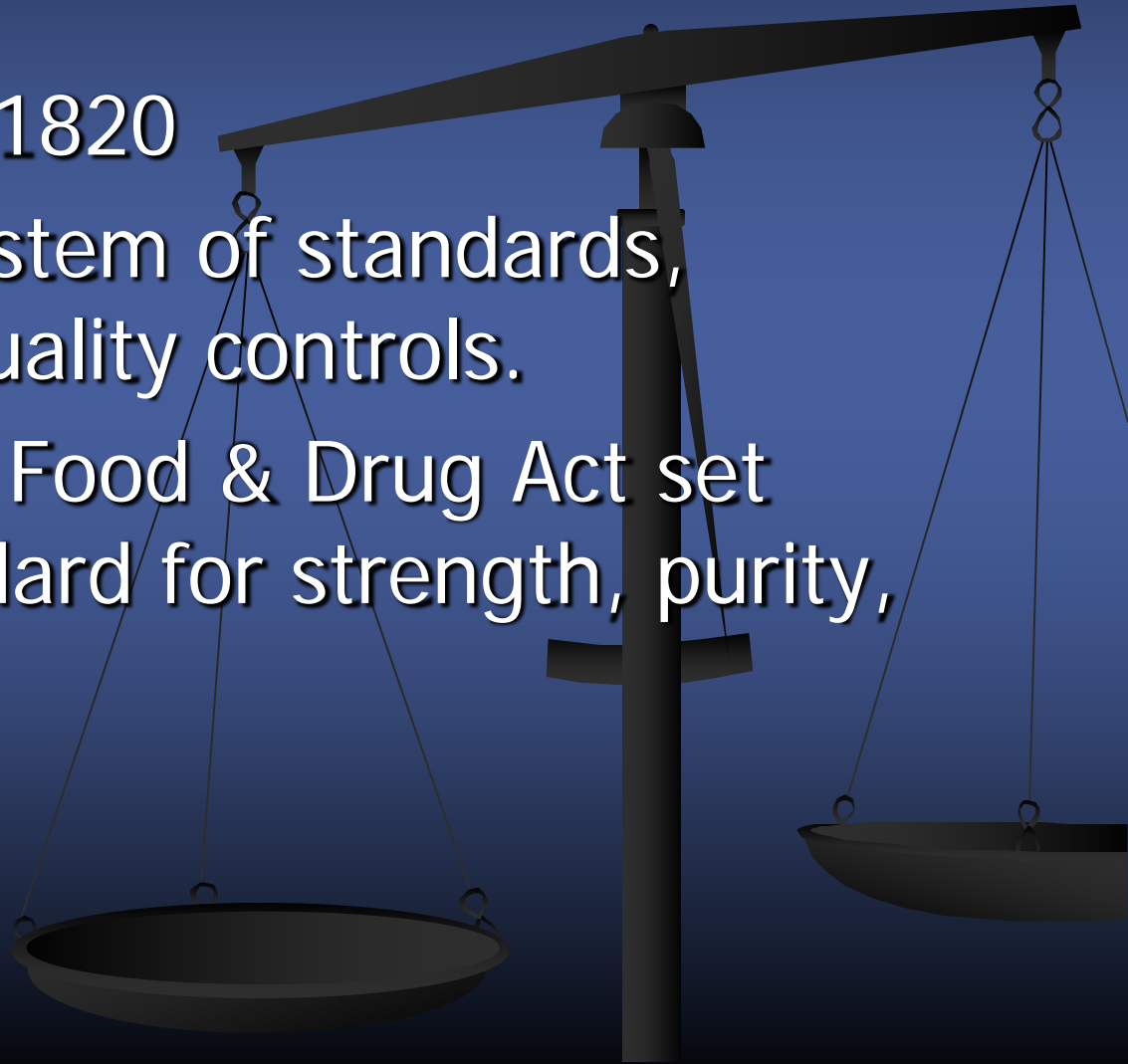
- USP
- Patent Medicine
- Biologics Control Act 1902
- Food and Drug Act 1906
- Harrison Act 1914
- Food, Drug and Cosmetic Act 1938
- Durham-Humphrey Amendment 1951
- Kefauver-Harris Drug Amendment 1962
- Medical Device Amendment 1976





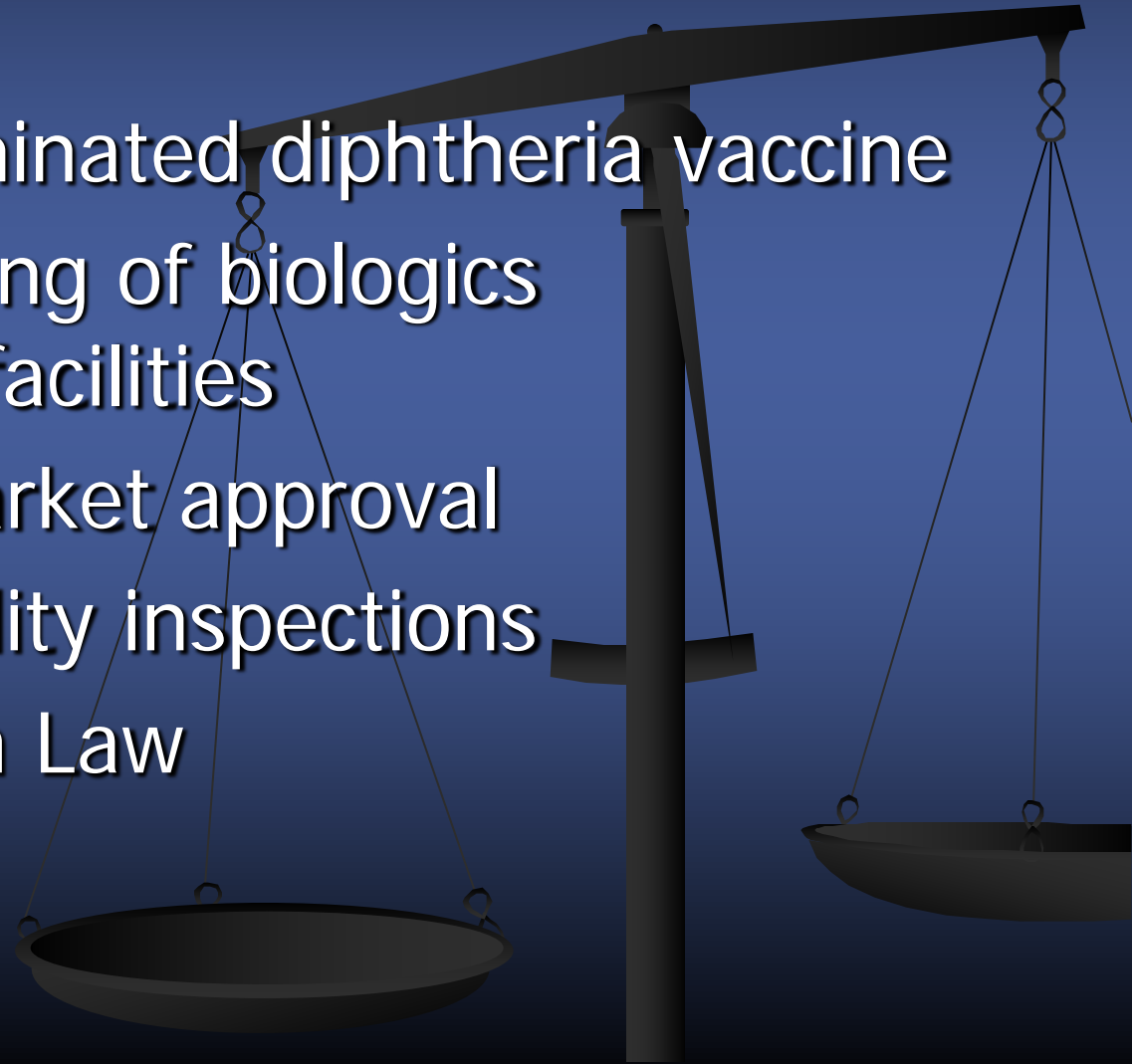
# US Pharmacopeia

- USP founded in 1820
- Established a system of standards, formulas, and quality controls.
- In 1906 Federal Food & Drug Act set USP/NF as standard for strength, purity, and quality



# Biologics Control Act 1902

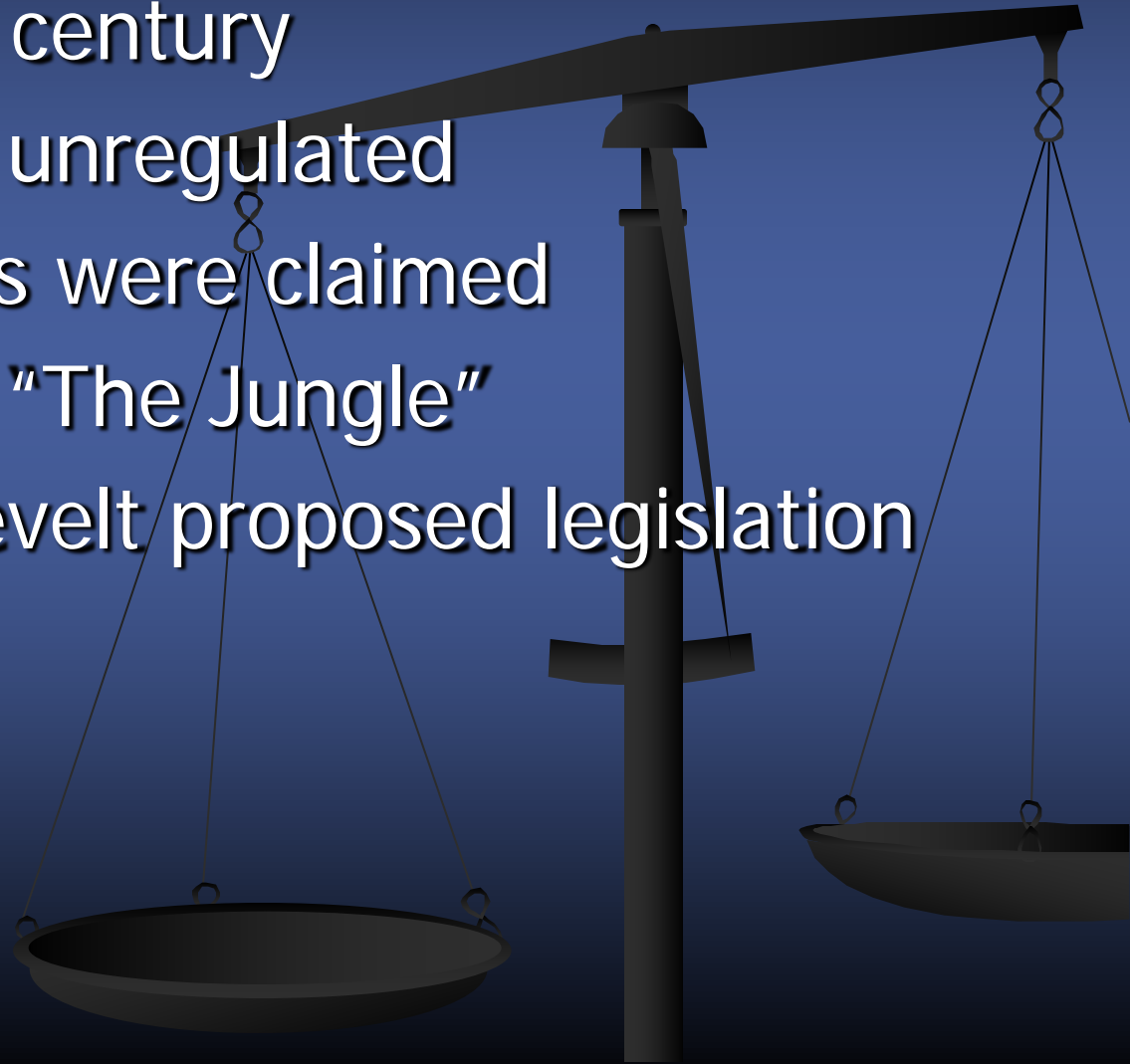
- Tetanus contaminated diphtheria vaccine
- Required licensing of biologics manufacturing facilities
- Required premarket approval
- Allowed for facility inspections
- AKA Virus-Toxin Law





