Overview
Preclinical & IND-Enabling Studies

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COLLEGE OF PHARMACY

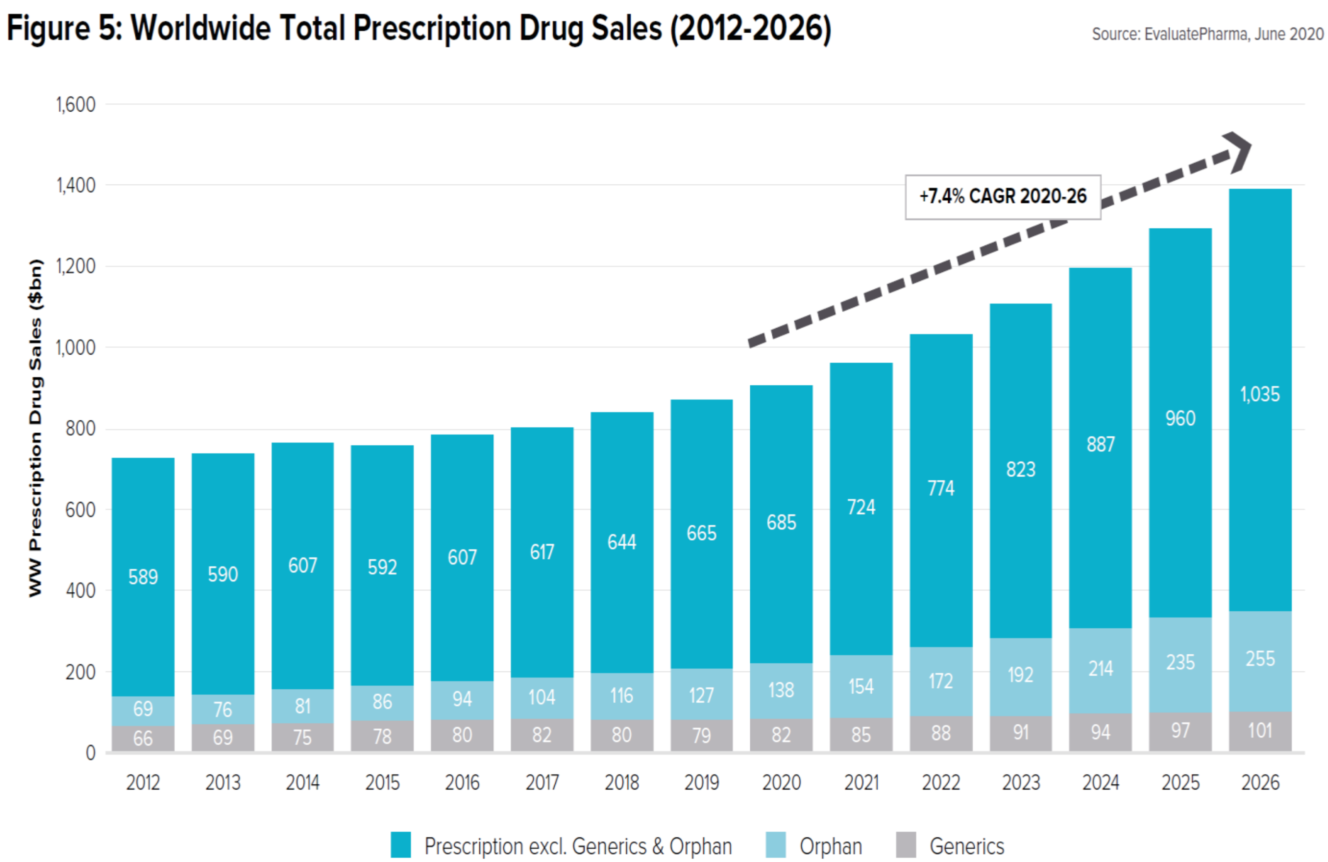
Learning Objectives

- Overall scope of drug product development: Bench top discovery to FDA product approval
- Regulatory milestones – IND & NDA
- IND – Key components
- IND-enabling preclinical studies

Evaluate Pharma
World Preview 2020, Outlook to 2026

Prescription drug sales expected to reach almost **$1.4 trn in 2026**.

Despite the COVID-19 pandemic causing near-term challenges across the healthcare sector, the industry **demand for innovative and effective therapies** continues to drive long-term growth.

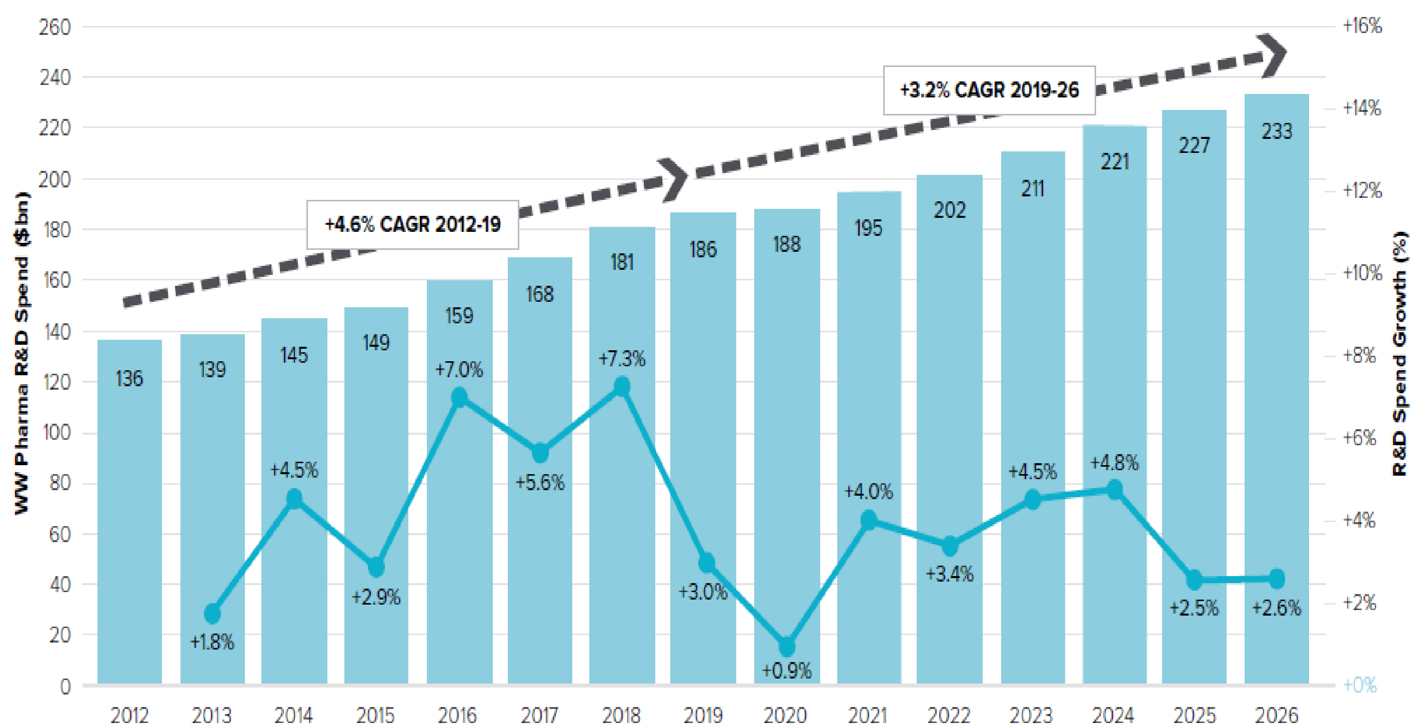


*CAGR: Compound Average Growth Rate

Evaluate Pharma, World Preview 2020, Outlook to 2026

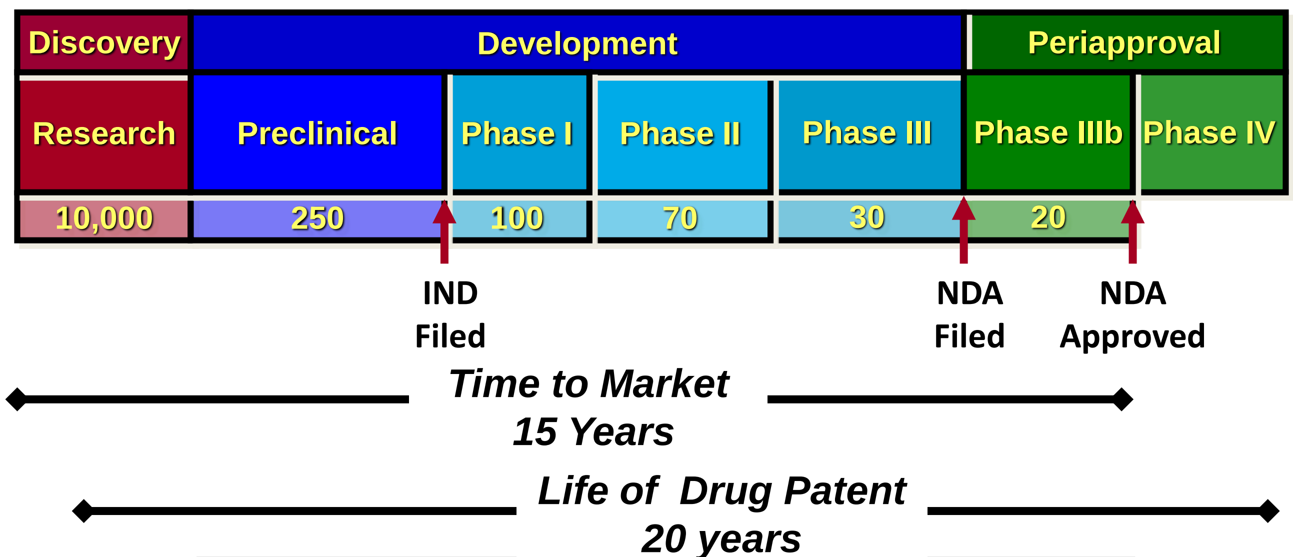
Figure 9: Worldwide Total Pharmaceutical R&D Spend in 2012-2026

