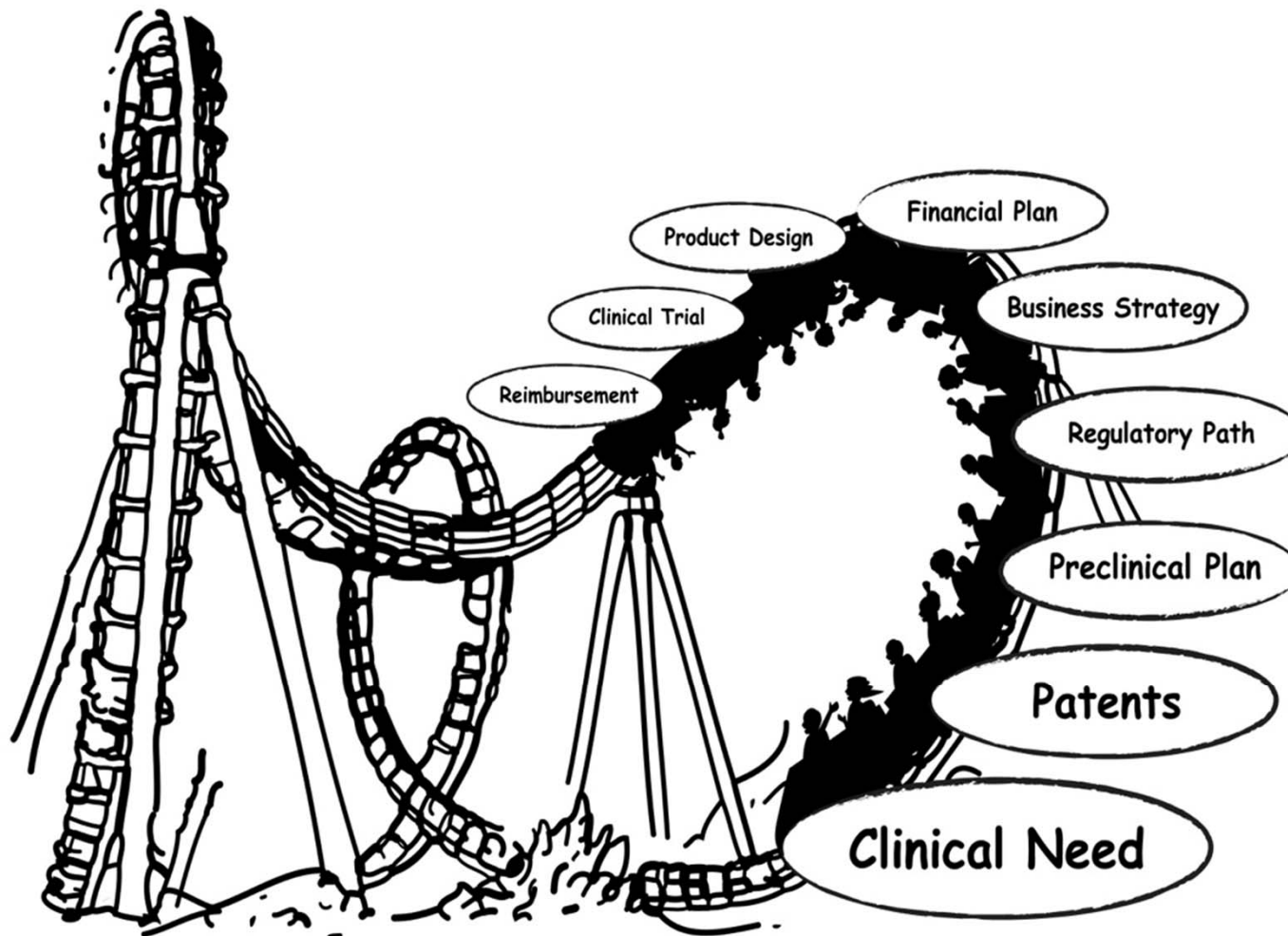


# Translational Medicine Symposium 2013: *The Roller Coaster Ride to the Clinic*





# Translational Medicine Symposium 2013

## Preclinical Development

Bench to Business to Bedside:  
The Roller Coaster Ride to the Clinic

# Introductions

- Moderator:
  - Barbara Wirostko (Moran Eye Institute, Jade Therapeutics)
- Panelists:
  - Robert Selliah (American MedChem Nonprofit Corporation)
  - Alan Mueller (Navigen)