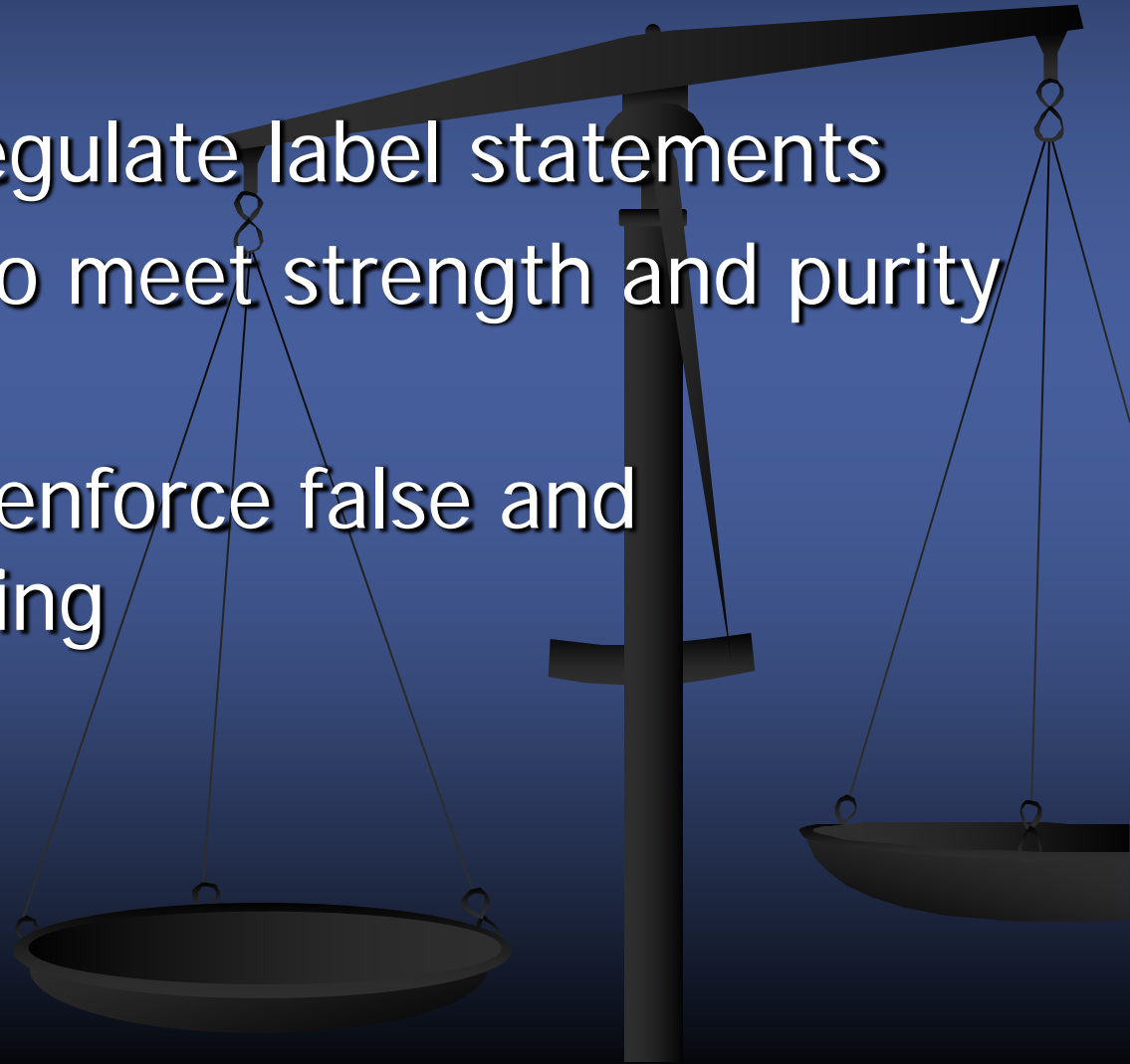
# Patent Medicine

- Turn of the last century
- Medicines were unregulated
- Miraculous cures were claimed
- Upton Sinclair's "The Jungle"
- President Roosevelt proposed legislation



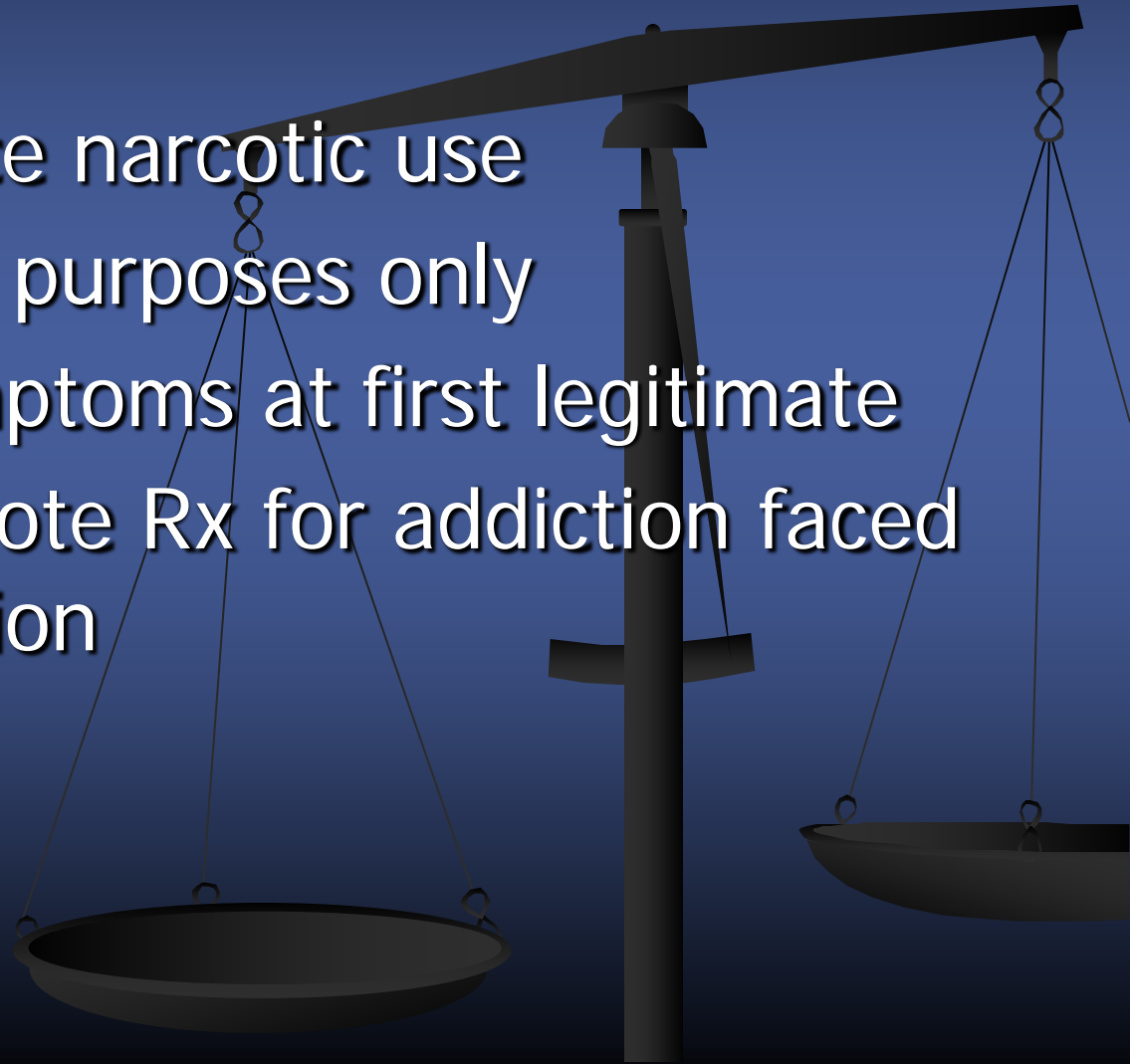
# Pure Food and Drug Act 1906

- Intent was to regulate label statements
- Drug products to meet strength and purity standards
- FDA created to enforce false and fraudulent labeling

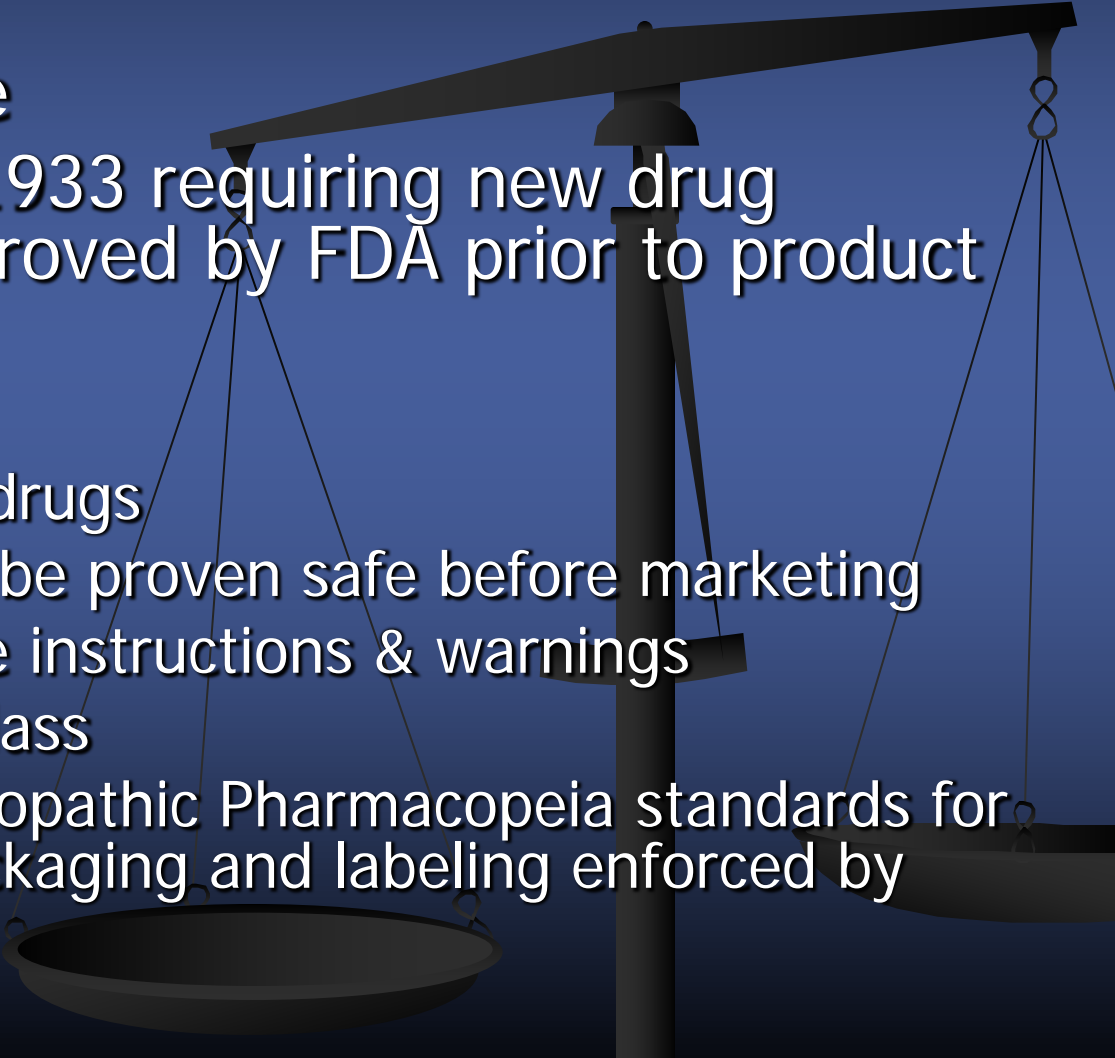


# Harrison Act 1914

- Passed to reduce narcotic use
- Use for medical purposes only
- Withdrawal symptoms at first legitimate
- Doctors who wrote Rx for addiction faced criminal conviction