Source: EvaluatePharma, June 2020



Evaluate Pharma, World Preview 2020, Outlook to 2026

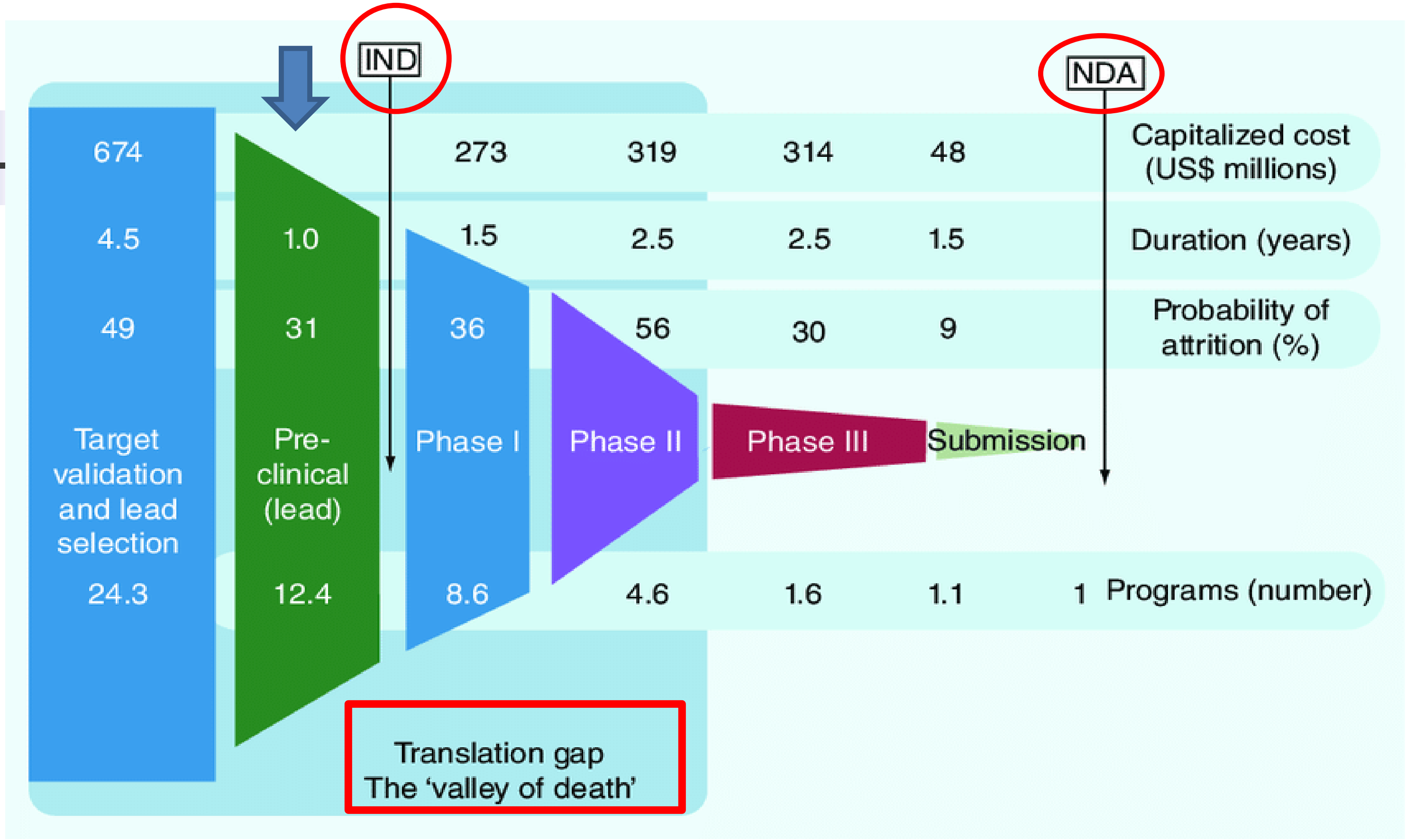
Drug Development Process
from Discovery to Market



The industry spends, on average, approximately

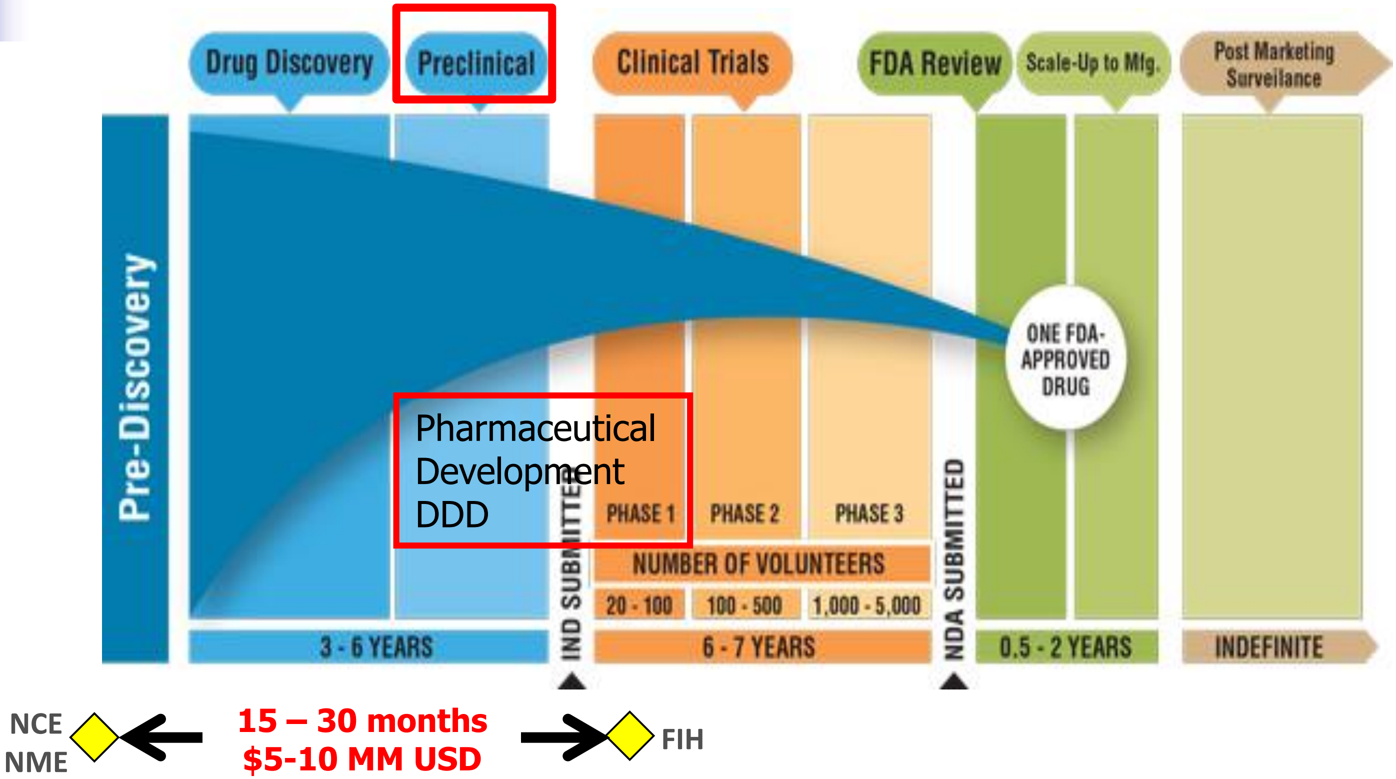
$1 to $2 billion

to bring a new medical therapy from discovery to market



•Pharmaceutical Bioprocessing 1(1):29-50, April 2013

Drug Discovery and Development Timeline



Drug Development Process
from Discovery to Market

Development process is **expensive, risky & time-consuming**

Cost & time depend on complexity, **platforms**, raw materials, analytical methods, & **experience**

Do it <u>right the first time</u> for IND-enabling preclinical studies, including formulation/drug delivery development

Pharmaceutical Development in Preclinical Phase

(1-3 yr, $ 5-10 MM)

- Scope of work
  - 1. Bioanalysis: LC-MS/MS, HPLC
  - 2. Preformulation: Physicochemical properties, Stability, Compatibility; DSC
  - 3. Formulation Development Strategies
  - 4. *In vitro* Assessments and Formulation Optimization
  - 5. *In vivo* Preclinical Evaluations in Rodent & Non-rodent Models :
    Pharmacokinetics (Pkin) & Bio-distribution
    Proof-of-concept Efficacy

Early Drug Discovery

- Target Identification & Validation
- Hit Discovery
- Assay Development & Screening
- High Throughput Screening
- Hit to Lead
- Lead Optimization

Preclinical Studies

- In Vivo, In Vitro & Ex Vivo Assays
- ADME
- Proof of Concept
- Drug Delivery
- Formulation Optimization & Bioavailability
- Dose Range Finding
- IND-enabling Studies
- IND Application

Clinical Development

- Phase I – Healthy Volunteer Study
- Phase II and Phase III – Studies in Patient Population
- Dose Escalation, Single Ascending & Multiple Dose Studies
- Safety & Efficacy
- Pharmacokinetic Analysis
- Bioanalytical Method Development and Validation

