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Questions or Comments?

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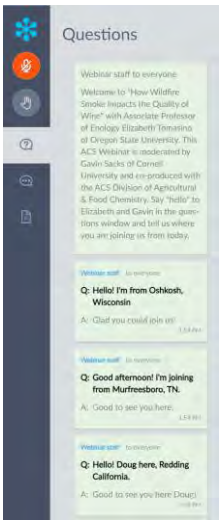

"Why am I muted?"
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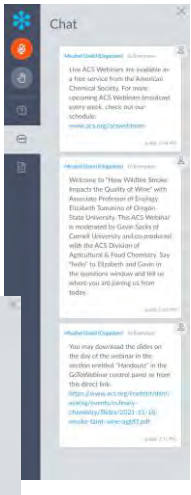
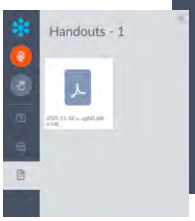
Announcements and hyperlinks from our team



Handouts

Download the PDF of today's slide deck



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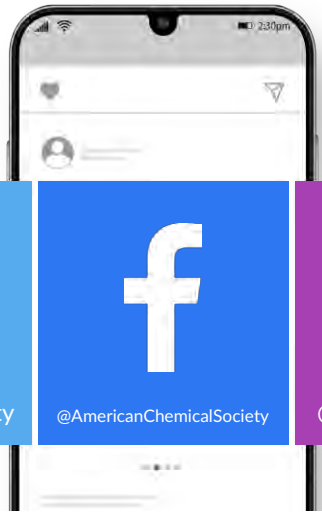

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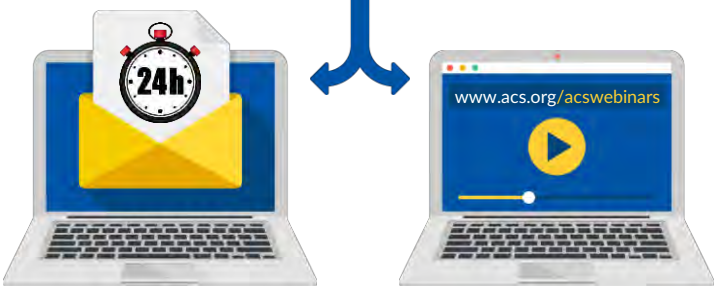

All Registrants

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ACS Webinars

Thurs., March 3, 2022 | 2pm – 3:15pm ET

The Evolving Landscape of RNA Therapeutics

Co-produced with Chemical Abstracts Service (CAS)

Tues., March 8, 2022 | 2pm – 3pm ET

Launch Your Career to the Next Level

Co-produced with the ACS Women Chemists Committee

Thurs., March 10, 2022 | 1pm – 2pm ET

How Data Maps Help Vaccinate the World

Co-produced with the Science History Institute

Register for Free

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5

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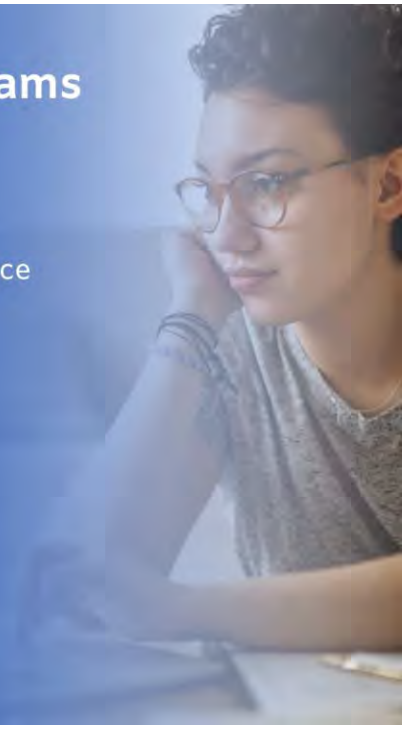