# Discussion Points

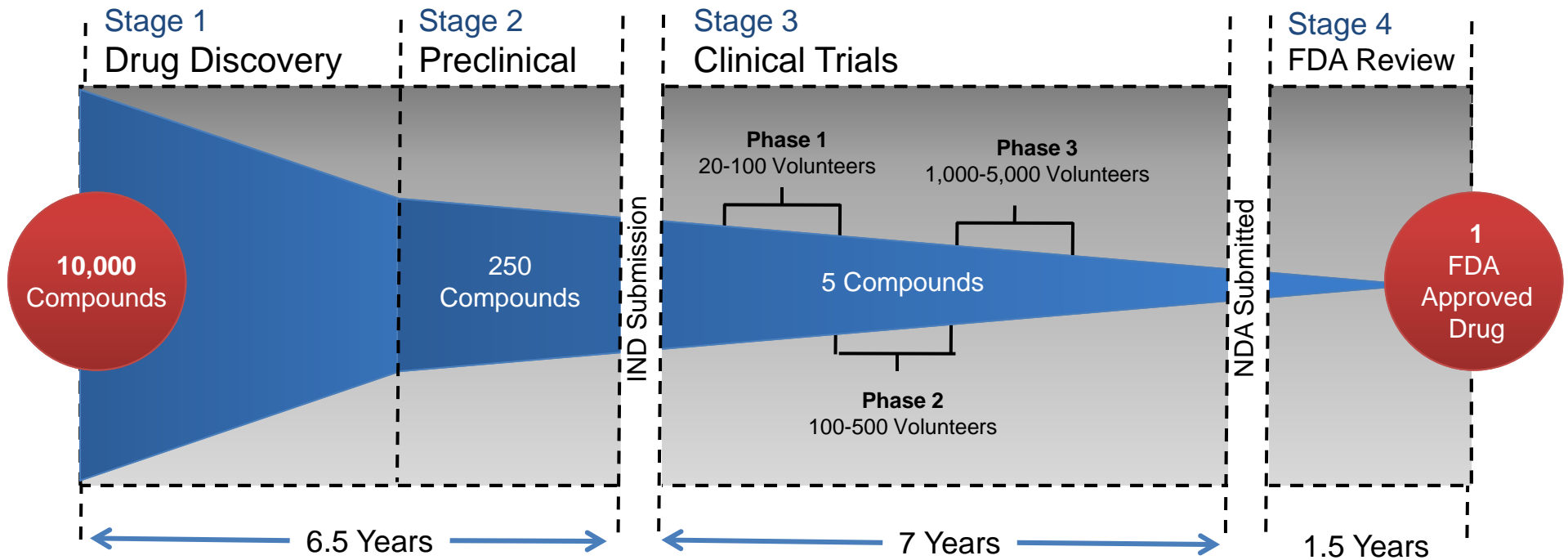
- Diseases, Mechanisms, Signaling Pathways & Targets
- Drug Discovery toward Preclinical Candidate Selection
- IND enabling Studies toward IND Filing & Clinic

# Drug Discovery and Development



- How are drugs discovered and developed?