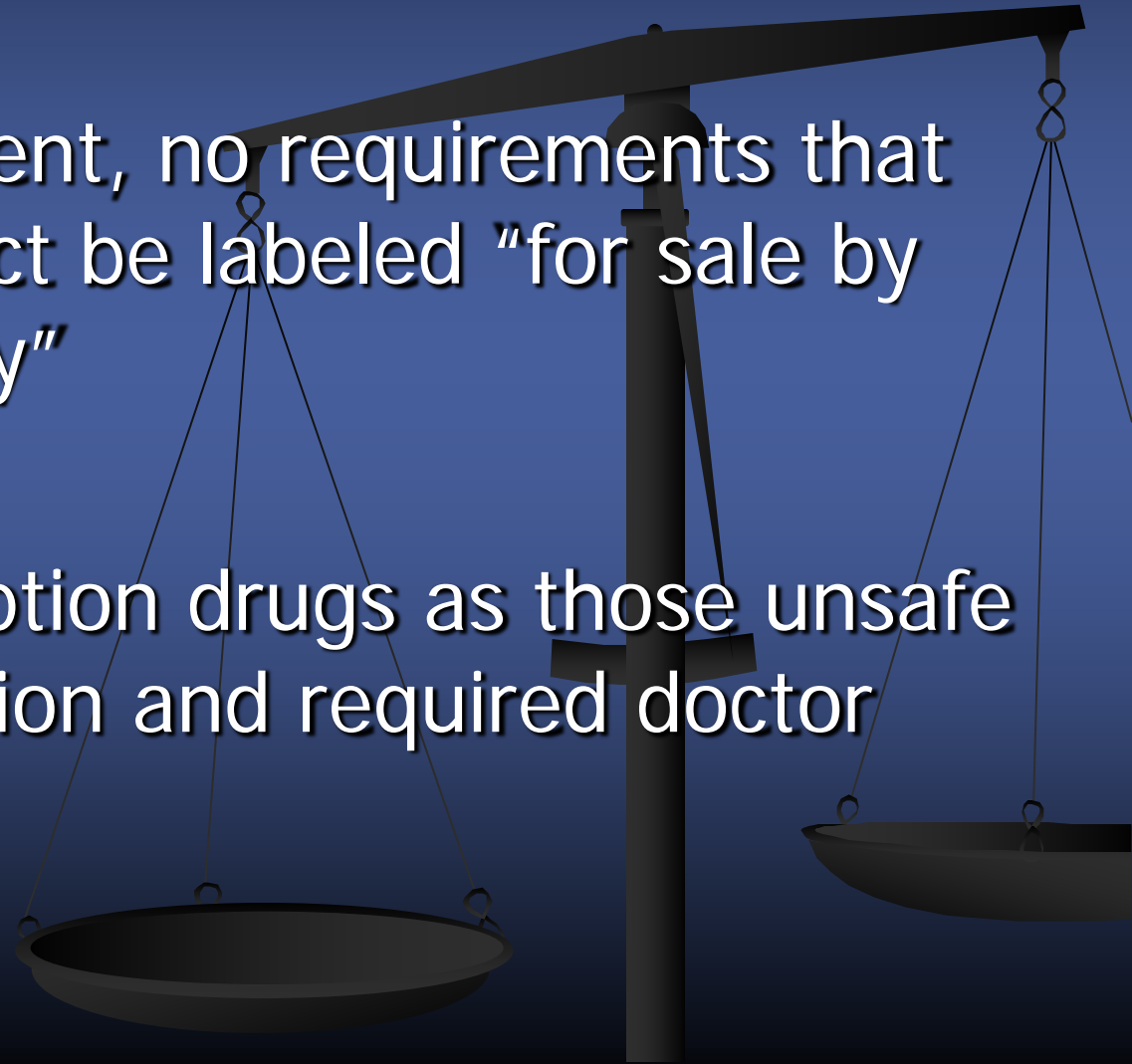


# Food, Drug and Cosmetic Act 1938

- Elixir Sulfanilamide
  - Bill introduced in 1933 requiring new drug application be approved by FDA prior to product marketing
  - Passed in 1938
    - Excluded existing drugs
    - New drugs had to be proven safe before marketing
    - Labels had to have instructions & warnings
    - Created Rx drug class
    - USP, NF and Homeopathic Pharmacopeia standards for quality, purity, packaging and labeling enforced by FDA
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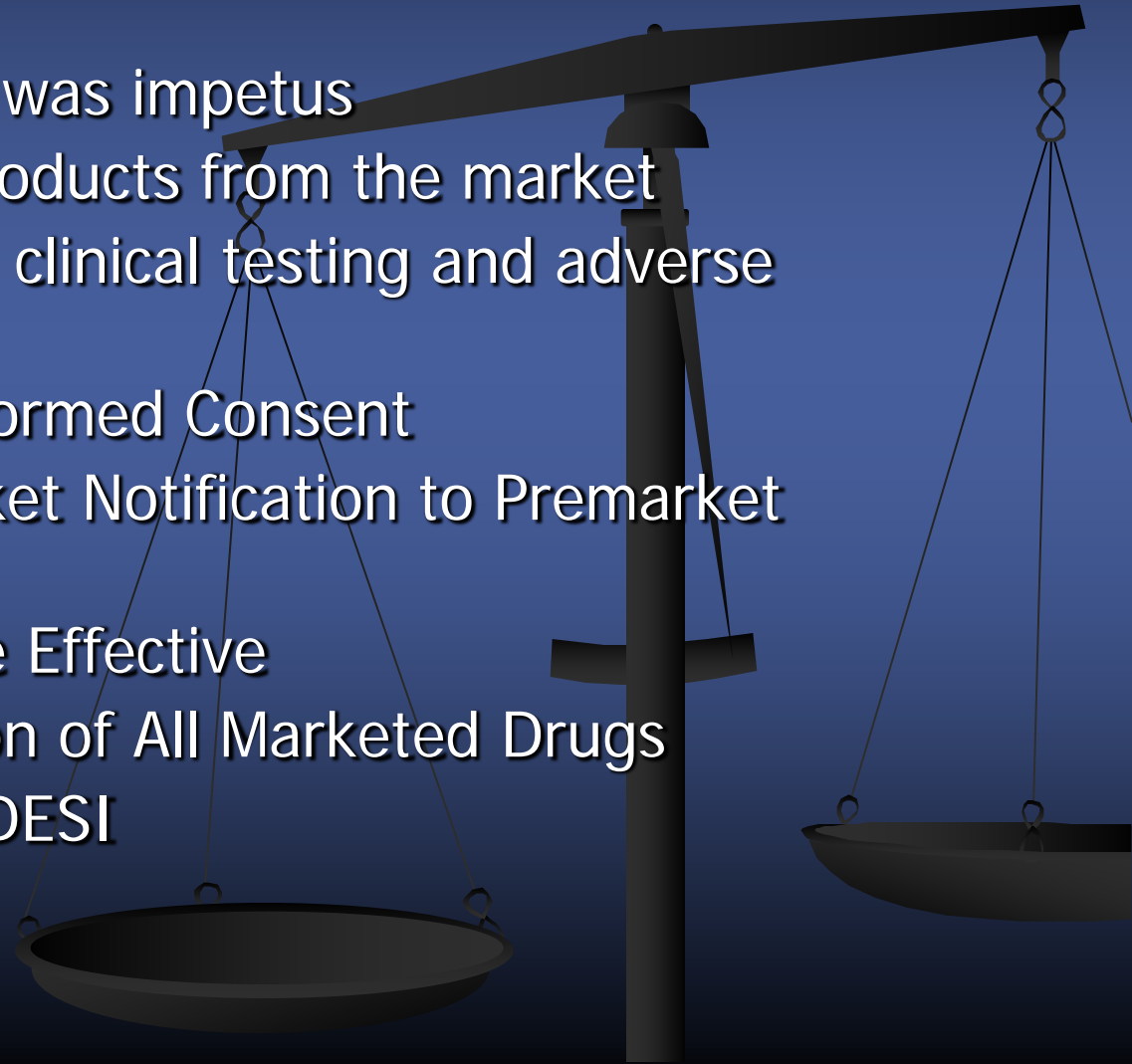
# Durham-Humphrey Amendment 1951

- Prior to enactment, no requirements that any drug product be labeled "for sale by prescription only"
- Defined prescription drugs as those unsafe for self-medication and required doctor supervision



# Kefauver-Harris Drug Amendments 1962

- Thalidomide tragedy was impetus
- FDA can withdraw products from the market
- FDA oversight cGMP, clinical testing and adverse reactions
- Required Subject Informed Consent
- Shifted from Premarket Notification to Premarket Approval
- Required Drugs to be Effective
- Required Reevaluation of All Marketed Drugs
- Still not Completed, DESI



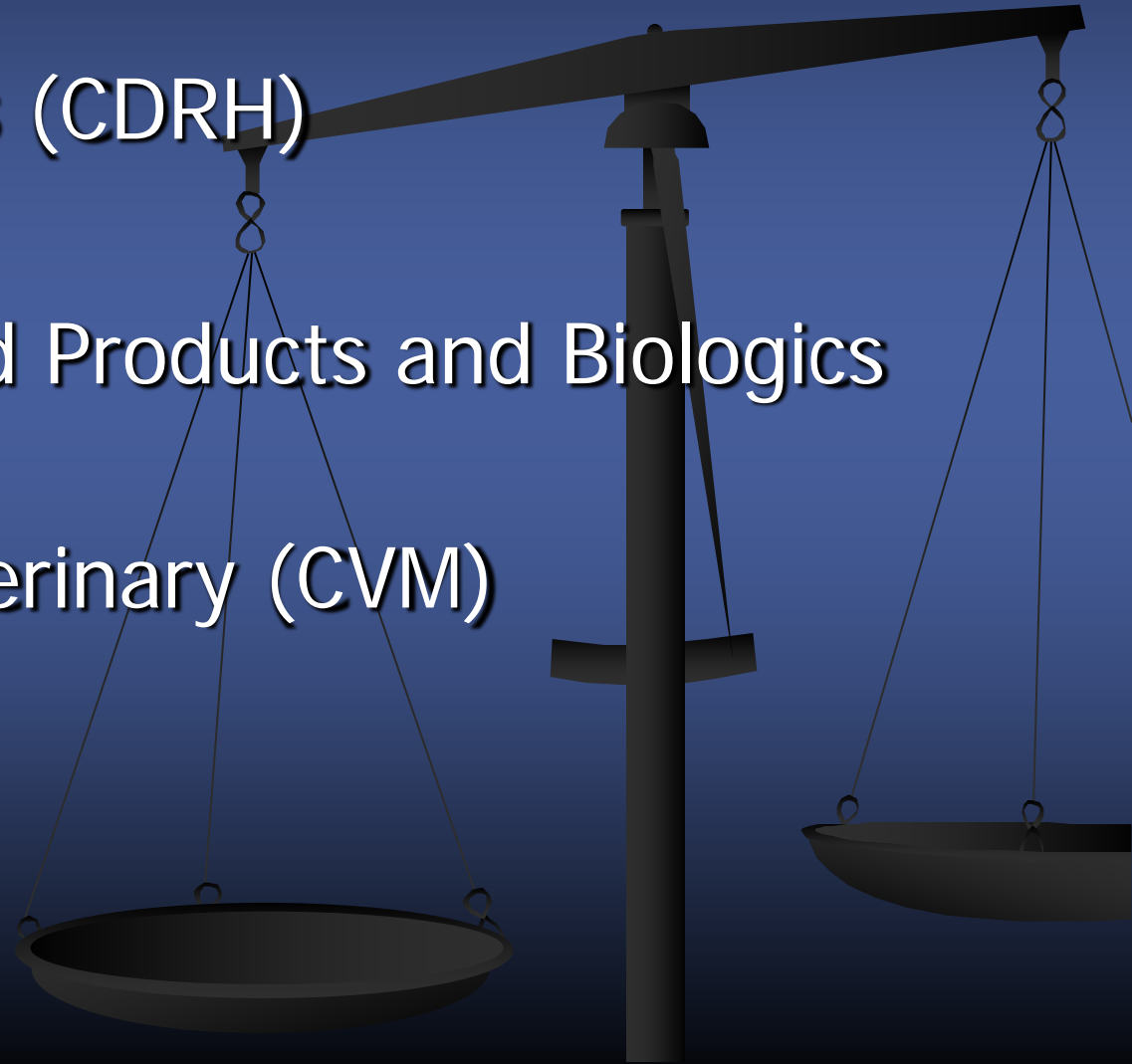


# Medical Device Amendment 1976

- Established three regulatory classes for medical devices
  - Registration and Listing
  - Premarket Control
  - Production following GMPs
  - Obligation for post-market reporting
  - Investigation Device Exemption (IDE)
- 