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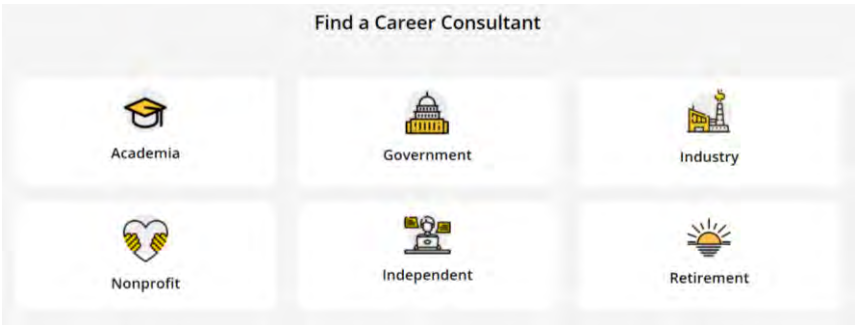
https://chemidp.acs.org

9

Career Consultant Directory



- ACS Member-exclusive program that allows you to arrange a one-on-one appointment with a certified ACS Career Consultant.
- Consultants provide personalized career advice to ACS Members.
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10

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The Office of Diversity, Equity, Inclusion & Respect (DEIR) is the central hub at the American Chemical Society that coordinates, supports, and guides all efforts by staff, members, and governance toward Strategic Goal 5, "Embrace and Advance Inclusion in Chemistry." The Office of DEIR at ACS is committed to empowering everyone, irrespective of lived experience and intersectionality of identities, to fully participate in the chemistry enterprise. The Office of DEIR welcomes comments, suggestions, and questions around issues of diversity, equity, inclusion, and respect from members at any time. Please do not hesitate to reach out to the Office through this form.

Please do not hesitate to reach out to the Office of DEIR at diversity@acs.org

https://fs7.formsite.com/acsdiversity/ACSMemberFeedback/index.html

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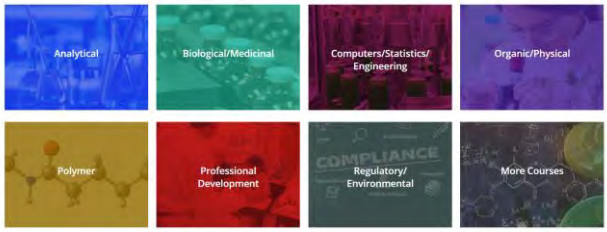
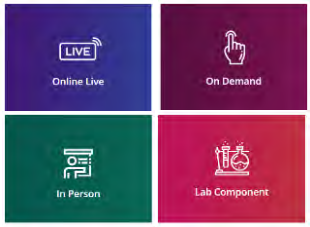
Course Categories



Course Formats



https://www.acs.org/proedweb

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Pharmacokinetics for Chemists in Drug Discovery and Development

ACS Chemistry for Life®
American Chemical Society

April 19 - 24, 2022 | Online

Learn the concepts and tools required to make molecules suitable to be drug candidates.

Key topics include:

- **Drug-like properties of molecules**
- **Absorption (IV, oral, other routes)**
- **Volume of distribution**
- **Metabolism (hepatic assays, clearance)**
- **Excretion (renal clearance)**
- **In vivo PK (PK-PD models, allometric scaling)**
- **Drug-drug interactions (hepatic, nonlinear PK)**
- **Candidacy for human studies**

Register today at **ACS.org/DrugDiscovery**

Facilitated By: Terry Kenakin
Professor of Pharmacology
University of North Carolina
School of Medicine

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THIS ACS WEBINAR® WILL BEGIN SHORTLY...

Say hello in the questions window!

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Essentials of Pharmacokinetics for Drug Development

TERRY KENAKIN

Professor, Department of Pharmacology, University of North Carolina School of Medicine

BRYAN TWEEDY

Assistant Director, Office of Career and Professional Education, American Chemical Society