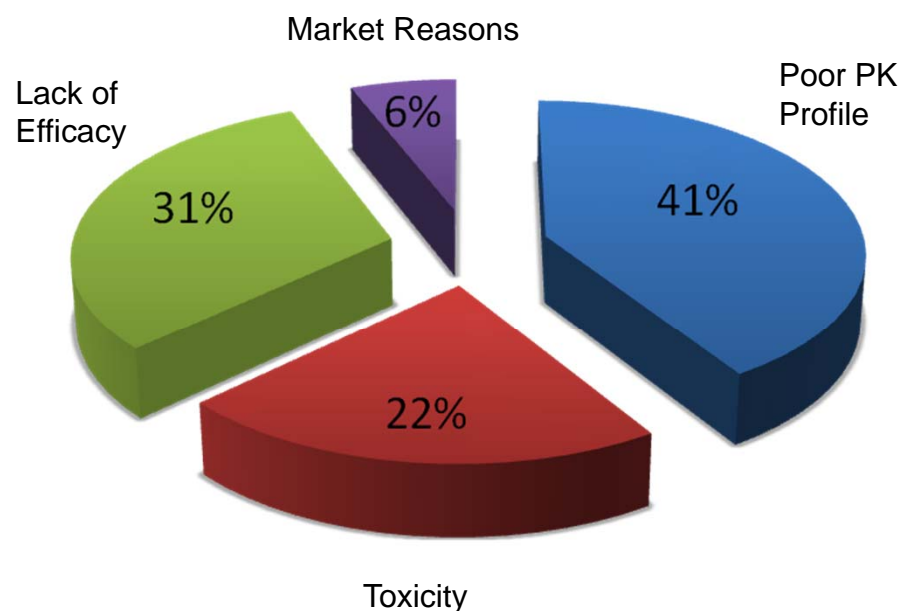
# A Slow and Costly Process



Source: Pharmaceutical Research and Manufacturers of America

# Why Compounds Fail or Slow Down in Development

## FAILURE



## SLOWED DEVELOPMENT

- Synthetic Complexity
- Low Potency
- Ambiguous Toxicity Finding
- Inherently Time-Intensive Target Indication
- *Poor Biopharm Properties*

Tufts Center for the Study of Drug Development, Tufts University

# Drug Discovery to IND

Target Identification and Validation	Hit Identification	Lead Identification	Lead Optimization	Preclinical Development
Molecular target proposed/identified	High-Throughput Screening of compound library	Medicinal chemistry effort to turn "hits" into "leads"	Extensive med chem to improve potency and selectivity	GLP-compliant toxicology and PK studies
Biological hypothesis relevant to disease	Virtual or <i>in silico</i> screening	Potency and selectivity	<i>In vivo</i> efficacy in additional models	GLP-compliant safety pharmacology studies
Genetic models to demonstrate proof of concept	Confirm potency and selectivity of "hits" in 1 <sup>o</sup> and 2 <sup>o</sup> assays	<i>In vitro</i> PK: CYP inhibition, metabolic stability	<i>In vivo</i> PK characterization	Drug formulation
	Initial <i>in vitro</i> pharmacokinetic (PK) assessment	<i>In vivo</i> efficacy in relevant animal models of disease	Initial dose-ranging toxicology studies	Pre-IND meeting with FDA



# Identifying Drug Targets



- Drug Targets
  - Enzymes, receptors, protein-protein interactions (e.g gene, key enzyme, receptor, ion-channel, nuclear receptor)
  - Biological system, signaling pathways

# Discovery Biology

- Disease of Interest (unmet medical need): understand the mechanism of disease and its progression
- Identify a viable therapeutic target and validate
  - Knock-out studies in whole cell or animal models
  - RNAi, antibodies, tool compounds
- Develop and validate robust biological assays for testing compounds
  - Whole cell, transformed cells, cell-free biochemical

# Screening for Hit Identification

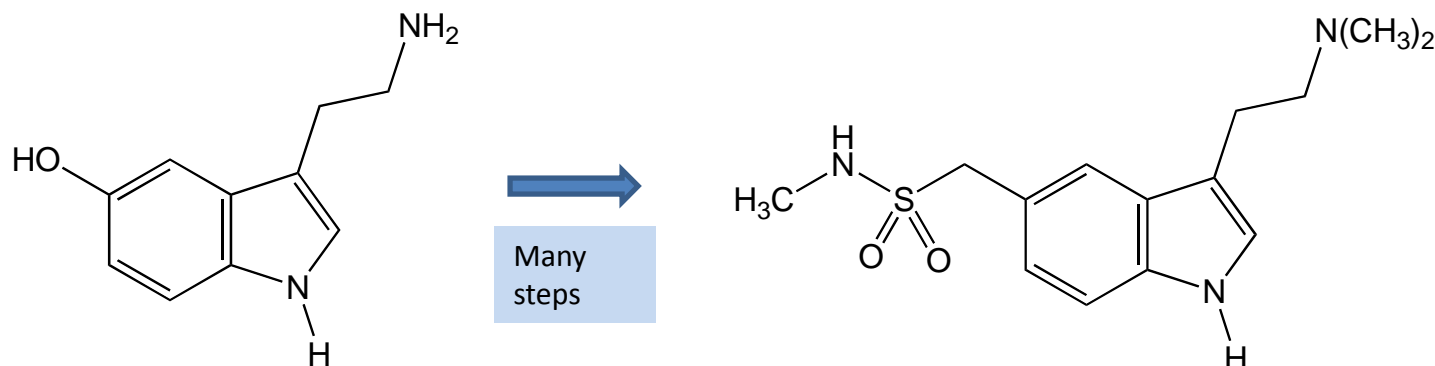


- State-of-the-art technology is available to screen large libraries of compounds against various types biological assays
- Compounds which affect the assay in a favorable manner are called “Hits”
- Each set of hits are tested separately against the target assay to identify validated hits