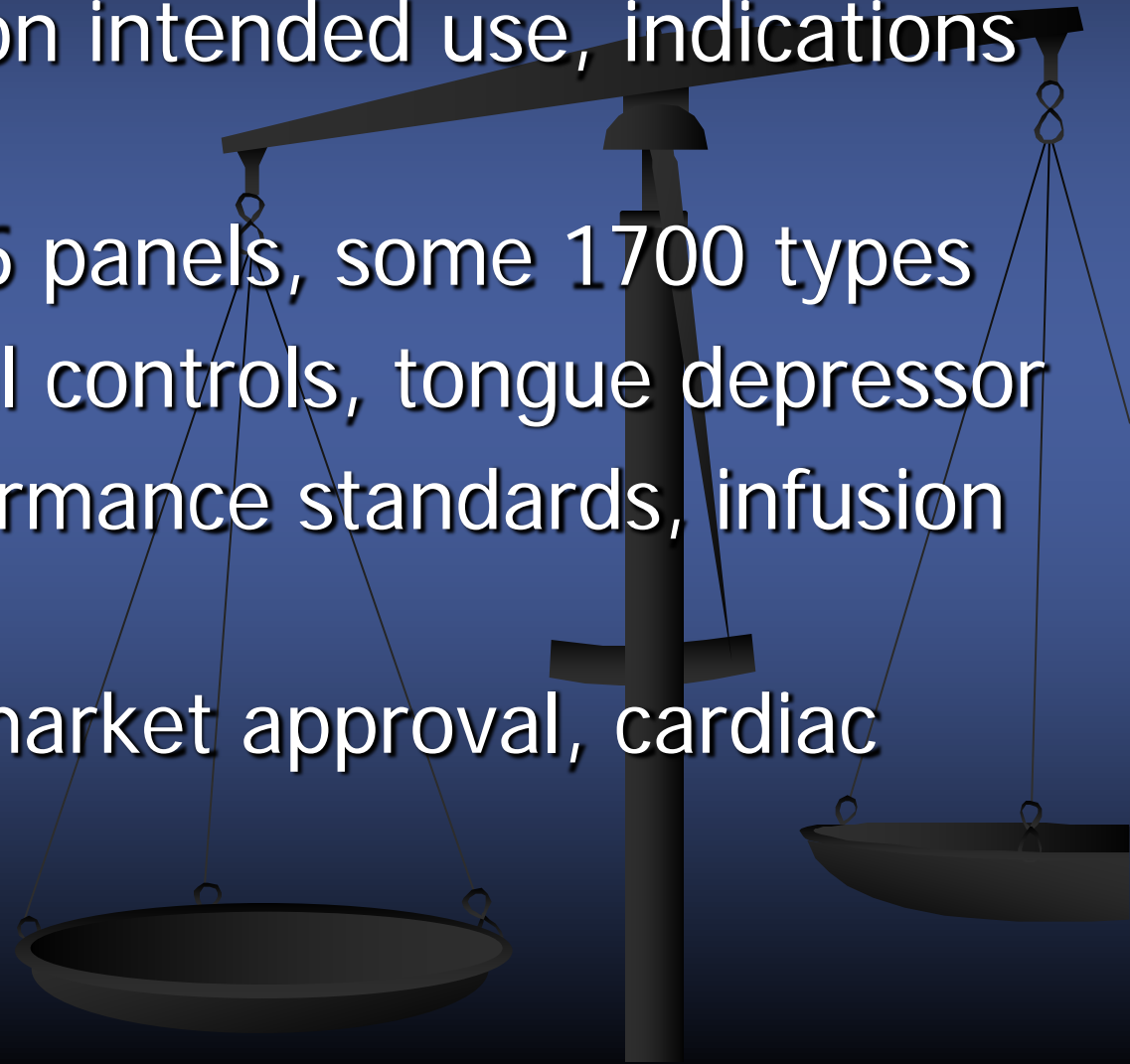
# REGULATORY CLASSIFICATION

- Medical Devices (CDRH)
- Drugs (CDER)
- Vaccines , Blood Products and Biologics (CBER)
- Animal and Veterinary (CVM)

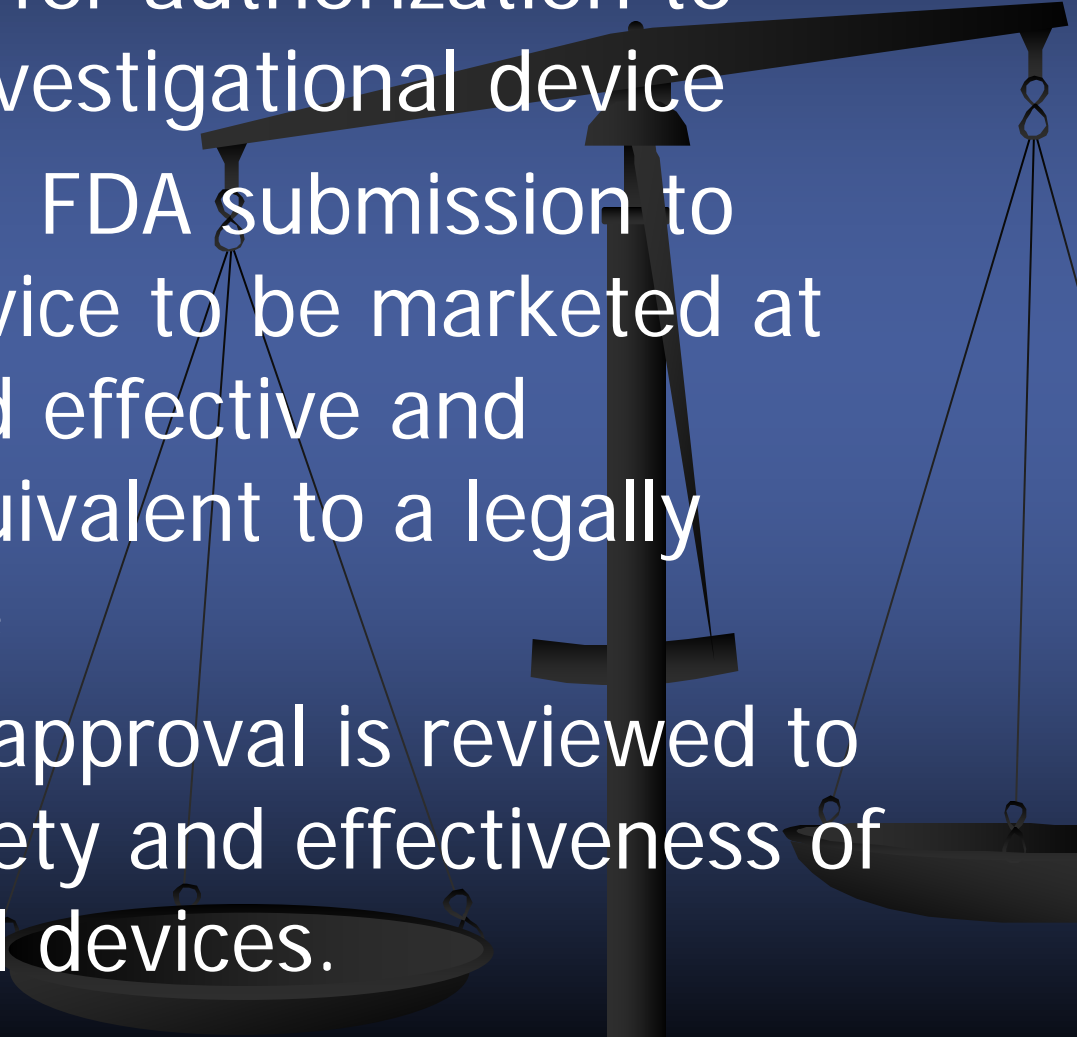


# Medical Devices Classification

- Class depends on intended use, indications for use and risk
- Grouped into 16 panels, some 1700 types
- Class I : general controls, tongue depressor
- Class II : performance standards, infusion pump
- Class III : premarket approval, cardiac heart pacer.



# Medical Devices Registration

- IDE is a request for authorization to administer an investigational device
  - 510K premarket FDA submission to demonstrate device to be marketed at least as safe and effective and substantially equivalent to a legally marketed device
  - PMA Premarket approval is reviewed to evaluate the safety and effectiveness of Class III medical devices.
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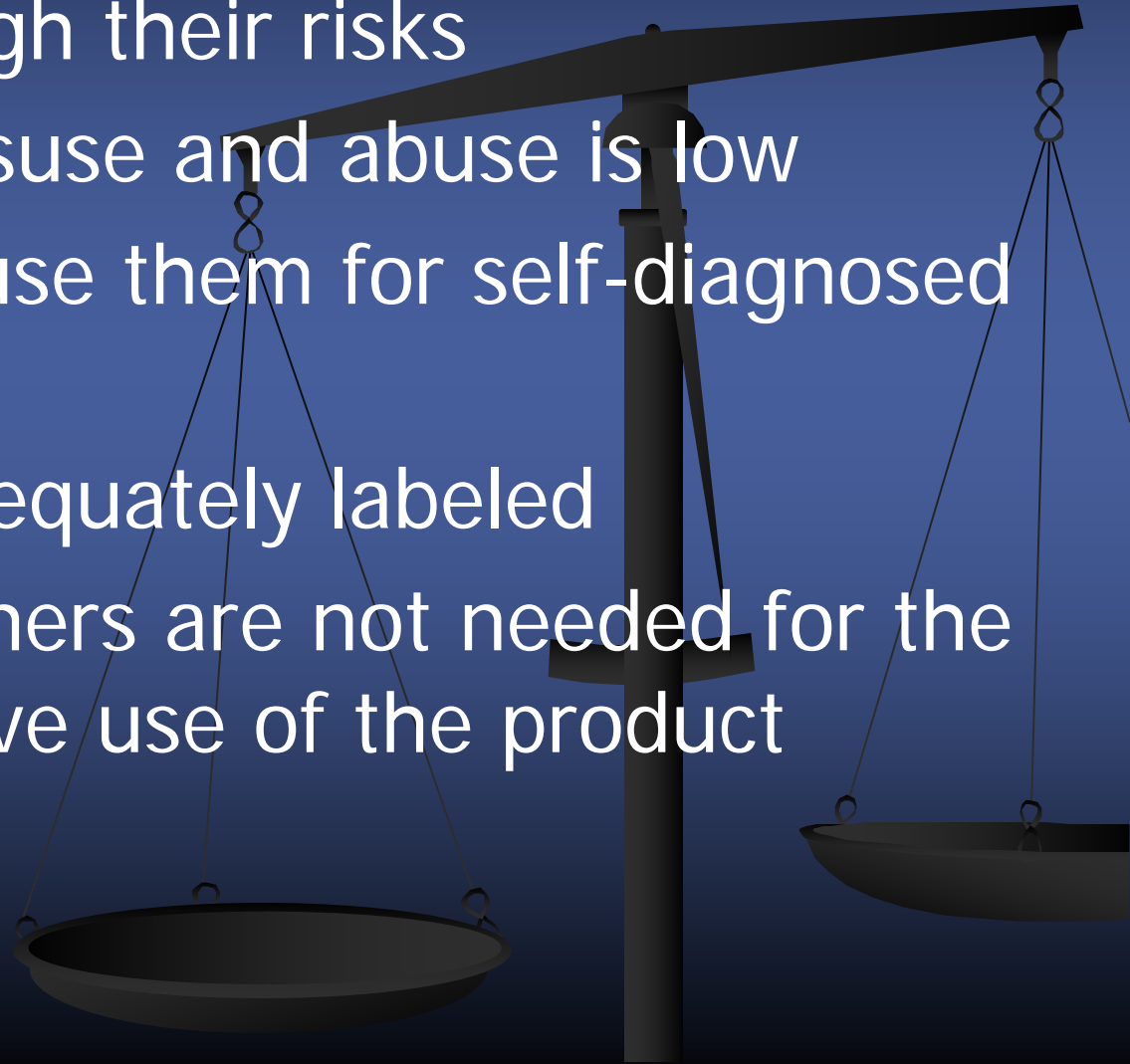
# Drug Registration