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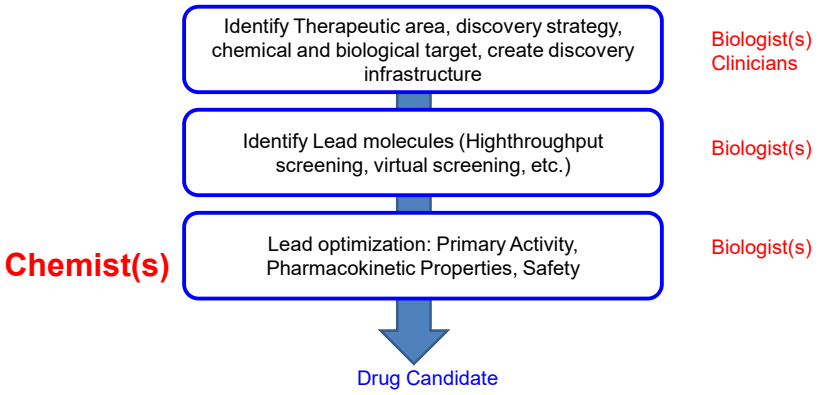
16

Pharmacology in Drug Discovery and Development: The Impact of Pharmacokinetics and Early Safety on Discovery and Development

Terry Kenakin Ph.D.
Department of Pharmacology
University of North Carolina School of Medicine
Chapel Hill, NC

1

The Drug Discovery Process



2

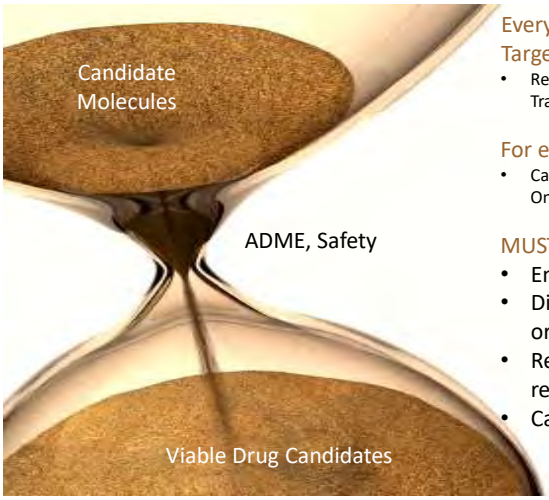
3

Development: PK

- The impact of Pharmacokinetics on Drug utility
- The power of medicinal chemistry to modify PK/Safety in early stages of discovery programs
- Influence of druglike properties on drug pK
- Impact of chemical structure on drug disposition in vivo
- The impact of early safety studies

4

Drug-like Properties for Therapeutic Influence…..



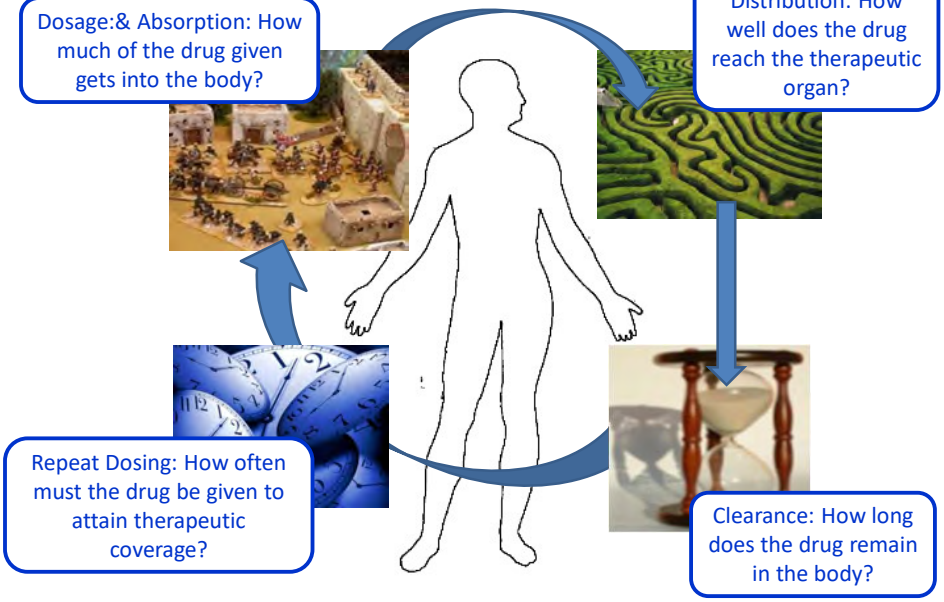
Every biological Drug Target
- Receptors, Enzymes, ion Channels, Transporters, Nuclear Receptors