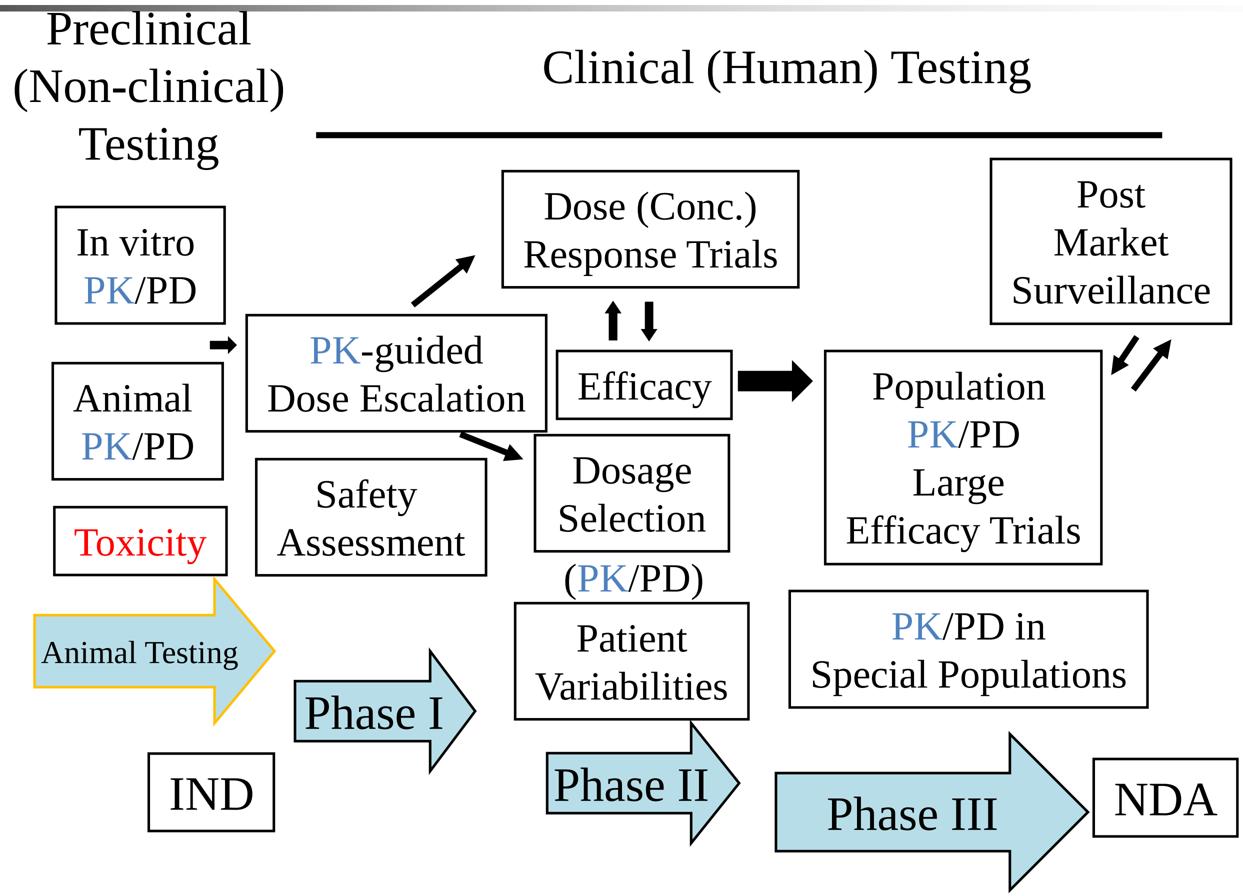
FDA Review

- NDA / ANDA / BLA Application
- FDA Approval
- Drug Registration

Post-market Monitoring

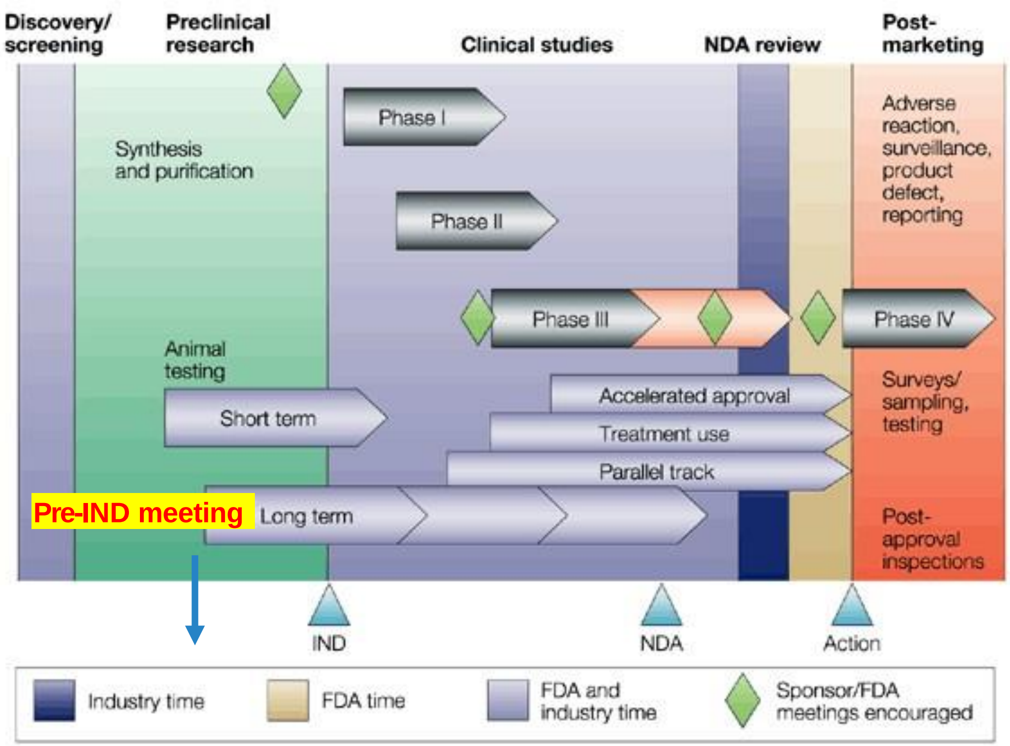
- FDA Adverse Event Reporting System (FAERS)

Pivotal Role of PK in Drug Development



What is IND?

Investigational New Drug Application



- A request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.
- Such authorization must be secured **prior to interstate shipment and administration** of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.
- After IND submitted, the molecule **changes in legal status** under the Federal Food, Drug, and Cosmetic Act and becomes a new drug **subject to specific requirements of the drug regulatory system**.

Pre-clinical Development

- Definition(WIKI PEDIA):

  - In drug development, preclinical development, also named **preclinical studies and nonclinical studies**, is a stage of research that begins **before clinical trials** (testing in humans) can begin, and during which **important feasibility**, iterative testing and **drug safety** data are collected.

  - The **main goals** of pre-clinical studies are to determine the **safe dose for first-in-man study** and assess a **product's safety profile**. Products may include new medical devices, drugs, gene therapy solutions and diagnostic tools.

Preclinical Experiment

- <u>Pre-clinical Development</u>

- **Chemistry, Manufacturing, and Controls (CMC)**
- Pharmacology studies (*in vivo* and *in vitro* studies)
- Toxicology studies (genetic/animal toxicology, toxicokinetic, acute and chronic toxicology)
- Clinical information/ proposed clinical studies to be conducted

What is CMC?

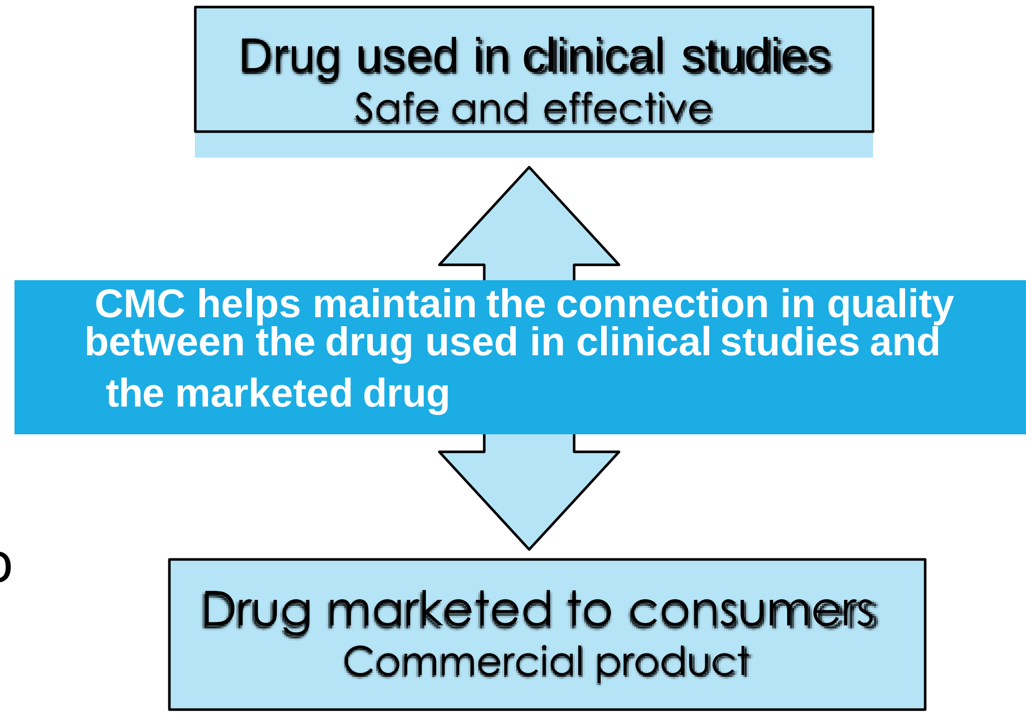
- To appropriately manufacture a pharmaceutical or biologic specific manufacturing processes, product characteristics, and product testing must be defined in order to ensure that the product is safe, effective and consistent between batches.

- These activities are known as CMC, Chemistry, Manufacturing and Control.

The ability to consistently produce the same product to meet the same specifications time after time !

Why is there CMC?

- To assure that the quality of the drug meets appropriate standards and is consistent
- To assure that the drug you are using is the drug described on the label
- To assure that the drug sold to the public will have quality attributes similar to those of the drug demonstrated to be safe and effective



Critical Elements of CMC

- How and where is the drug made?
- How are raw materials tested and monitored?
- What control procedures are in place to assure product consistency and quality?
- Are quality attributes adequately identified and characterized for the product?
- Are the test methods used to monitor product quality appropriate?
- How long does the product maintain its quality after it is made (shelf life)?

CMC is specific for the products

- *Sterile injectable product* – **sterility and endotoxin concentration**
- *Oral tablet* – **dissolution profile**
- *Controlled release product* – **release profile of active ingredient over time**
- *Soluble powder for drinking water* – **moisture content as powder, solubility in water**

- **Stability** test is required for all products.

Preclinical Experiment

- <u>Pre-clinical development</u>

- Chemistry, manufacturing, and controls (CMC)
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Pharmacology Studies

Guidance for Industry

S7A Safety Pharmacology Studies for Human Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

ICH
July 2001

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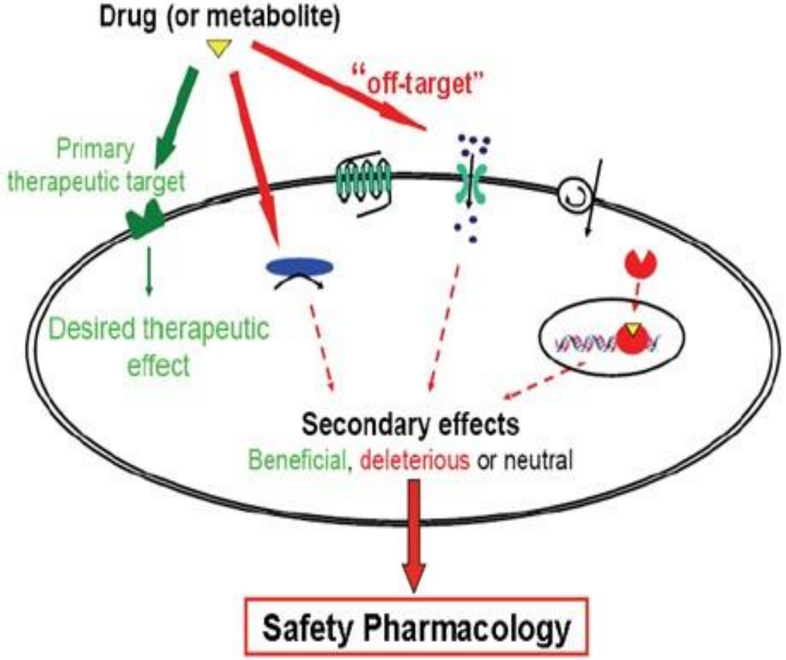
Pharmacology Studies

- Primary pharmacodynamics
- Secondary pharmacodynamics
- Safety pharmacology



https://www.creative-biolabs.com/drug-discovery/therapeutics/safety-pharmacology.htm

Primary and Secondary PD

- The primary and secondary PD should be conducted in vitro, using animal and human-derived material and in vivo using animal models, as relevant.

- These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration of effect and dose- response relationships.