- IND Investigational New Drug Application is a request for authorization from the FDA to administer an investigational biological product to humans
- NDA New Drug Application application to market a new drug product
- 505b2 application to market a modified drug product
- ANDA application to market a generic drug
- OTC

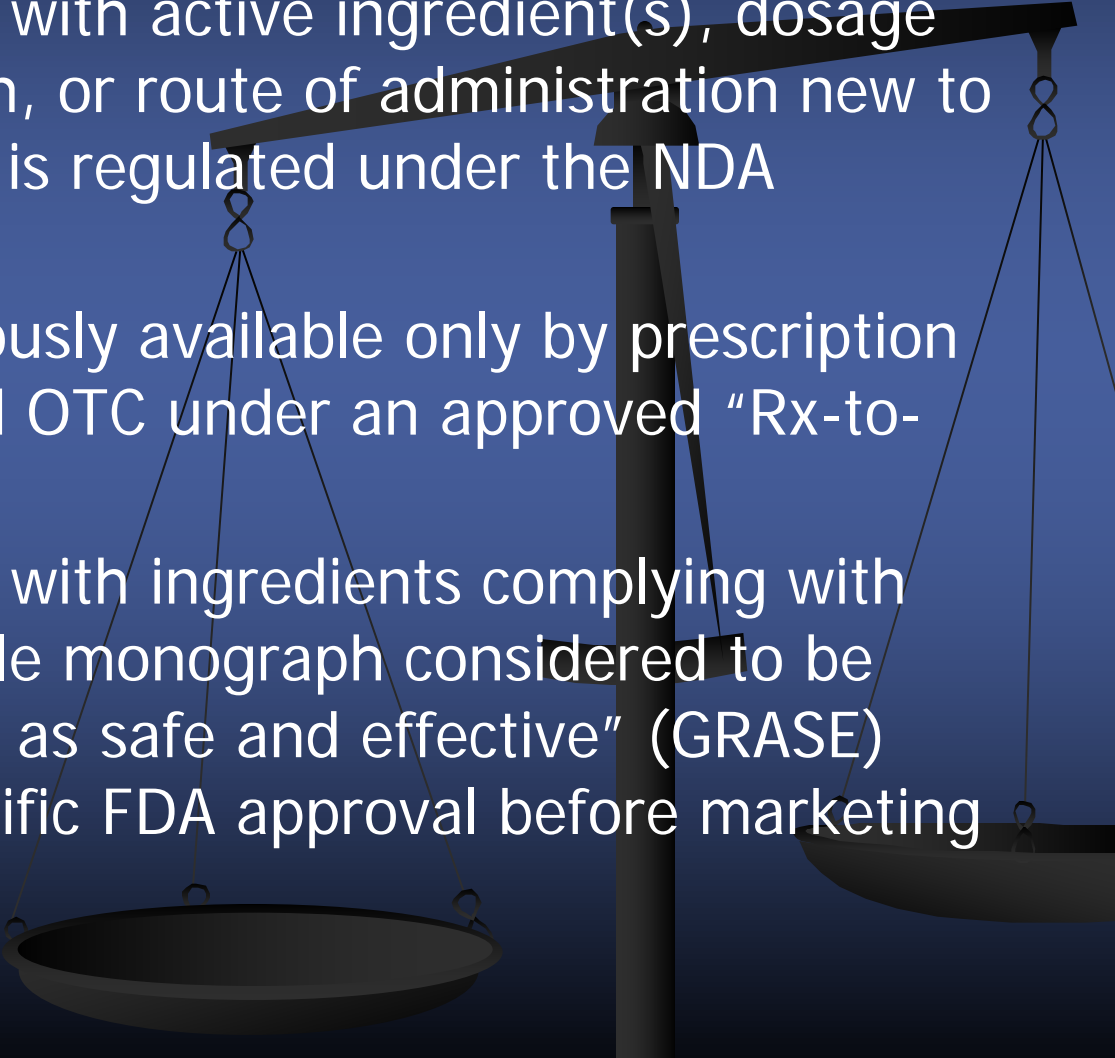
# OTC Drugs

- Benefits outweigh their risks
- Potential for misuse and abuse is low
- Consumer can use them for self-diagnosed conditions
- They can be adequately labeled
- Health practitioners are not needed for the safe and effective use of the product





# OTC Registration

- An OTC drug product with active ingredient(s), dosage form, dosage strength, or route of administration new to the OTC marketplace is regulated under the NDA process
  - A drug product previously available only by prescription (Rx) can be marketed OTC under an approved “Rx-to-OTC switch” NDA
  - An OTC drug product with ingredients complying with standards of applicable monograph considered to be “generally recognized as safe and effective” (GRASE) does not require specific FDA approval before marketing
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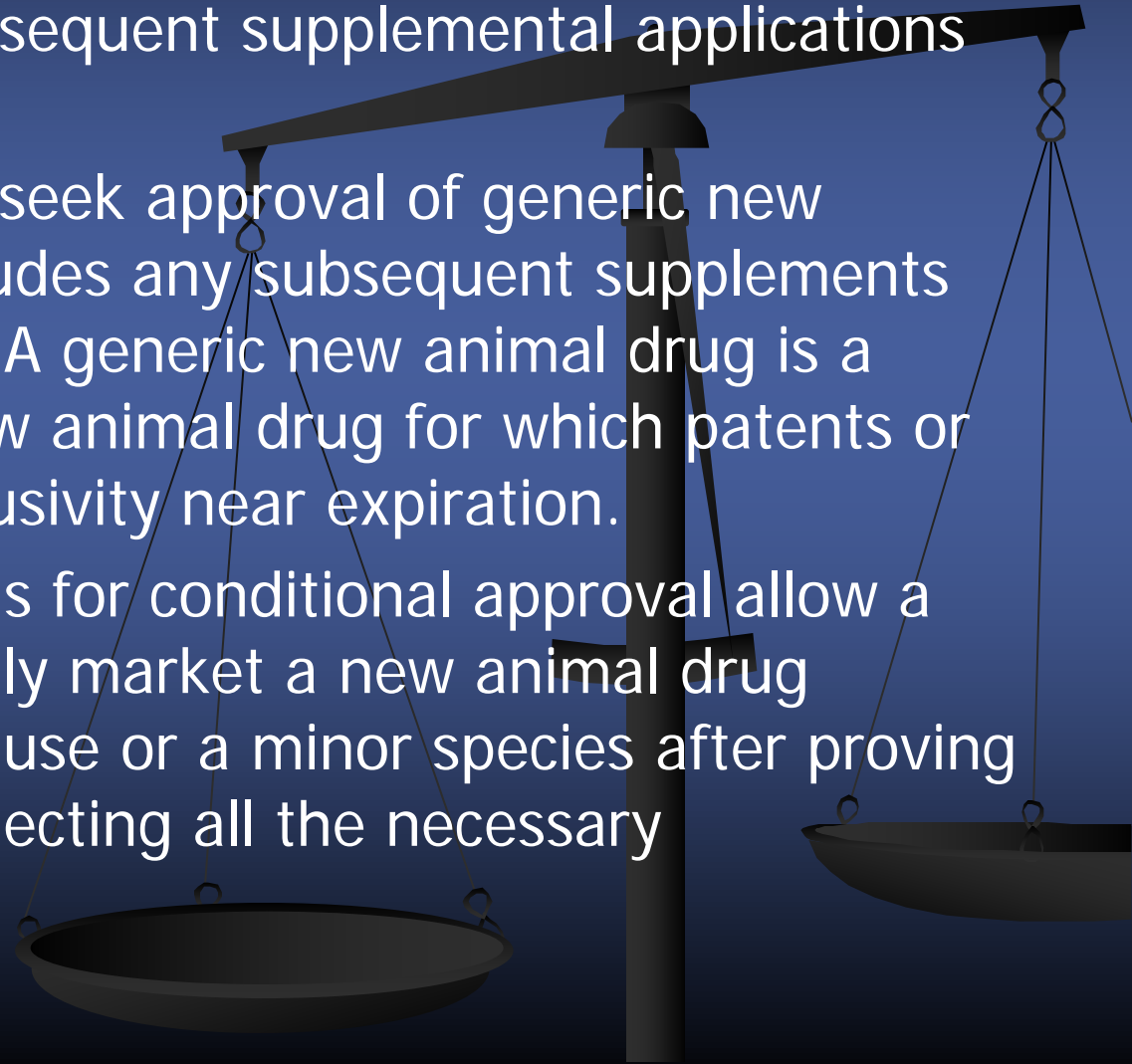
# Biologics



- IND An Investigational New Drug Application is a request for authorization from the FDA to administer an investigational biological product to humans
- BLA The Biologics License Application is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

# Animal and Veterinary

- **NADA** - Is used to seek approval of new animal drug and includes any subsequent supplemental applications made to an approval
- **ANADA** - Is used to seek approval of generic new animal drug and includes any subsequent supplements to approved ANADA. A generic new animal drug is a copy of approved new animal drug for which patents or other periods of exclusivity near expiration.
- **CNADA** - Applications for conditional approval allow a drug sponsor to legally market a new animal drug intended for a minor use or a minor species after proving it safe but before collecting all the necessary effectiveness data