For every Therapeutic Indication
- Cardiovascular, CNS, GI, Immunology, Oncology, Endocrinology

MUST be able to :
- Enter the Body
- Distribute to the Therapeutic target organ
- Remain there long enough to cause response
- Cause NO HARM

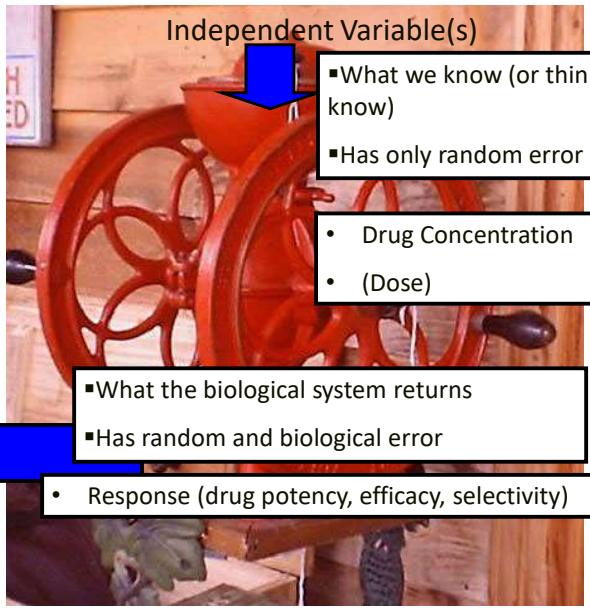
5

Pharmacokinetics



6

Biological (Pharmacological) Experiments



Independent Variable(s)

- What we know (or think we know)
- Has only random error

- Drug Concentration
- (Dose)

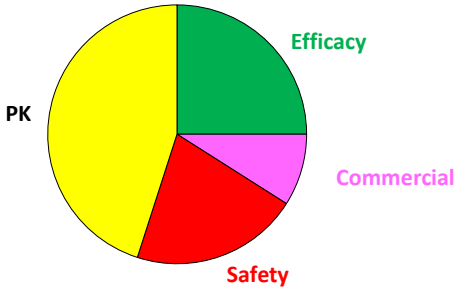
Dependent Variable(s)

- What the biological system returns
- Has random and biological error

- Response (drug potency, efficacy, selectivity)

7

Reasons for Drug Candidate Failures 1991



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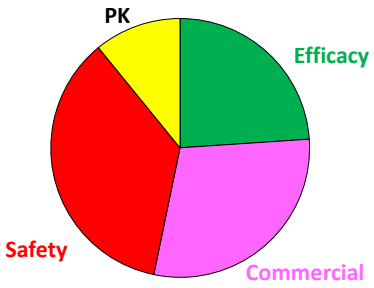
Reasons for Drug Candidate Failures 2000



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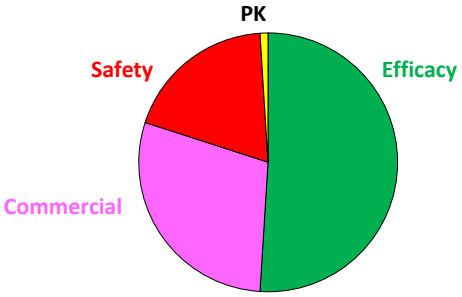
Reasons for Drug Candidate Failures 2008-2010



No reason to put forward a molecule that fails because of PK

10

Assays

Pharmacokinetic
- Solubility / LogP / LogD
- Permeation (PAMPA, CaCo-2
- Metabolism (microsomes / S9
- Plasma stability
- (Protein Binding)