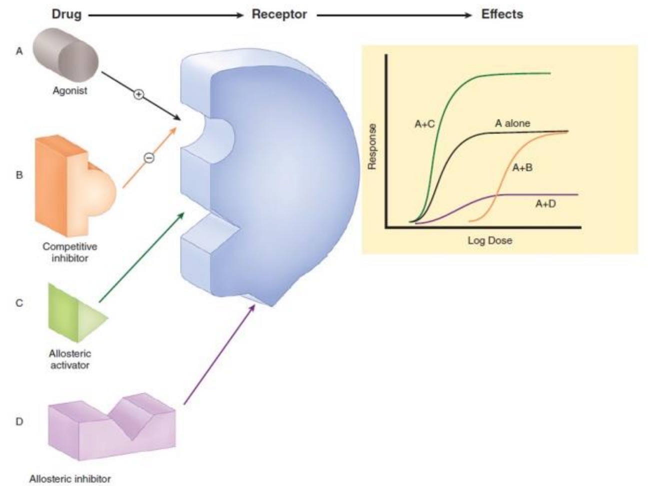
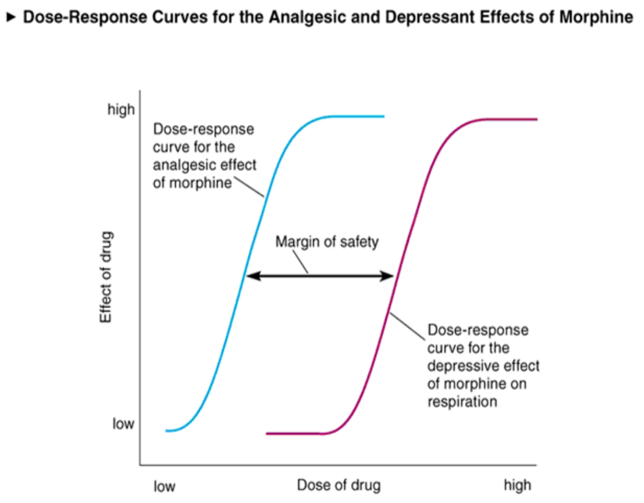


FIGURE 1–3 Drugs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the right. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), or act at separate (allosteric) sites, increasing (**C**) or decreasing (**D**) the response to the agonist. Allosteric activators (**C**) may increase the efficacy of the agonist or its binding affinity. The curve shown reflects an increase in efficacy; an increase in affinity would result in a leftward shift of the curve.

http://www.tomhsiung.com/wordpress/2014/06/the-properties-of-drugs-receptor-rationale/

Primary and Secondary PD

- **A dose/concentration--response curve** of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects with low doses and to identify active substances with U- shaped, bell-shaped or time dependant dose--response curves.



https://www.softchalk.com/lessonchallenge09/lesson/Pharmacology/Introduction_088.html

Safety Pharmacology Studies

- Definition: Studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.

- Purposes:
  a. To identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety
  b. To evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies
  c. To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected. The investigational plan to meet these objectives should be clearly identified and delineated.

Safety Pharmacology Studies

- **Ex vivo and in vitro systems**: **isolated organs and tissues, cell cultures, cellular fragments, subcellular organelles, receptors, ion channels, transporters and enzymes**, can be used in supportive studies (e.g., to obtain a profile of the activity of the substance or to investigate the mechanism of effects observed in vivo).

- **For in vivo studies**, it is preferable to use unanesthetized animals. Data from unrestrained animals that are chronically instrumented for telemetry, data gathered using other suitable instrumentation methods for conscious animals, or data from animals conditioned to the laboratory environment are preferable to data from restrained or unconditioned animals. **In the use of unanesthetized animals, the avoidance of discomfort or pain is a foremost consideration.**

Safety Pharmacology Studies

- The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous and respiratory systems, and should generally be conducted before human exposure, in accordance with ICH S7A and S7B.

Choice of Animal Species

- The choice of species is based on which will give the best correlation to human trials. Differences in the gut, enzyme activity, circulatory system, or other considerations make certain models more appropriate based on the dosage form, site of activity, or noxious metabolites.

Canine

May not be good models for solid oral dosage forms because the characteristic carnivore intestine is underdeveloped compared to the omnivore's, and gastric emptying rates are increased.

Choice of Animal Species

Rodents

Can not act as models for antibiotic drugs because the resulting alteration to their intestinal flora causes significant adverse effects.

Medical device

Most studies are performed in dogs, pigs and sheep which allow for testing in a similar sized model as that of a human. Some species are used for similarity in specific organs or organ system physiology.

☆ FDA, EMA, and other similar international and regional authorities usually require safety testing in at least two mammalian species, including one non- rodent species, prior to human trials authorization.

Toxicology Studies

- Acute and chronic toxicology
- Toxicokinetic
- Genetic toxicology

Acute Toxicology Testing

- To determine the effect of a single dose on a particular animal species.
- In acute toxicological testing, the investigational product is administered at different dose levels, and the effect is observed for 14 days.
- All mortalities caused by the investigational product during the experimental period are recorded and morphological, biochemical, pathological, and histological changes in the dead animals are investigated.

LD50 → Large mortality →

- The fixed dose procedure (FDP) **– CDER 1996**
- The acute toxic category (ATC) method
- The up-and-down (UDP) method.

Chronic Toxicity Testing

- Providing inferences about the long-term effect of a test substance in animals, and it may be extrapolated to the human safety of the test substance.
- The test compound is administered over **more than 90 days**, and the animals are observed periodically.
- A satellite group may be included in the study protocol. This group has both a control group and high-dose group.
- During the study period, the animals are observed for normal physiological functions, behavioral variations and alterations in biochemical parameters. At the end of the study, tissues are collected from all parts of the animal and subjected to histological analyses.

Toxicokinetics

- An extension of pharmacokinetics deals with the kinetic patterns of higher doses of chemicals/toxins/xenobiotics, helping study the metabolism and excretion pattern of xenobiotics.
- Animal toxicokinetic data help extrapolate physiologically based pharmacokinetics in humans.
- Carried out in rodents, rabbits, dogs, nonhuman primates and swine using many routes of administration.
- Blood sample: Area under the curve, drug distribution ratio, Cmax, tmax, and other pharmacokinetic parameters.
- Toxicokinetic studies may be performed using in vitro cell lines also.

Genetic Toxicity Testing

- To identify gene mutations, chromosome changes, and alterations in the DNA sequencing.
- These tests are usually conducted in various species including whole animals, plants, micro-organisms, and mammalian cells. In the whole animal model, rodents are preferred.
- Genetic toxicity is assessed using the rodent chromosome assay, dominant lethal assay, mouse-specific locus test, micronucleus test, heritable translocation assay, and sister chromatid exchange assay.

Other Toxicity Testing

- Carcinogenicity testing
- Skin sensitization tests
- Repeated dose toxicity testing
- Mutagenicity testing
- Subchronic oral toxicity testing (repeated dose 90-day oral toxicity testing)
- One-generation reproduction toxicity testing
- Two-generation reproduction toxicity studies

Once a lead compound is found, drug development begins with **preclinical research** to determine the **efficacy** and **safety** of the drug.

Researchers determine the following about the drug:

- Absorption, distribution, metabolism, and excretion
- Potential benefits and mechanisms of action
- Best dosage, and administration route
- Side effects/adverse events
- Effects on gender, race, or ethnicity groups
- Interaction with other treatments
- Effectiveness compared to similar drugs

Desirable DMPK Properties of a Candidate Substance Intended for Oral Route Administration

- **Good water solubility**

- **High permeability and low efflux in Caco-2 cells**
- **Sufficient bioavailability**

- **Adequate half-life time for dosing in human**
- **Linear PK**

- **Elimination not dependent on a single route or on a single metabolizing enzyme; without forming active or reactive metabolites in large amounts and without interacting with metabolizing enzymes in relevant concentrations**
- **Acceptable safety margin (therapeutic index, preferably higher than 10 times)**

- **Established PK-PD relation**

Animal Dosing and Sampling

Metabolic cage

Rat dosing:

- IV bolus
  - 5 mL/kg to 20 mL/kg
  - In solution; or o/w emulsion
- Oral gavage
  - 10 mL/kg, but < 20 mL/kg
  - In solution, emulsion, suspension
- Intraperiotoneal
  - 5-10 mL/kg, but < 20 mL/kg
  - In solution, emulsion, suspension

Blood sampling:

- Collect at least 5 plasma half-lives
- IV study, "powers of 2" series, i.e., sample at 2, 4, 8, 16, and 30 (32) min, 1, 2, 4, 8, and 16 hours.
- Oral dosing study, 15 min, 30 min, 1, 2, 4, 8, 24, 48, 72 hours, ensuring the excretion of 95% of the absorbed dose

BASICS OF ALLOMETRIC SCALING

Allometric (Interspecies) Scaling

An empirically established relationship between physiological variables or pharmacokinetic parameters and body weights of mammals,

in power equation

$P = a\,(BW)^b$

Where P is the dependent biological variable of interest

a is allometric coefficient

a normalization constant

NOT dimensionless

dependent on P and BW

b is allometric exponent, often < 1

P as Physiological Variables or Pharmacokinetic Parameters

Pysiological variables

- Heart rate
- Blood flow
- Blood volume
- Organ size (Brain)
- Urine output
- Longevity

Pkin parameters

- **CL**
- **CL_{int}**
- **V**
- **$t_{1/2}$**
- **AUC**
- **C_{max}**
- **F**

Allometric (Interspecies) Scaling(Cont’d)

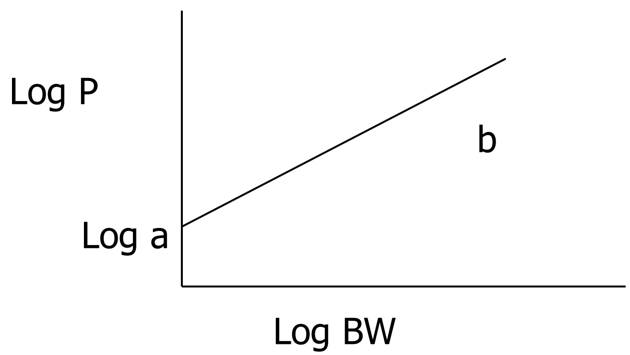
Power Equation

$P = a\,(BW)^b$

$\text{Log } P = \text{Log } a + b\,(\text{Log } BW)$

BW of mammals, $10^0 - 10^9$ gm

(3 gm, shrew – 6000 kg, elephant, 136,000 kg Blue whale)



Allometric (Interspecies) Scaling (Cont'd) Applications

- Improve and expedite drug selection and development-**Selection of FIH**
- Widely used to extrapolate PK parameters from **animal to human**, based on the similarity of anatomical, physiological and biochemical variables in mammals
- Clinical trial simulation and optimization of phase I dosing strategies for **pediatric** patients, based on PK in adults, and in neonatal and juvenile animal models.
- Clinical trial simulation and optimization of phase I dosing strategies for **obese** patients, based on PK in lean patients

Allometric (Interspecies) Scaling (Cont'd) Applications

Predict toxicological endpoints in humans
Select equivalent dosage regimens in humans
less D, longer τ

Allometric (Interspecies) Scaling (Cont'd)
Approaches

1. PK parameters derived in 4 or more species (Compartmental or non-compartmental analysis)
2. Linear regression of Log P –Log BW for each parameter, with or without MLP (Maximun Life-Span Potential), brain wt, fu modifications
3. Extrapolate the parameter values to 70 kg