# DEVELOPMENT PROCESS

- Pre-Clinical
- Phase 0
- Phase 1
- Phase 2
- Phase 3
- Phase 4

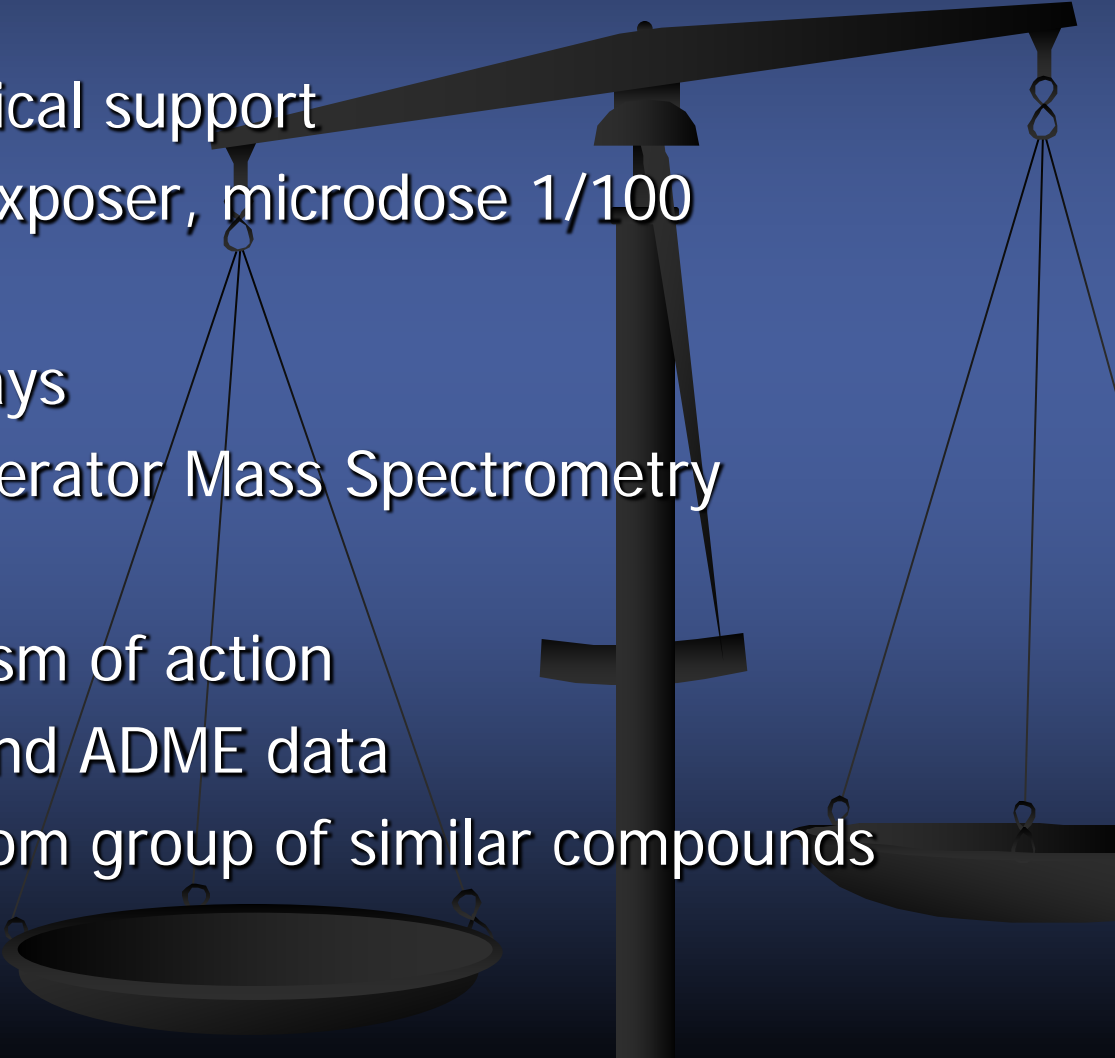


# Pre-Clinical

- Toxicology
- ADME
- Bioavailability/Pharmacokinetic Studies
- POC



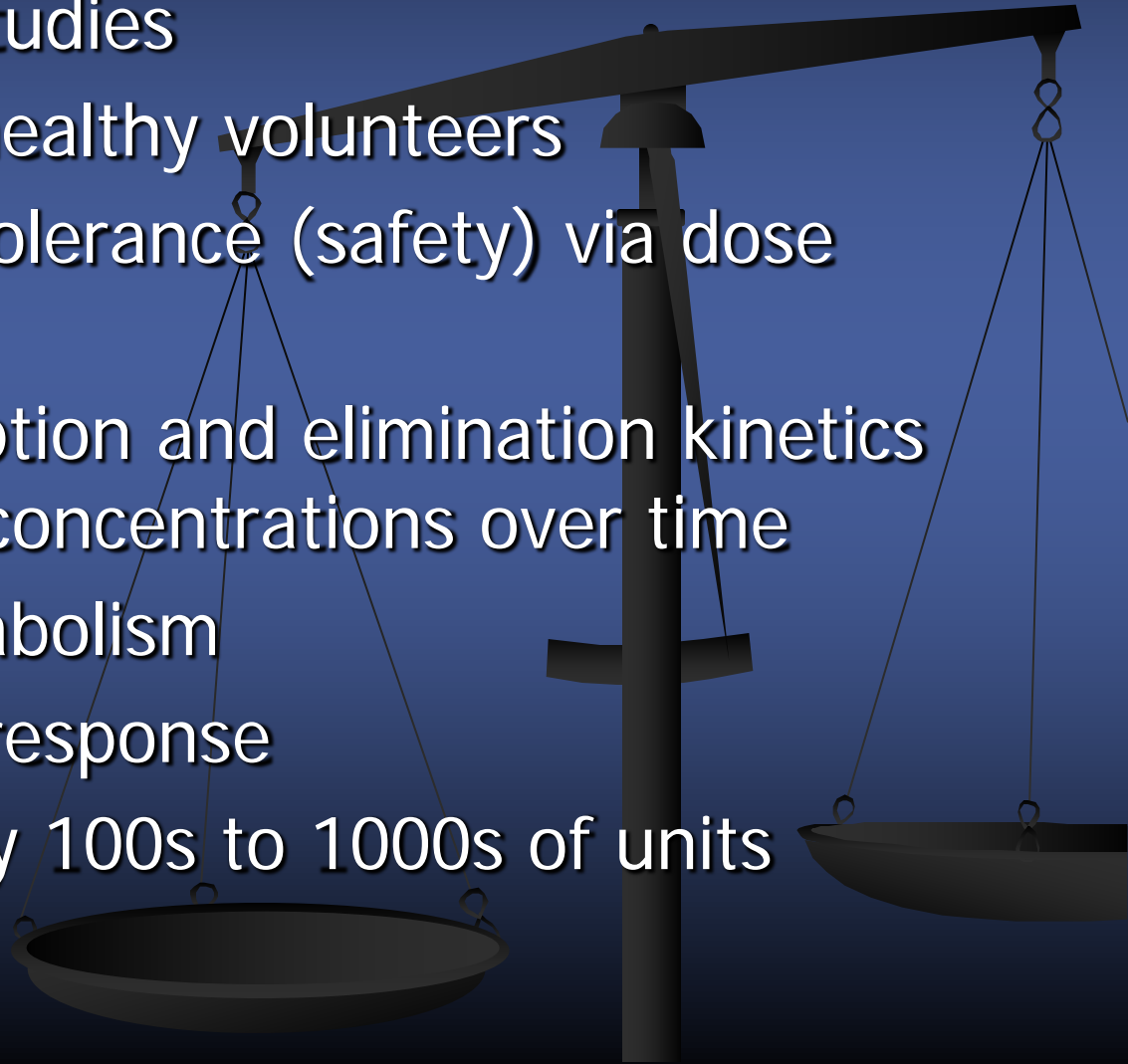
# Phase 0

- Exploratory IND
  - Requires less pre-clinical support
  - Very limited human exposure, microdose 1/100
  - No therapeutic intent
  - Short duration < 7 days
  - Requires use of Accelerator Mass Spectrometry
  - Used to:
    - Elucidate mechanism of action
    - Provide early PK and ADME data
    - Select lead NCE from group of similar compounds
- 



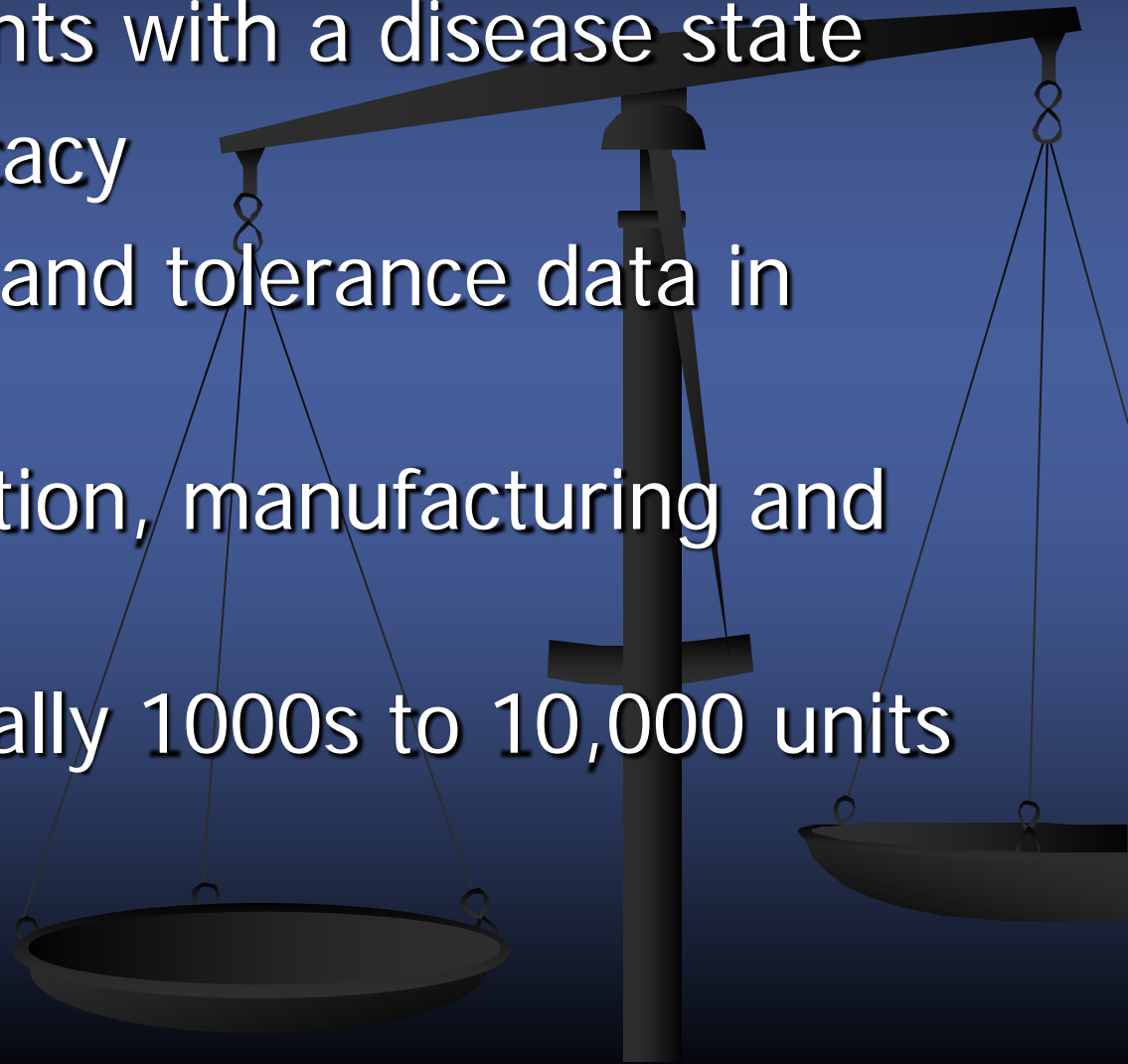
# Phase 1

- First-in- Human Studies
- Typically normal healthy volunteers
- Establishes drug tolerance (safety) via dose escalation
- Establishes absorption and elimination kinetics and drug plasma concentrations over time
- Defines drug metabolism
- Determines dose response
- Batch size typically 100s to 1000s of units

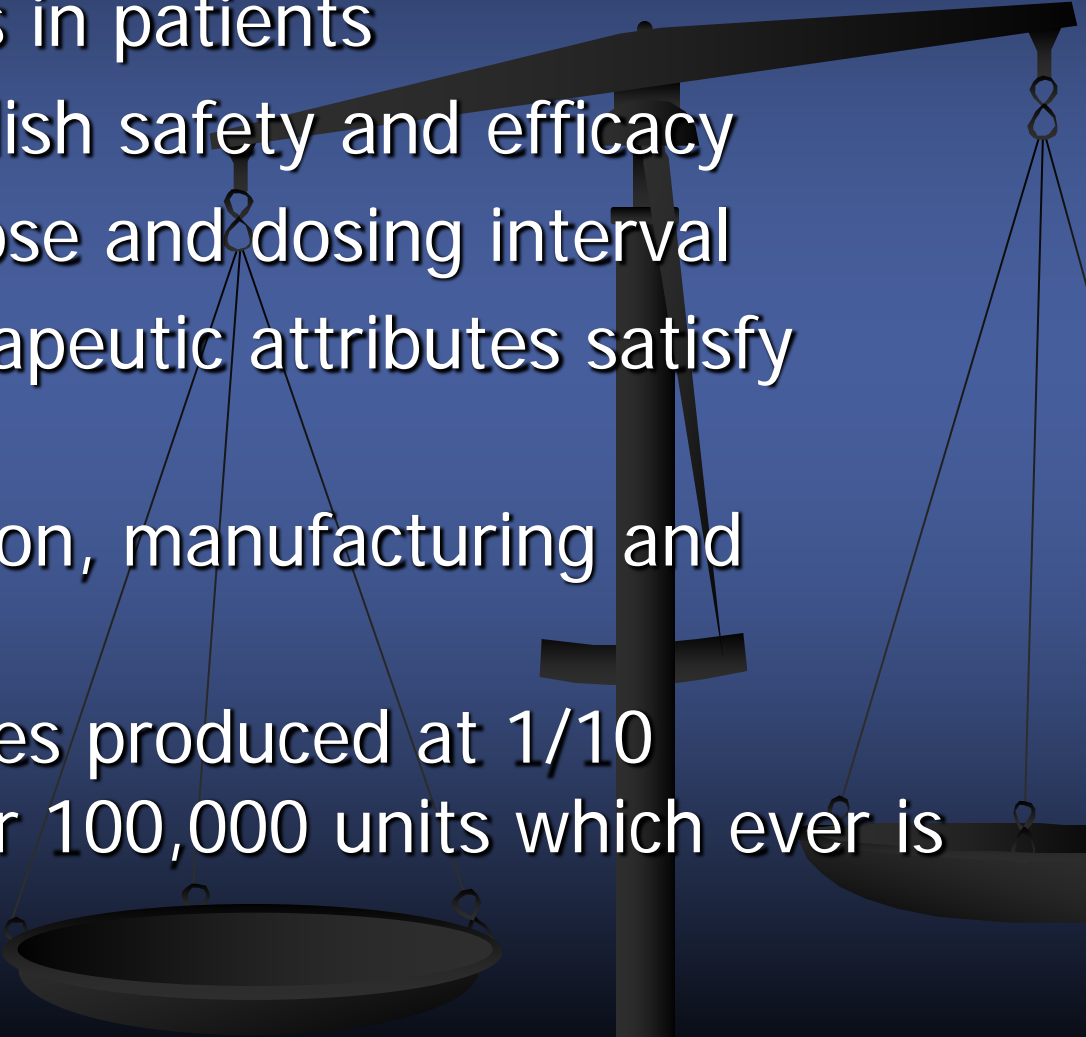


# Phase 2


- Studies in patients with a disease state
- Establishes efficacy
- Provides safety and tolerance data in patients
- Solidify formulation, manufacturing and controls
- Batch size typically 1000s to 10,000 units