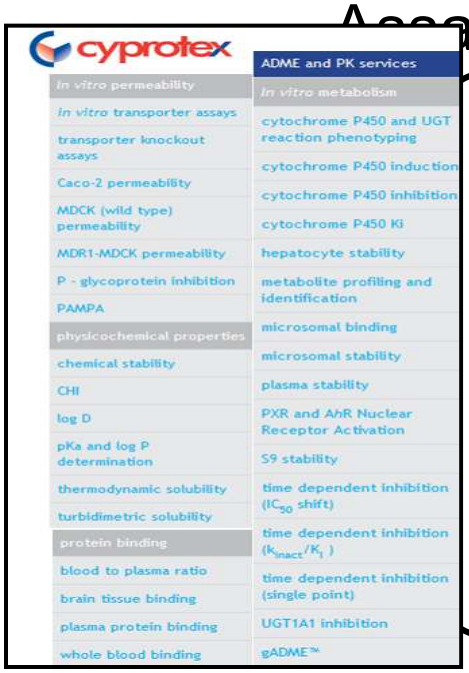
Safety Pharmacology
- hERG
- Autonomic Receptor profile
- Cytotoxicity
- Ames test

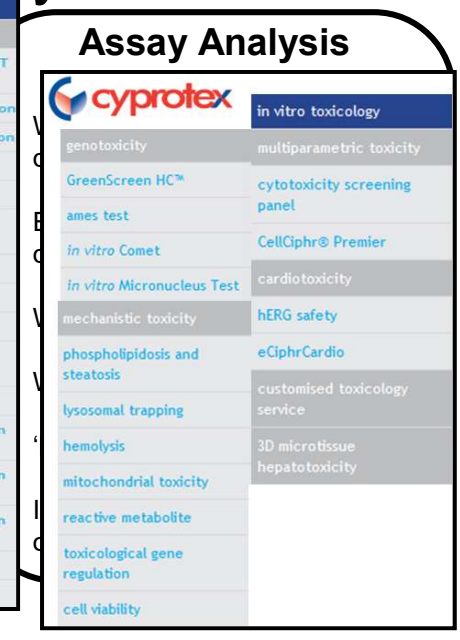
Assay Analysis

1. What question is the assay designed to answer?
2. Elements of the assay (how it is done?)
3. What does the assay require?
4. What data does the assay give?
5. 'Ball park' figures for drugability
6. Interpretation of data / limitations of data

11

Assays





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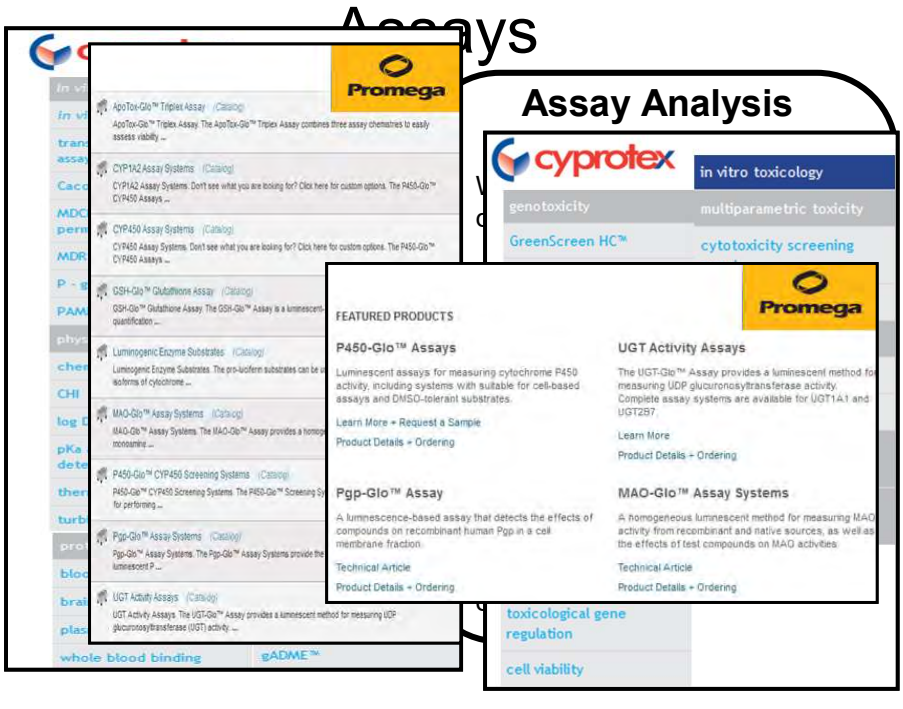