Allometric (Interspecies) Scaling (Cont'd) Approaches

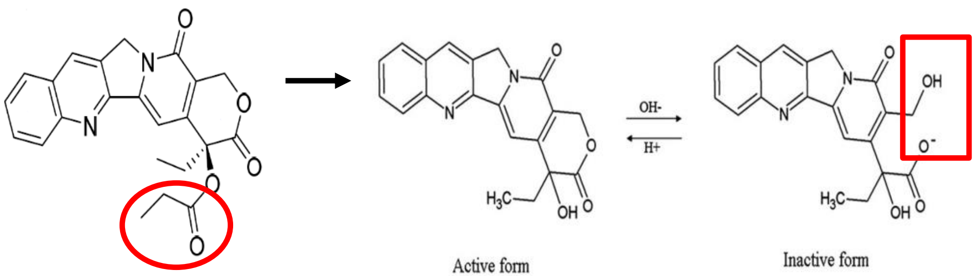
4. Use predicted parameters to predict PK equation for drug disposition in humans
5. The prediction helps to choose dose and serum (plasma) sampling time for FTIH (First time in Humans) study
6. Observed PK of FTIH study and compare with predicted values

PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

Excellent Example
Solving Phase I Clinical Trial Issue by thorough PK Knowledge from PK modeling with Preclinical PK profile data
The EHC models were developed based on knowledge gained from preclinical PK in rats
EHC is the significant contributing factor to the accumulation of CPT levels and potentially resulting toxicity in humans

PK Modeling & Simulation (Cont'd)
Prodrug CZ48 & CPT

Advantage: Lactone stability



at physiological pH (7.4)

CZ48

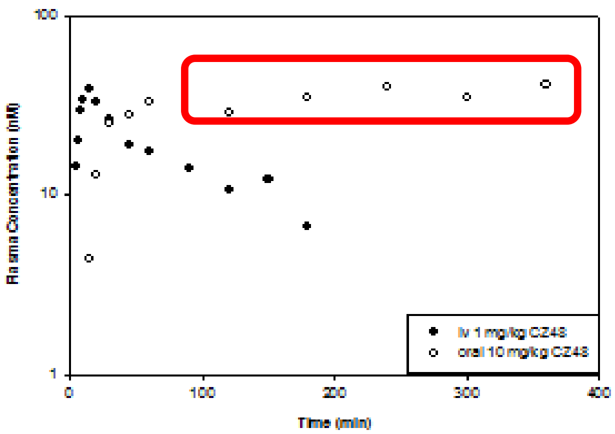
CPT

Lactone form

Carboxylat e form

PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

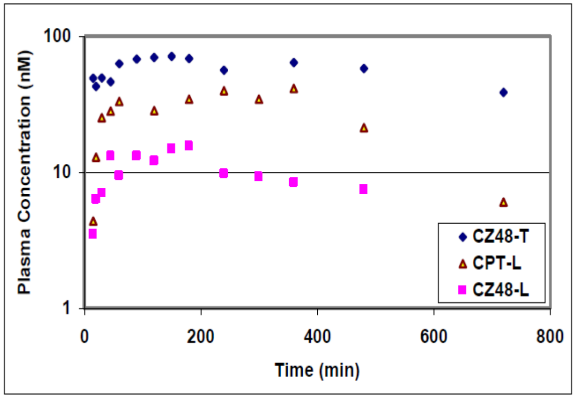
Sustained Concentrations of CZ48/CPT for up to 6 hr after the oral dose of CZ48



(●): IV dose of 1 mg/kg of CZ48 in co-solvents (DMSO: PEG400: EtOH, 2:2:1, v/v/v)

(○): PO dose of 10 mg/kg of CZ48 in the same co-solvents

Potential enterohepatic recycling of CZ48 and CPT

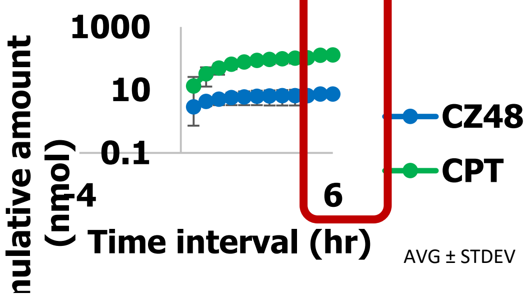


(*Xaohui Li's Dissertation at UH*, 2004)

PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

Biliary Excretions of CZ48 and CPT after an IV Dose of CZ48

- IV Dose: 5 mg/kg of CZ48 in co-solvent formulation



AVG ± STDEV

Parameter	Units	CZ48	CPT
$AUC_{0\text{-}6h}$ in plasma	hr*ng/mL	3203.03 ± 1785.24	722.13 ± 397.72
CL_{total}	ml/hr	540.61 ± 236.31	2058.90 ± 888.87
CL_{bile}	ml/hr	0.87 ± 0.20	56.38 ± 15.37

AVG ± STDEV

3% of Dose

~3% of CL_{bile} in CL_{total}

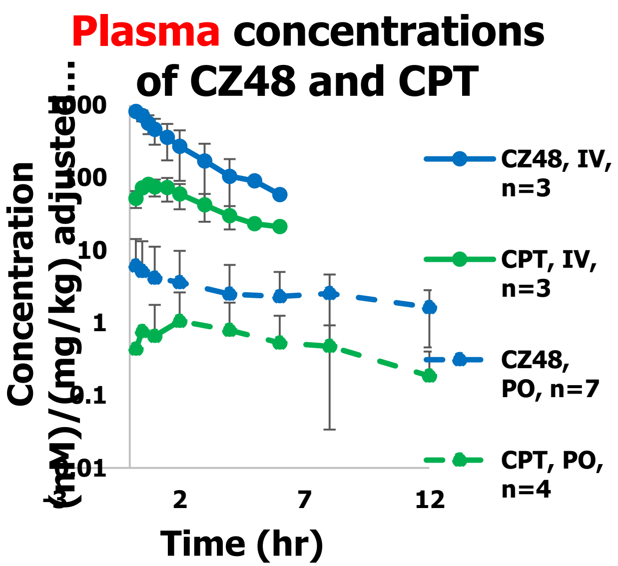
- Clearance of a drug in bile (CL_{bile}):

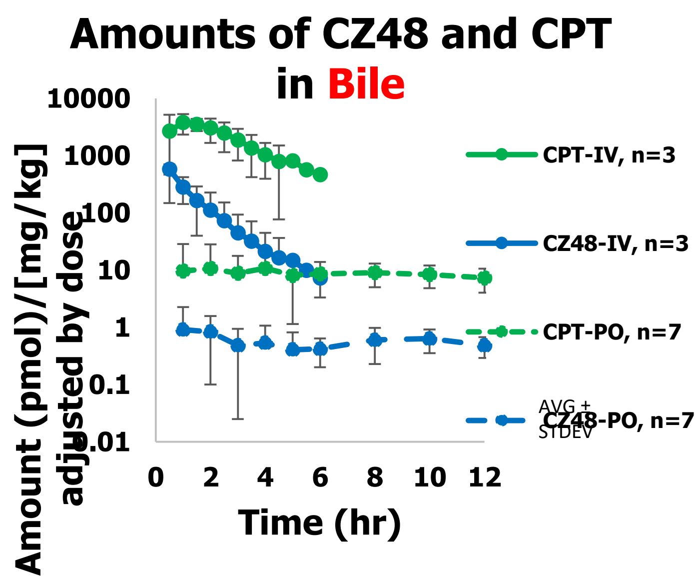
  CL_{bile} = (Amount of a drug excreted into bile during a time interval)/(AUC_{plasma})

PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

Biliary Excretion: IV and PO

- Doses: 5 mg/kg of CZ48 in co-solvent formulation (IV) or 25 mg/kg of CZ48 in the same formulation (PO)





PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

Biliary Excretions of CZ48 and CPT

- Biliary secretions of CZ48 and CPT as their parent forms
- Biliary clearance (CL_{bile}) of CPT (56.38 ml/hr) > CL_{bile} of CZ48 (0.87 ml/hr)
- Approximately 3 % of the dose recovered in bile as CPT
- Increased biliary secretions of CZ48 and CPT after an oral dose, compared to those after an IV dose
- Sustained biliary secretions of CZ48 and CPT for 12 hr post oral dose
- **Enterohepatic recycling (EHC)** of CZ48 and CPT was minor in rats

PK Modeling & Simulation (Cont'd)
Prodrug CZ48 & CPT

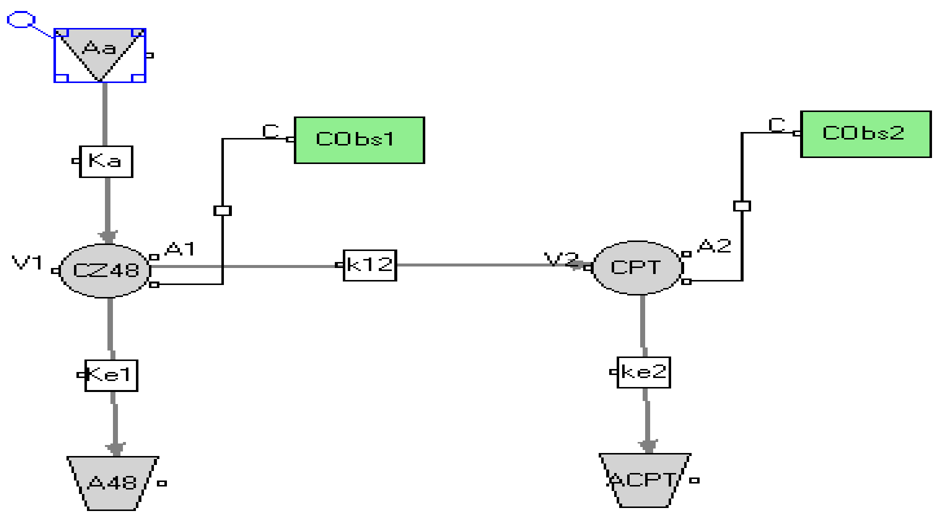
Phase I Clinical Trial Issues

For screening patients, blood samples were collected up to 48 h time points after a single oral dose.