# Phase 3

- Broad clinical trials in patients
  - Designed to establish safety and efficacy
  - Defines optimal dose and dosing interval
  - Determines if therapeutic attributes satisfy market need
  - Finalized formulation, manufacturing and controls
  - Registration batches produced at 1/10 production scale or 100,000 units whichever is greater\*
- 

# Phase 4

- Clinical studies conducted post market approval
  - Commitment in writing to FDA
  - Can be used for a variety of reasons:
    - To establish long-term efficacy and adverse events
    - New indication
    - New or specific patient population
    - Drug/Drug comparison
    - Drug/Drug interaction
- 

# cGMP

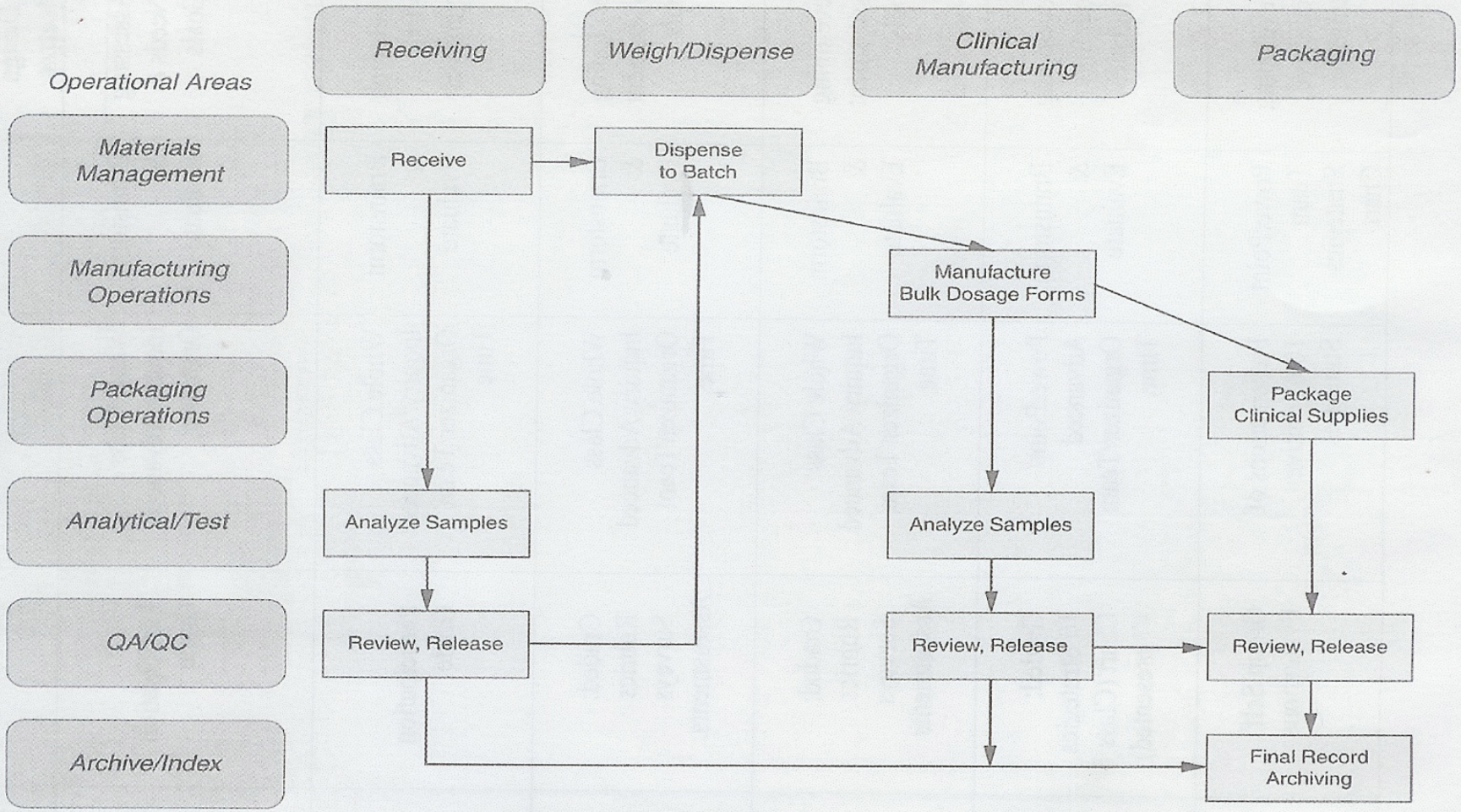


- Good Manufacturing Practices (GMPs) are required for clinical trial material and commercial manufacturing, not so for Pre-clinical
- Equipment must be IQ/OQ/PQ and swabbed before use
- Analytical Methods must be validated appropriate to the Clinical Phase
- All materials used in preparing CTM must be tested against specifications as well as the final product
- QA reviews MBR/PBR and release testing results before issuing C of A