# Discovery Chemistry or Medicinal Chemistry – Iterative Process

- Start with hits and create lead compounds (a.k.a., Hit-to-Lead, H2L)
  - Synthesize and test analogs of hits to optimize certain properties: biological activity (potency), identify off target effects, selectivity (related or unrelated targets to avoid side effects or toxicity)
  - Use drug design to create novel compounds and optimal compounds
    - Computer-aided drug design (CADD)
    - Intuitive drug design based on medicinal chemistry experience
  - Novel compounds could result in valuable intellectual property (IP)
- *In vitro* ADME characterization of optimized compounds
- Explore proof of concept efficacy in animal models (non GLP)

# Another Way to Find Leads – Modify Existing Active Compound



**5-Hydroxytryptamine (5-HT)**  
Serotonin (a natural neurotransmitter synthesized in certain neurons in the CNS)

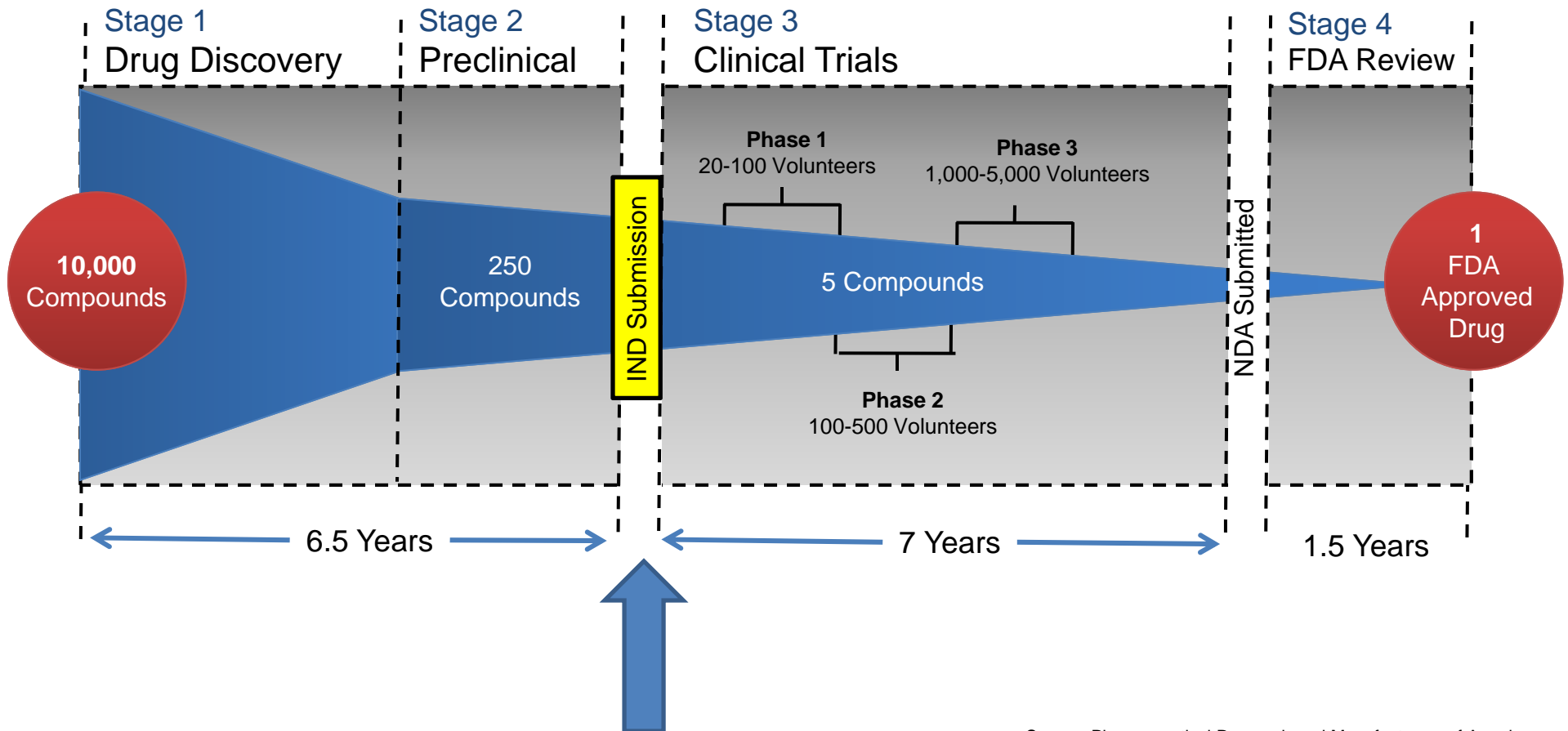
**Sumatriptan (Imitrex)**  
Used to treat migraine headaches known to be a 5-HT<sub>1</sub> agonist