CZ48 reached steady state after 3 doses

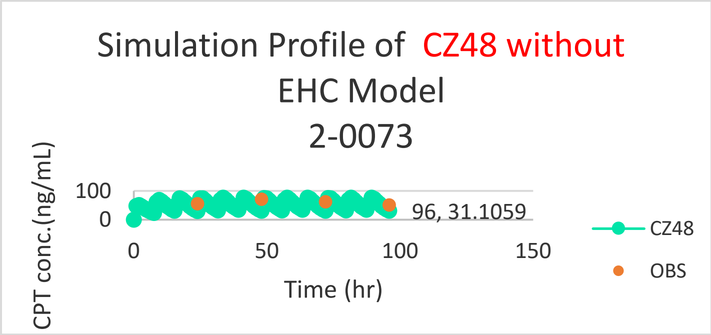
Significant accumulation of CPT levels and resulting potential toxicity in humans

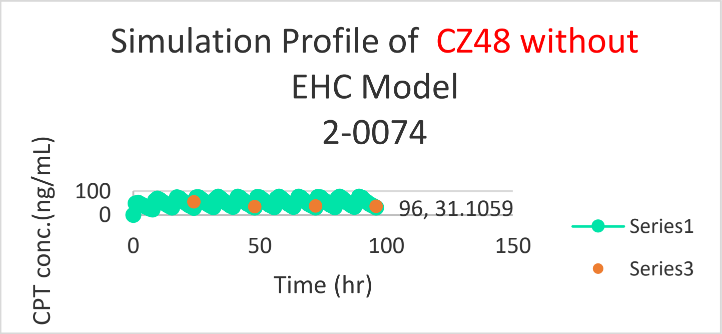
PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

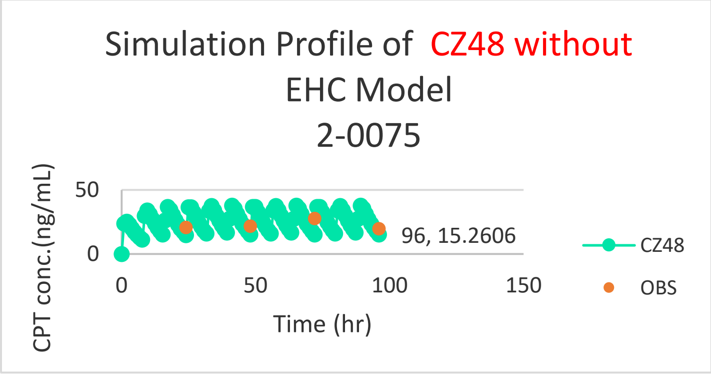


Model-A

PK Modeling & Simulation (Cont'd) Prodrug CZ48 & CPT

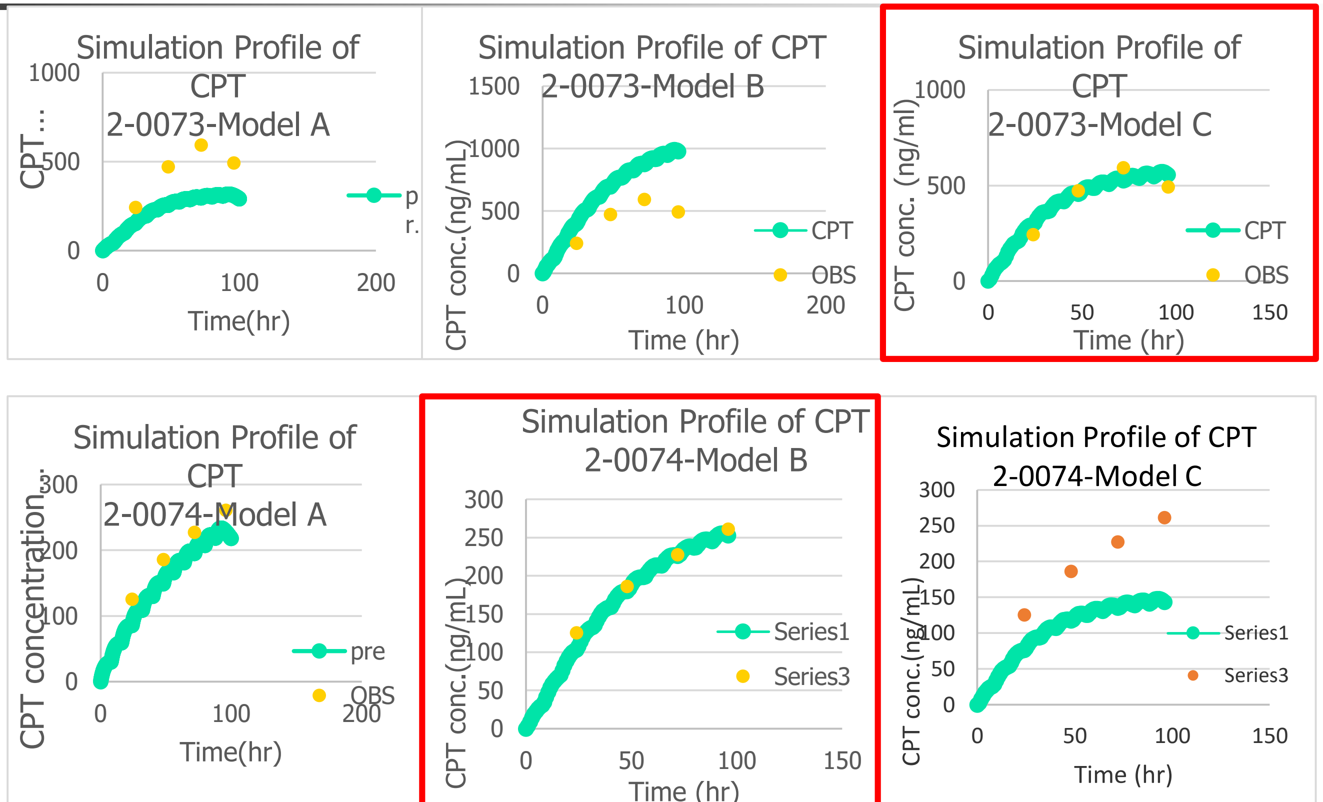




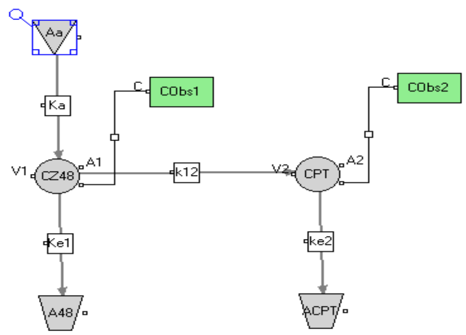


PK Modeling & Simulation (Cont'd)
Prodrug CZ48 & CPT

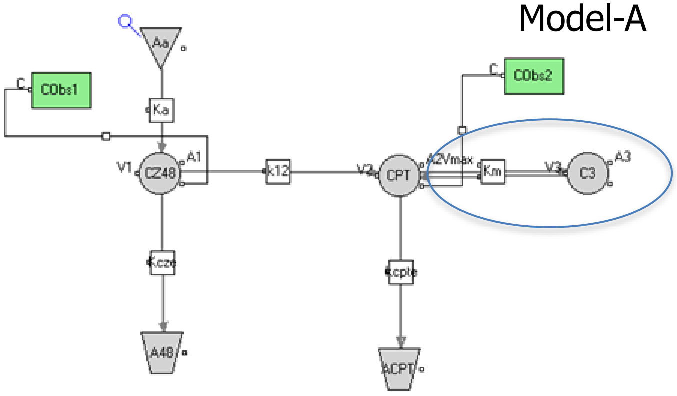
Simulation Profiles of CPT



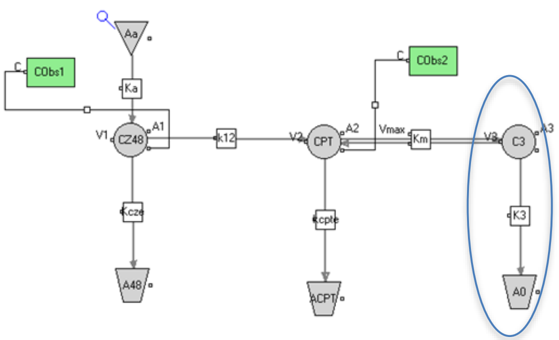
PK Modeling & Simulation (Cont'd)
Prodrug CZ48 & CPT



Model-A

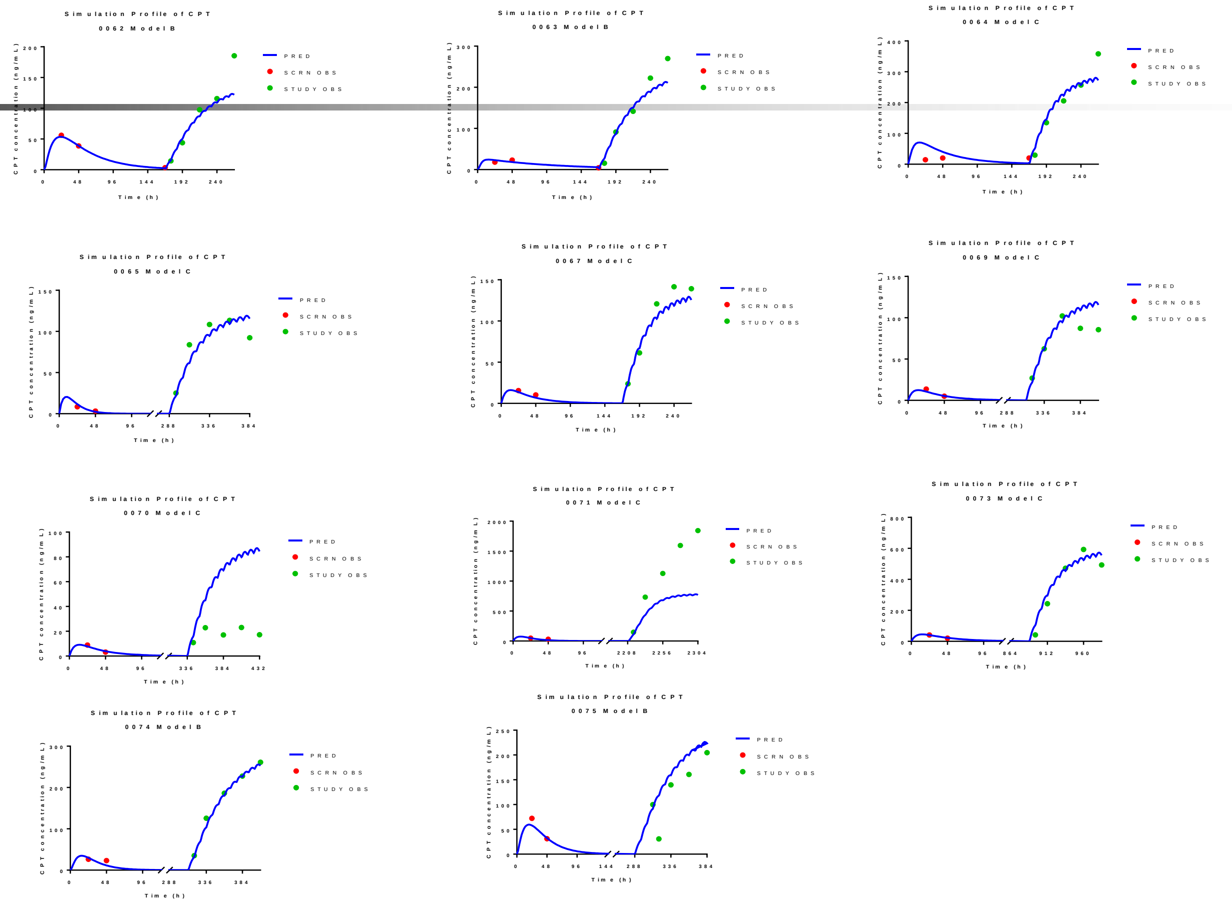


Model-B



Model-C

Simulation Profiles of CPT with Best Fit Model



CENTER FOR COMPREHENSIVE PK|PD + FORMULATION

CPRIT

CPRIT Grant Support (RP180748)

GCC Center for Comprehensive PK/PD & Formulation (CCPF)