# CTM Process Flow Schematic

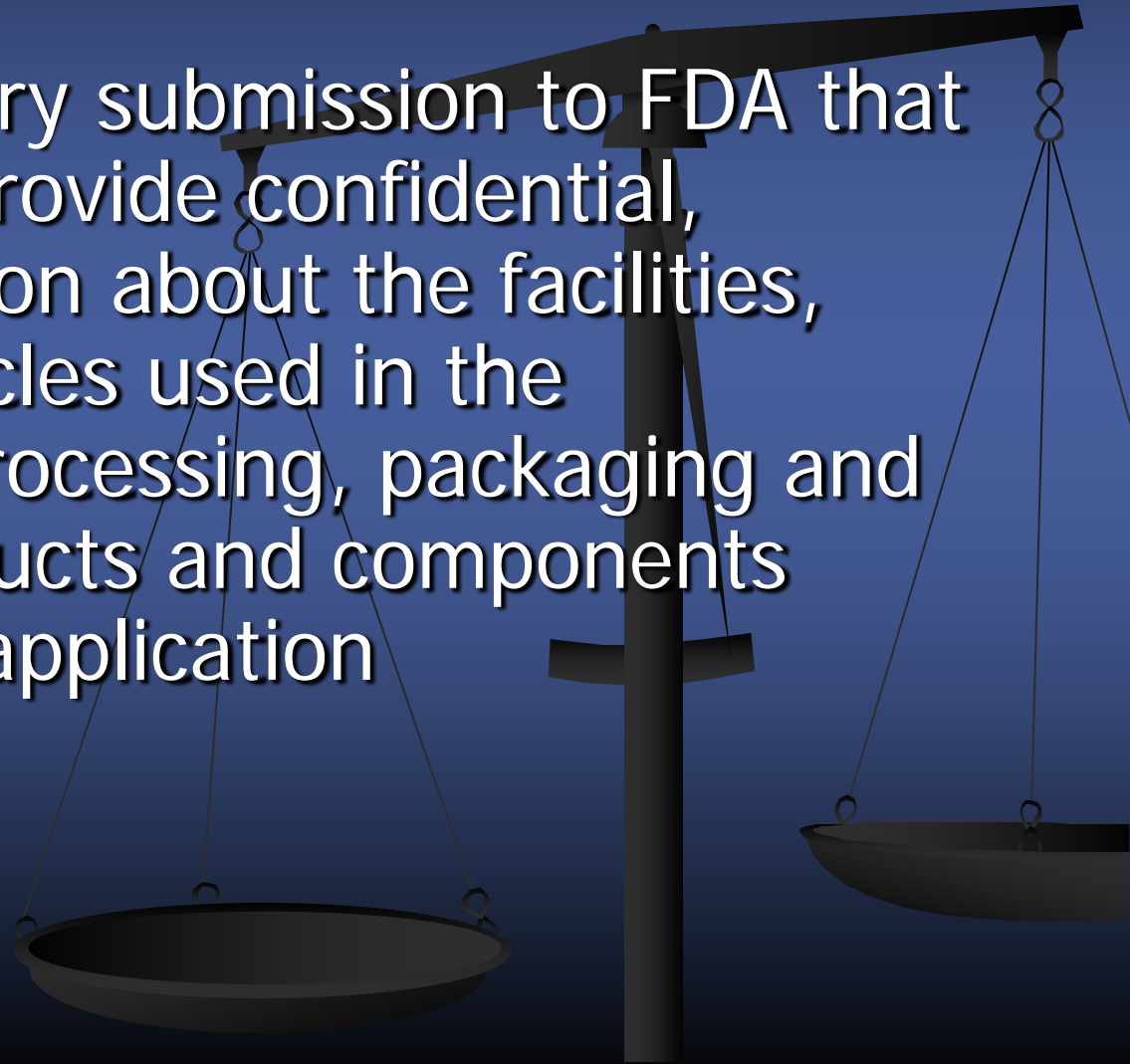
Operational Activities Over Time →



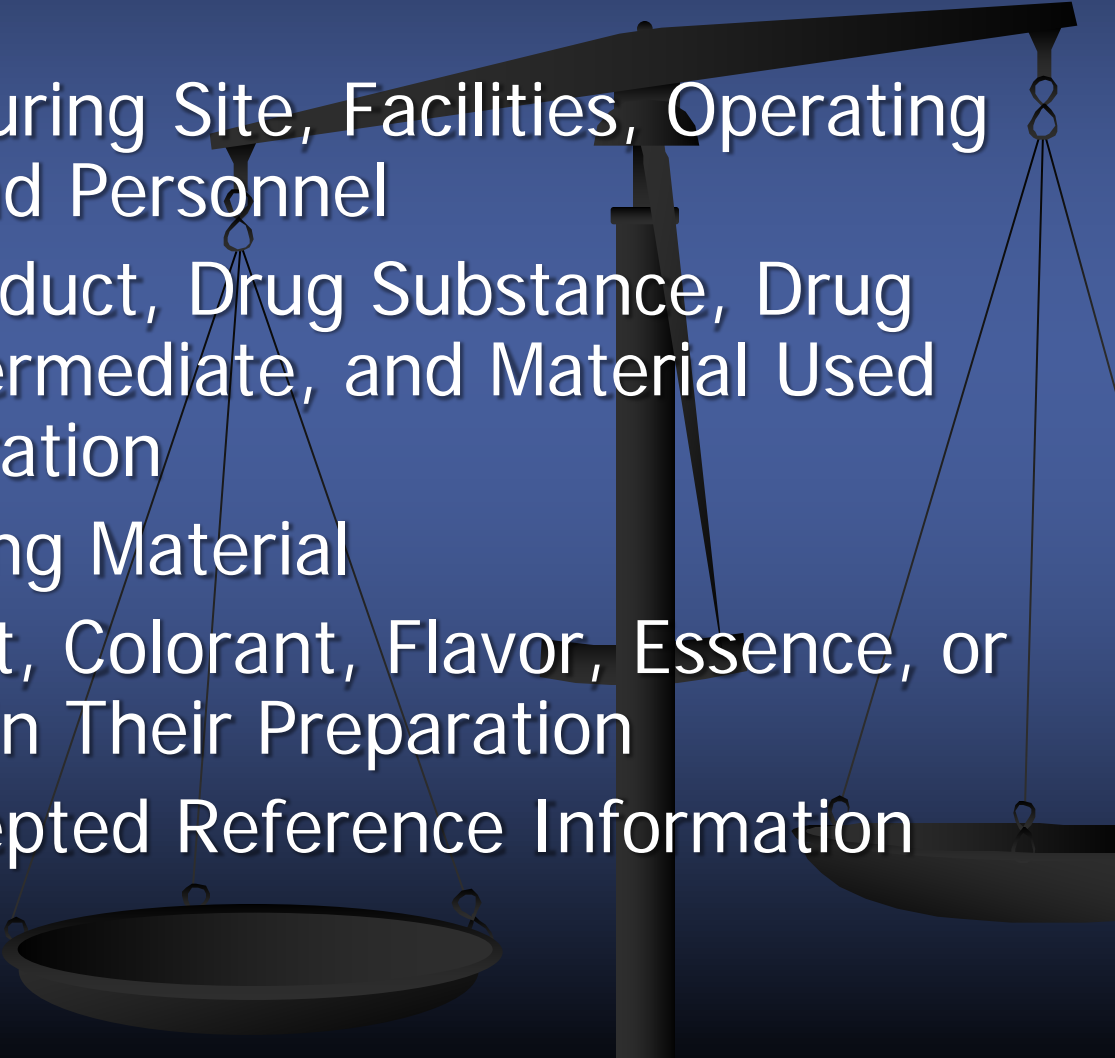


# DMF (Drug Master File)

DMFs is a voluntary submission to FDA that may be used to provide confidential, detailed information about the facilities, processes, or articles used in the manufacturing, processing, packaging and storing drug products and components referenced in an application

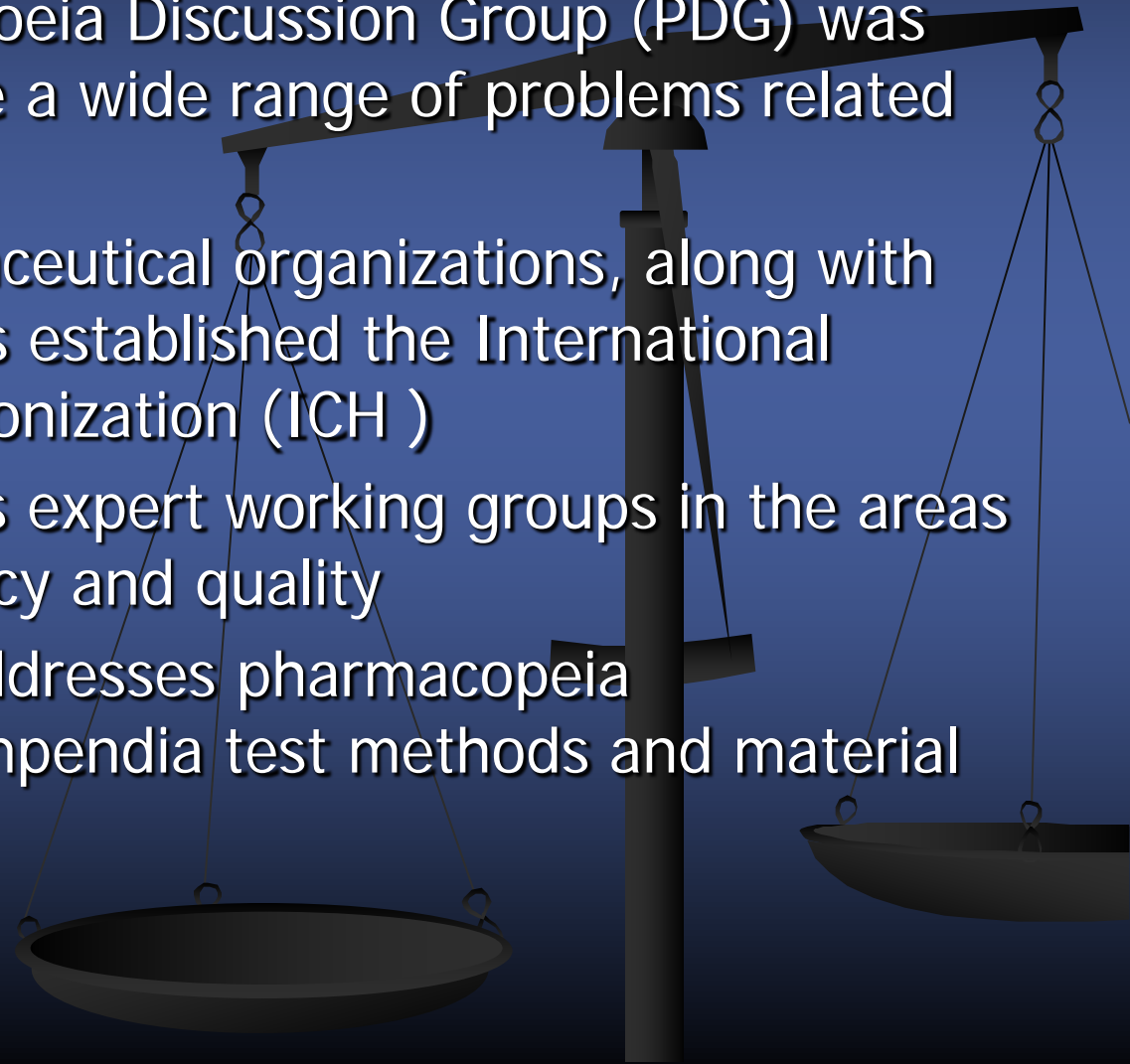


# DMF Classifications

- *Type I* : Manufacturing Site, Facilities, Operating Procedures, and Personnel
  - *Type II* : Drug Product, Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation
  - *Type III* : Packaging Material
  - *Type IV* : Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
  - *Type V* : FDA Accepted Reference Information
- 

# ICH and Harmonization

- 1989 the Pharmacopoeia Discussion Group (PDG) was formed to investigate a wide range of problems related to pharmacopoeia
- 1990 various pharmaceutical organizations, along with regulatory authorities established the International Conference on Harmonization (ICH )
- It established various expert working groups in the areas of drug safety, efficacy and quality
- One of the groups addresses pharmacopoeia harmonization of compendia test methods and material monographs



# Important Organizations

- USP/NF [www.usp.org](http://www.usp.org)
- Ph. Eur. [www.europa.eu](http://www.europa.eu)
- FDA [www.fda.gov](http://www.fda.gov)
- EMEA [www.ema.europa.eu](http://www.ema.europa.eu)
- PDG [www.pdgroups.org](http://www.pdgroups.org)
- ICH [www.ich.org](http://www.ich.org)
- IPEC [www.ipecamericas.org](http://www.ipecamericas.org)



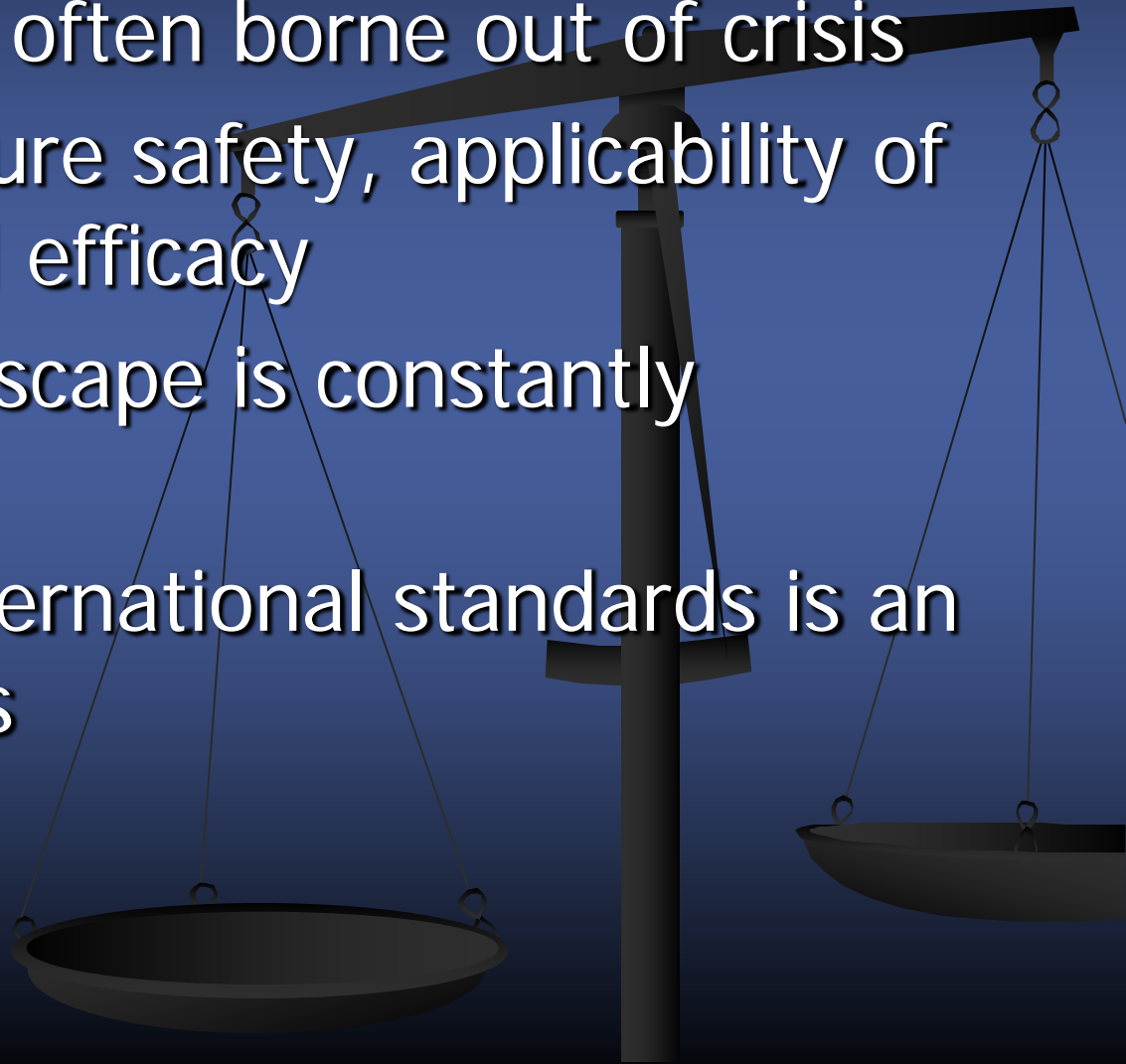
# Regulatory Listings



- FDA's Inactive Ingredient database along with the approved dosage forms and concentrations  
[www.fda.gov/cder/drug/iig/inact1.pdf](http://www.fda.gov/cder/drug/iig/inact1.pdf)
- GRAS designation is for those materials that have been shown to be safe by way of a food additive petition or GRAS notification [www.cfsan.fda.gov/~dms/eafus.html](http://www.cfsan.fda.gov/~dms/eafus.html)
- Colors: Synthetics use, specifications and restrictions found in 21 CFR Parts 74, 81 and 82
  - Permanently listed: 21 CFR 74
  - Provisionally Listed: 21 CFR 82
  - Exempt: 21 CFR 73
- Flavors
  - Natural: 21 CFR Parts 182.10, 20 and 40 and Parts 182 and 172.50
  - Artificial: 21 CFR parts 172.515 and 182.60

# Summary

- Regulations are often borne out of crisis
- Designed to insure safety, applicability of use, quality and efficacy
- Regulatory landscape is constantly changing
- Harmonizing international standards is an ongoing process





Thank You

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