- Design structural changes and create compounds to:
  - Improve biological activity and selectivity for the target
  - Eliminate side effects
  - Carve out patent space (IP)
  - Improve physicochemical properties
  - Improve therapeutic index (TI) (effectiveness vs. unfavorable side effects)

# Lead Optimization – Iterative Process

- Identify optimal compound(s) for preclinical studies with favorable parameters
  - synthetic scalability
  - *in vitro* potency and selectivity
  - In vivo efficacy in proof of concept and diseases models
  - toxicology (dose-ranging toxicology studies in vivo)
  - patentability
  - In vivo pharmacokinetics (PK: half-life, C<sub>max</sub>, T<sub>max</sub>, etc)
  - *in vitro* ADME characterization
  - Optimal mode of delivery
- Highly collaborative work with pharmacology, toxicology, biology, process chemistry, patent law, etc

# Goal - Get to an IND Application (Investigational New Drug)



Source: Pharmaceutical Research and Manufacturers of America



# IND process

- What is an IND
- What are GXP criteria
- FDA expectations
- Real life example



# Investigational New Drug Application (IND)

Primary goal - present the data package to the FDA to allow the initiation of the clinical program:

- To present data to justify that the compound exhibits pharmacological activity to meet an unmet need,
- To support the product being reasonably safe for initial use in humans,
- To justify exposing humans to reasonable risks when used in limited, early-stage clinical studies.

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA Guidances for Investigational New Drugs](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA%20Guidances%20for%20Investigational%20New%20Drugs)

# IND (Investigational New Drug) Application

The IND application must contain information in three broad areas:

Manufacturing Information (GMP) - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

Animal Pharmacology and Toxicology Studies (GLP) - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

Clinical Protocols and Investigator Information (GCP)- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators - professionals (generally physicians) who oversee the administration of the experimental compound - to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA Guidances for Investigational New Drugs](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA%20Guidances%20for%20Investigational%20New%20Drugs)

# GxP Criteria

Quality systems and requirements (quality control and assurance (QC and QA)) that have been put into place to ensure the uniformity, consistency, reliability, quality and integrity of the product manufacturing, toxicology and clinical trial conduct.

- GMP – Good Manufacturing Practice
- GLP – Good Laboratory Practice
- GCP – Good Clinical Practice

Code of Federal Regulations (CFR 21)

<http://www.fda.gov/ScienceResearch/SpecialTopics>

# IND Enabling Preclinical Studies

- Efficacy pharmacology (animal models)
- Safety pharmacology
- General toxicology – oral and specific route of administration
- Genetic toxicology (geno tox)
- Pharmacokinetics (PK- local and systemic)
- ADME (absorption, distribution, metabolism, excretion)
- Reproductive toxicology
- Carcinogenicity ( ask for a waiver based on genotox)
- Special studies

# IND Enabling Studies Needed

- Will determine with FDA during the pre IND meeting
- What studies are needed – dependent on product & indication
  - Who are the patients ?
  - What is the unmet need ?
  - What is the expected dosing – acute or chronic?
  - Where will it be delivered – systemic or local?
- Need to demonstrate safety preclinically for that First in Human Study (FIH)

# Ophthalmology: topical NCE

- NCE (new chemical entity) for glaucoma
- First study was a 28 day study in subjects WITH glaucoma > 45 yrs of age
  - Systemic safety – Oral in 2 species
  - Local tolerability for 28 days in 2 species
  - NCE – genotox studies (DNA damage)
  - Older population (No reprotox for the first studies)
  - Carcinogenicity studies during clinical development
  - Chronic tox AHEAD of the longer phase 2/3 studies



# Conclusion

- Drug discovery from target identification to IND filing is a long process
- Highly collaborative work – expertise comes from biology, genetics, medicinal chemistry, pharmacology, toxicology, process chemistry, computational design & regulatory
- Yet, this is how we discover drugs which help heal patients, provide comfort, reduce pain, and allow for longer and improve quality of life

# Q & A





# Finding the Lead (cont.)

## Enhance a side effect



# Pharmacology

- In Vivo animal models to demonstrate efficacy
  - Efficacy studies are conducted more for candidate selection/ prioritization
- Understanding the pharmacology impacts interpretation of toxicology studies