- Dong Liang, Ph.D. (TSU)
- Huan Xie, Ph.D. (TSU)
- Diana S-L Chow, Ph.D. FNAI (UH)
- Omonike Olaleye, Ph.D., MPH (TSU)
- Suzanne Tomlinson, Ph.D. (GCC)

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TSU

Gulf Coast Consortia QUANTITATIVE BIOMEDICAL SCIENCES

FORMULATION DEVELOPMENT

PK/PD CHARACTERIZATION

Pre- and Formulation

Pre-clinical PK/PD Evaluations

1. Drug Characterization
- Solubility
- pka
- Log P
- Stability

2. Basic Formulation:
- Cosolvent
- Cyclodextrin
- Dispersed systems

3. Advanced Drug Delivery:
- Micro/nanoemulsions
- Liposomes
- Nanoparticles

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4. Bioanalysis
- Method development and validation to quantitate concentrations of drug or metabolite in biological matrix
- Identification of unknown metabolites using accurate mass

5. In Vitro Metabolism
- Drug metabolism characterization using tissue microsomes, S9 fraction, and Recombinant enzymes
- Metabolite profiling & identification

6. In Vitro Biopharm Characterization
- Membrane permeability and transporter identification
- Bindings to plasma proteins, albumin or α-glycoprotein

7. In Vivo PK
- PK studies in rats and mice after IV, oral, IP and SC drug administration
- Dose linearity PK studies
- Bioavailability studies
- PK studies on tissue distribution

8. In Vitro/In Vivo PD
- Cell proliferation assay
- Apoptosis assay
- DNA damage assay
- Migration/invasion assays
- Xenograft assay
- Biomarker assays on tumors from xenograft models
- Genetic mouse models for PD assays

9. PK/PD Modeling and Simulation
- Consultation on experimental design
- PK modeling development and simulation
- PD modeling and determination of parameters
- PK/PD modeling

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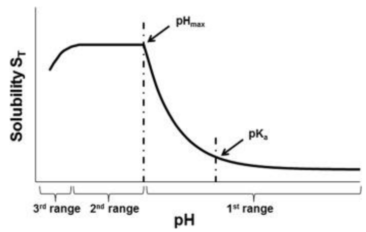
Pre-formulation and Formulation

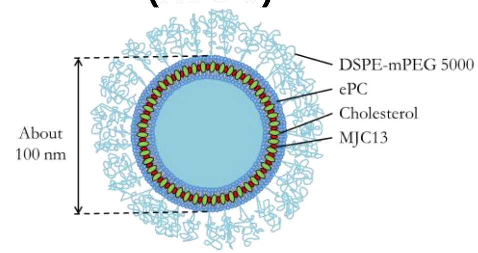
Pre-formulation characterization:

pKa, pH-solubility profiles, logP

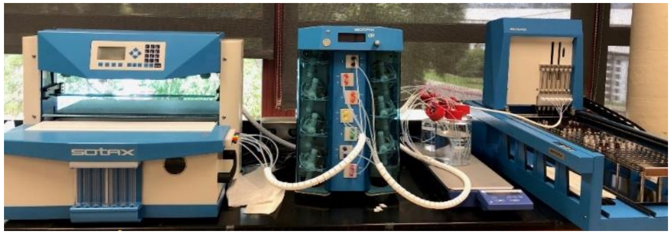
Pion SiriusT3



Nano drug delivery systems (NDDS)

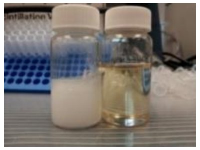


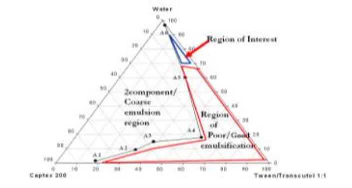
Label	Material			Encapsulation efficiency (%)
	MJC13 (mg)	Egg PC (mg)	Cholesterol (mg)	
A	10	200	0	43.4
B	10	200	10	62.8
C	10	200	20	75.2
D*	10	200	25	78.3
E	10	200	30	74.8
F	10	200	40	67.1



SOTAX CE 7smart USP Apparatus 4

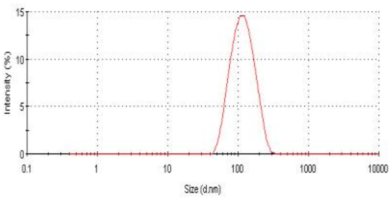
Formulation development

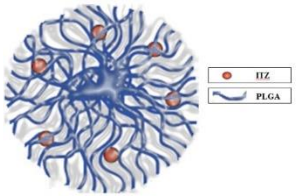


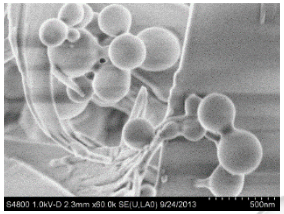


Microfluidics

Zetasizer







Bian et al, Int J Nanomedicine, 8:4521-31, 2013

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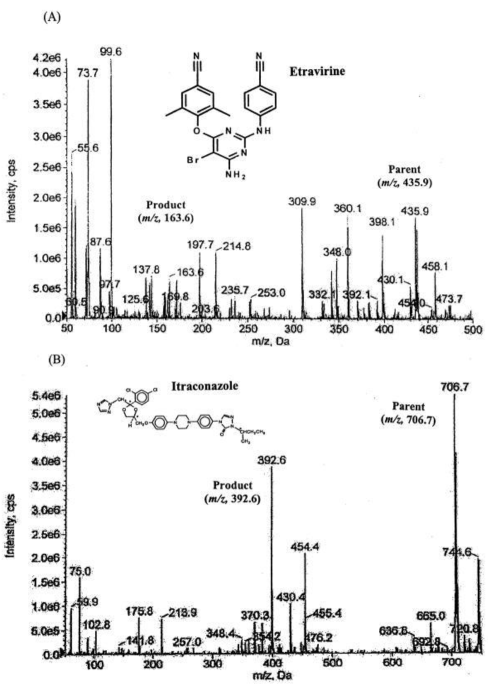
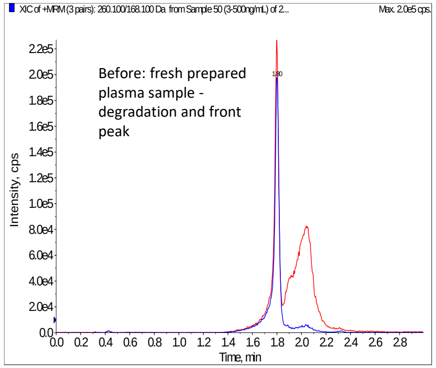
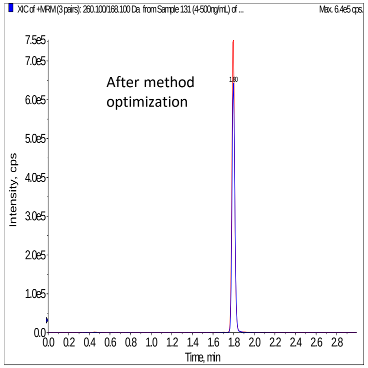
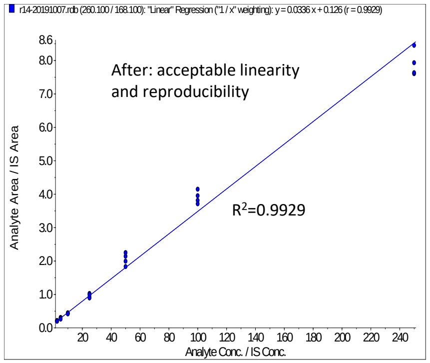
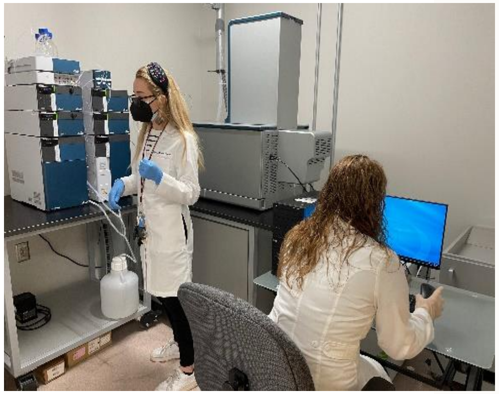
BIOANALYSIS: LC-MS/MS QUANTITATION OF DRUGS & METABOLITES IN BIOLOGICAL SAMPLES

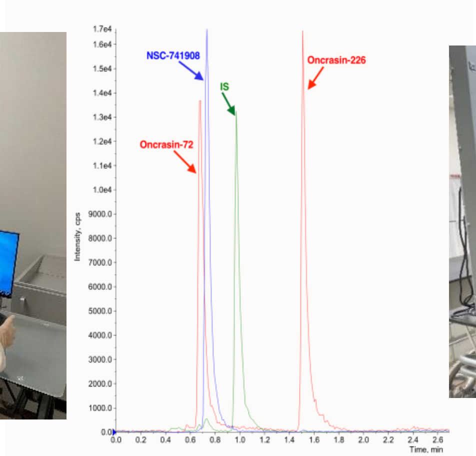












White L, et al. J Chromatogr B, 1033-4:106-11, 2016

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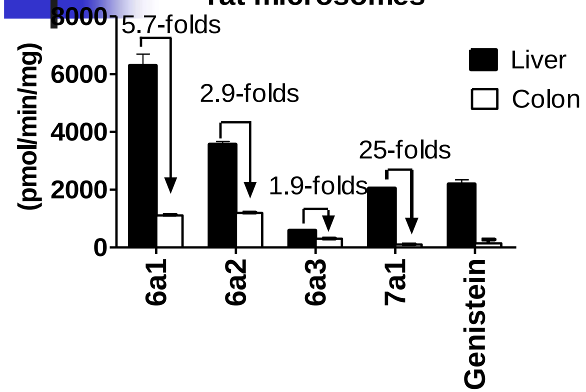
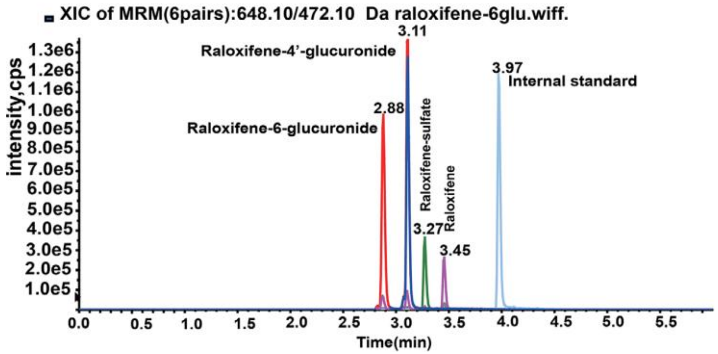
In Vitro Drug Metabolism & In Situ Permeability