# Safety Pharmacology

- Investigate potential undesirable pharmacodynamic effects on the physiological function of vital organs
  - Generally given at higher than indicated dose orally
- Core battery
  - Cardiovascular system
  - Respiratory system
  - Central nervous system

# General Toxicology

- Pivotal to determining whether the proposed clinical trial is safe to proceed
  - Identify toxicities (doses) to be avoided
  - Direct monitoring in the clinic
  - Calculate safety margins (exposure at the NOAEL/ clinical exposure)
- Species selection
- Dose selection
- Duration of administration
- Route of administration
- Endpoints

# General Toxicology

## Species Selection

- Two species including one rodent
  - Typically mouse or rat and dog or primate
- Metabolic profile should be similar to human
  - Rodent specific metabolite could lead to a positive genotox signal (clastogen or anagen)

# General Toxicology

## Dose Selection

- Selection 1
  - Dosing should be up to Maximum Tolerated Dose
  - Dosing should include a No Adverse Effect level (NOAEL)
  - Doses should be spaced so to allow a dose response assessment
  - Generally 3 dose groups and a control group
- Selection 2
  - Dosing should NOT be determined merely by multiples of the human dose
  - Dosing regimen can be adjusted to mimic human exposure
    - If  $t_{1/2}$  is shorter in animals than humans such that exposure with daily dosing is limited, give drug multiple times per day

# General Toxicology

## Duration of Dosing

- For initial clinical trials – (up to 2 weeks duration) 2 weeks toxicology studies needed
- For later clinical trials, animal studies must be of equal duration
  - Can be managed sequentially if preclinical is run staggered with clinical
    - Need to discuss with FDA

# General Toxicology

## Route of administration

- Same as clinical route
- If adequate systemic exposure cannot be achieved by the clinical route supplement with systemic dosing
  - There does exist evidence that Avastin gets into the systemic vasculature with ocular dosing



# General Toxicology

## Endpoints

- Mortality
- Clinical signs
- Body weight, temperature, activity level
- Hematology
- Clinical chemistry
- Toxicokinetics
- Pathology (complete battery of tissues)

# Genetic Toxicology

- Core battery of tests
  - Microbial mutation test (AMES)
  - In vitro mammalian chromosomal aberration or mouse lymphoma tk test
  - In vivo micronucleus test ( clastogen or anagen)
- First 2 submitted with initial IND
- Last test submitted prior to Phase 2
- Positive signal may lead to additional testing
- Data conveyed in the label

# Pharmacokinetics

- Parameters include AUC, C<sub>max</sub>, T<sub>max</sub>, t<sub>1/2</sub>, Cl, V<sub>d</sub>
- Exposure parameters allow comparisons to be made with clinical data so that safety margins can be calculated
- Single and repeat dose studies to address accumulation and induction of metabolism

# Reproductive Toxicology

- Three types of studies
  - Fertility and early embryonic development
  - Embryofetal development
  - Peri and post natal development
- Combined studies are acceptable but require complex designs
- Data will be conveyed in the drug label

# Carcinogenicity

- Performed for Chronic use drugs
  - Continuous use for 6 months or more
  - Chronic intermittent use
- Performed for drugs for which there is concern based on
  - Drug class
  - Structure activity relationship
  - Preneoplastic lesions identified in the tox studies
  - Long term tissue retention
- Long Studies - start early in clinical development

# IND (Investigation New Drug) Application

The following regulations apply to the IND application process:

21CFR Part 312 [Investigational New Drug Application](#)

21CFR Part 314 [INDA and NDA Applications for FDA Approval to Market a New Drug \(New Drug Approval\)](#)

21CFR Part 316 [Orphan Drugs](#)

21CFR Part 58 [Good Lab Practice for Nonclinical Laboratory \[Animal\] Studies](#)

21CFR Part 50 [Protection of Human Subjects](#)

21CFR Part 56 [Institutional Review Boards](#)

21CFR Part 201 [Drug Labeling](#)

21CFR Part 54 [Financial Disclosure by Clinical Investigators](#)

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA Guidances for Investigational New Drugs](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA%20Guidances%20for%20Investigational%20New%20Drugs)



## **Serendipity: a chance occurrence**

- Must be accompanied by an experimentalist who understands the “big picture” (and is not solely focused on his/her immediate research goal), who has an open mind toward unexpected results, and who has the ability to use deductive logic in the explanation of such results.
- Example: Penicillin discovery
- Example: development of Viagra to treat erectile dysfunction