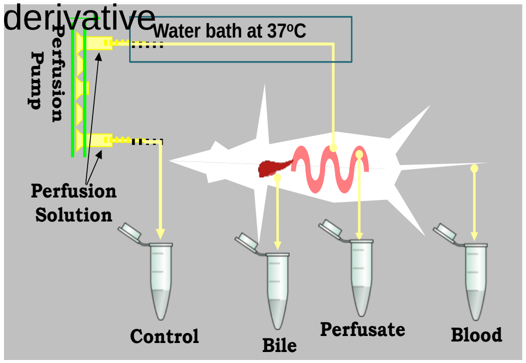
Glucuronidation rates with rat microsomes

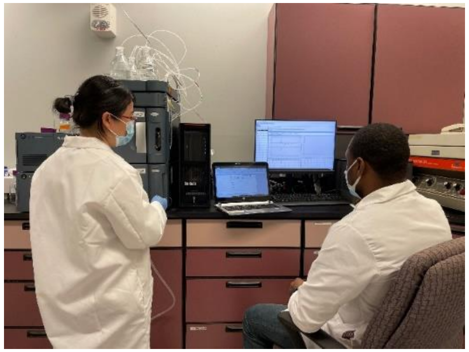


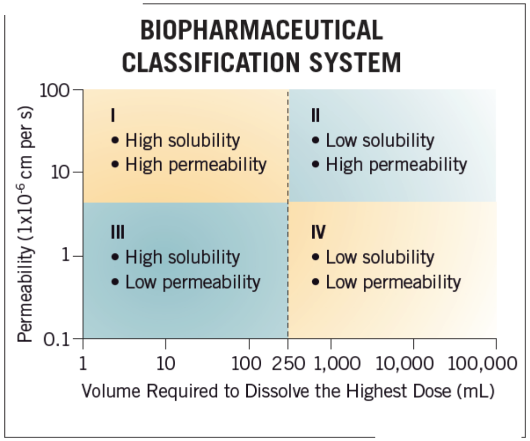


Du T, et al. J Sep Sci, 43:4414-23, 2020

Intestinal absorption and biliary secretion of a celecoxib derivative







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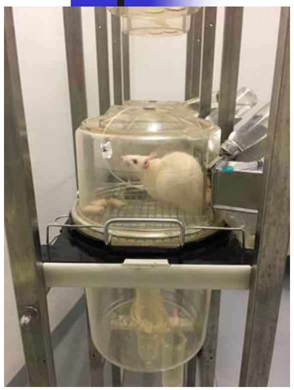
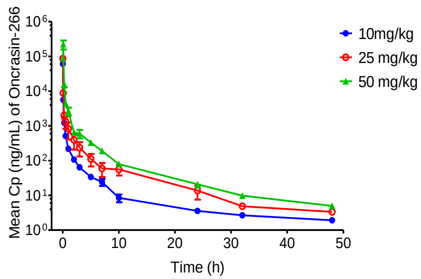
Pharmacokinetic (PK) & Biodistribution Studies

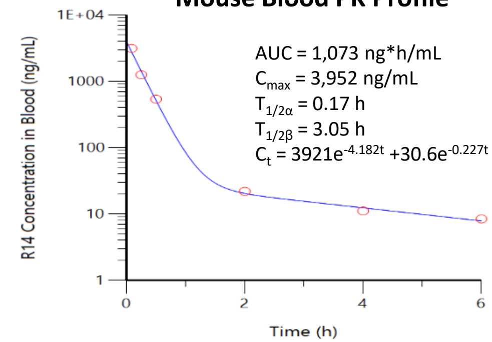
Jugular vein cannulated, rat PK studies in metabolism cage

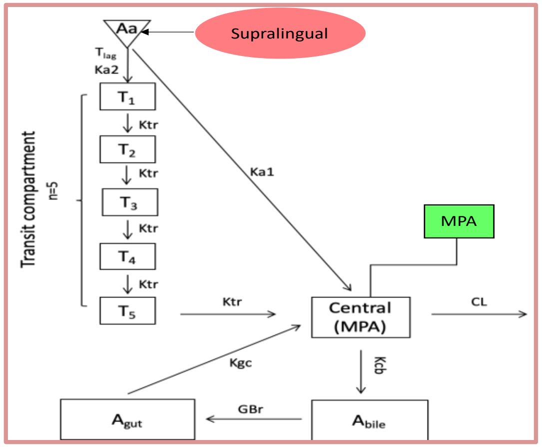




Mouse PK studies via tail vein

Mouse Blood PK Profile





Patch tongue distribution study

Gao et al, Pharmaceutics. 2021 Apr; 13(4): 574.

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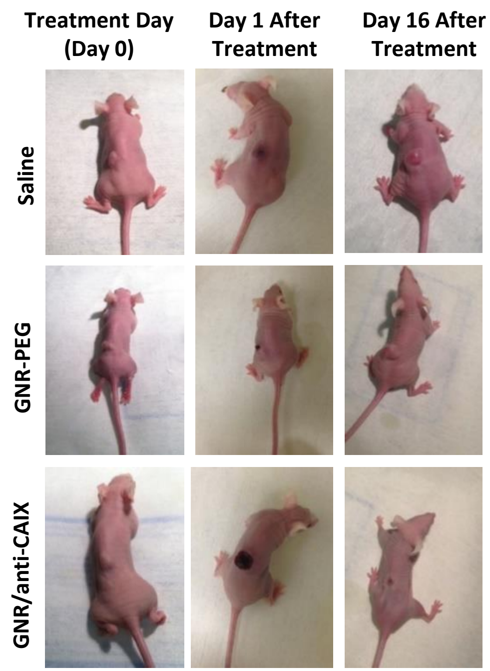
		IV (n=5)	Oral (n=3)	Supralingual (n=3)
Parameter	Unit	Mean	Mean	Mean
Dose	mg/kg	0.5	0.5	0.5
T_{au}	hr	1.5 ± 0.5	4.5 ± 4.7	31.5 ± 11.6
Half-life	hr	10.5 ± 1.2	7.4 ± 2.1	11.5 ± 3.0
CL	mL/(kg*hr)	116.6 ± 92.2	99.9 ± 61.7	16.4 ± 23.2
CL_2	mL/(kg*hr)	224.0 ± 65.5	194.5 ± 119.9	NA
K_{cb}	1/hr	1.4 ± 1.0	10.3 ± 0.8	0.1 ± 0.1
K_{gc}	1/hr	2.0 ± 2.0	7.8 ± 8.5	32.4 ± 52.3
V	mL/kg	110.3 ± 10.8	21.0 ± 7.3	232.1 ± 7.1
V_2	mL/kg	1739.2 ± 508.0	2242.0 ± 1458.4	NA
Ka_1	1/hr	NA	1.0 ± 0.3	21.6 ± 14.6
Ka_2	1/hr	NA	1.5 ± 0.4	37.3 ± 22.7
K_{tr}	1/hr	NA	1.3 ± 0.1	0.20 ± 0.0
AUC_{0-48}	ng*hr/mL	2172.8 ±355.3	1573.1 ± 217.6	132.1 ± 16.8
F_{abs}	%	NA	72.4 ± 10.1	7.6 ± 1.0 *

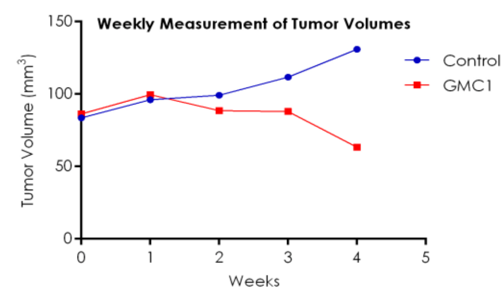
In vitro/ in vivo Pharmacodynamics (PD)

In Vitro PD
- Cell proliferation assay
- Apoptosis assay
- DNA damage assay
- Migration/invasion assays

In Vivo PD
- Xenograft assay
- Biomarker assays on tumors from xenograft models
- Genetic mouse models for PD assays



Chen et al, Oncotarget, 9:26556-71, 2018



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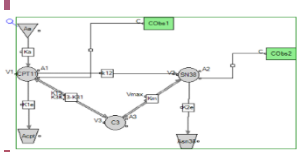
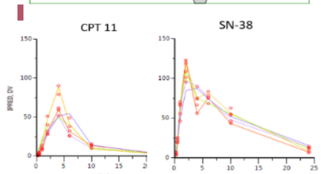
PK/PD MODELING AND SIMULATION

PK Modeling

Software
- Phoenix Modeling
  Individual and Pop PK
- GastroPlus
  PK Analysis and PBPK
- WinNonlin
  PK Analysis

Project Examples:
- Intranasal Scopolamine PK Analysis
- Irinotecan (CPT-11) PK Analysis
- Co-modeling of Parent Comp'd and Metabolite:

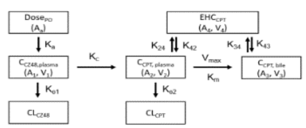


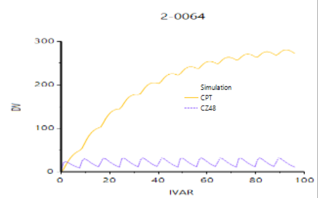


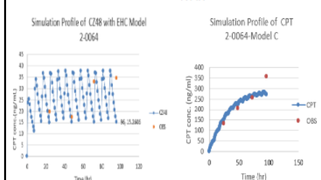
PK Modeling and Simulation

Software
- Phoenix Modeling
- GastroPlus

Project Example:
- Clinical Trail of CZ48 and CPT
- EHC and Simulation:



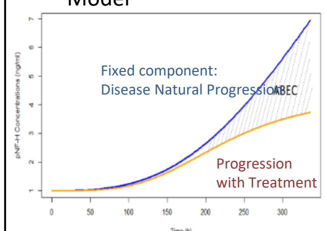


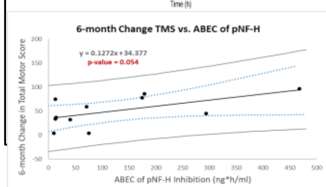


PD Modeling

Software
- Phoenix Modeling
- GastroPlus
- WinNonlin
- Design Expert
  Factors Correlation

Project Example:
- Riluzole PD Study in Acute Spinal Cord Injured Patients
  - Progressive Disease Model

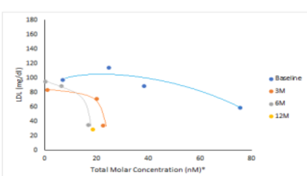


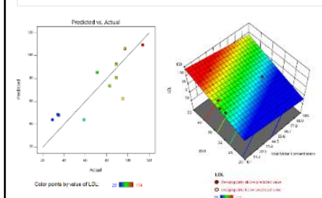


PK/PD Modeling

Software
- Phoenix Modeling
- GastroPlus
- WinNonlin
- Symcyp
  PKPD and Simulation

Project Example:
- Clinical Statin PK/PD Analysis Post Gastro Bypass Surgery
- Atorvastatin PK/PD Modeling:





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Concluding Messages

*Development process is **expensive, risky & time-consuming***

*Recognize **significance of** IND-enabling preclinical studies*

***Do it right the first time** for IND-enabling preclinical studies*

***Maximize utilization** of local resources*

https://www.gcc-ccpf.com/


Q
&
A