13

Regulatory Guidelines

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 7, 10, 14, 19, 25, 101, 107, 110, 114, 170, 310, 312, 314, 316, 500, 514, 601, 803, 814, and 860

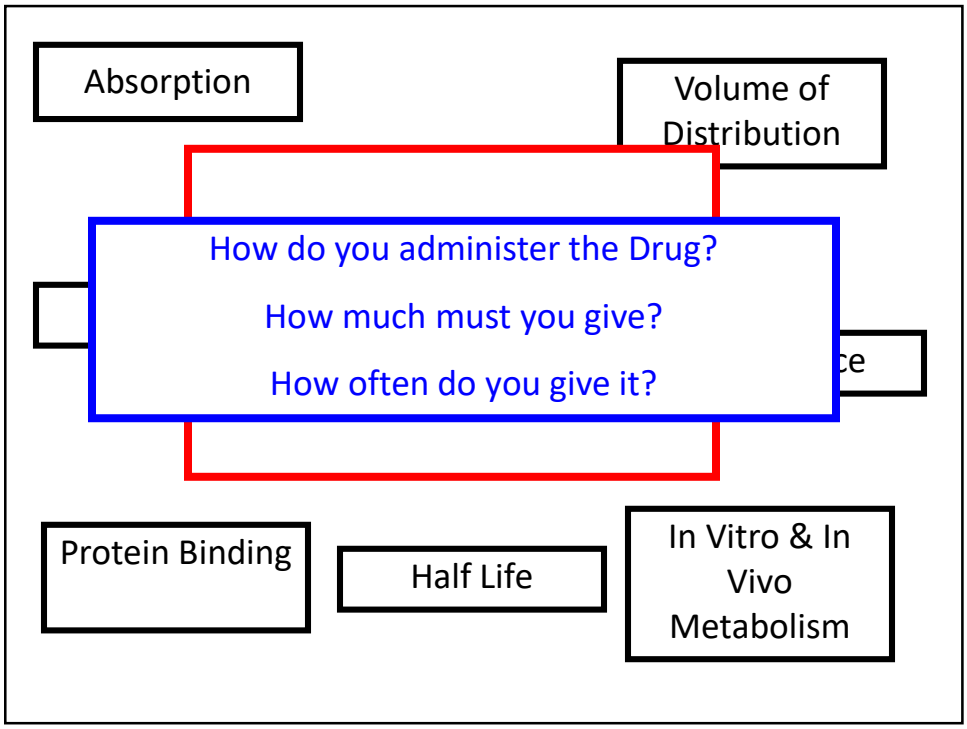
[Docket No. 99N–4783]

Administrative Practices and Procedures; Good Guidance Practices

AGENCY: Food and Drug Administration, HHS.

US FDA (Food and Drug Administration) or EMA (European Medicines Agency)

14



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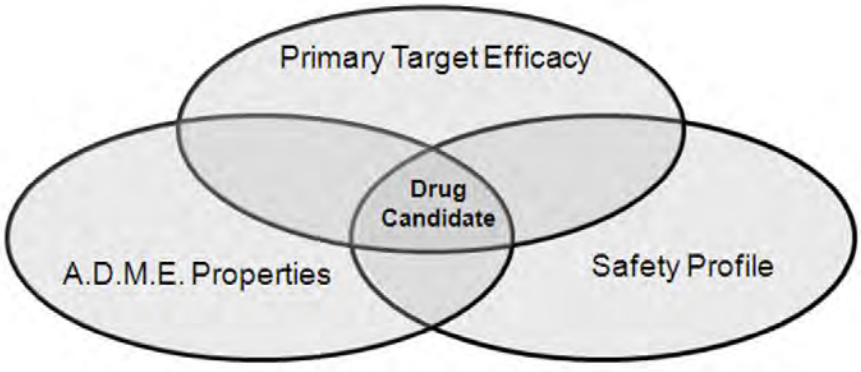
3 Separate Structure-Activity Relationships



36

16

Independence of Drug SAR

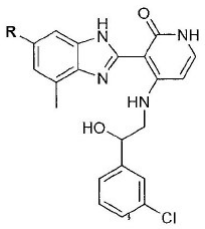
Primary Target SAR

● IGF-1R pKi

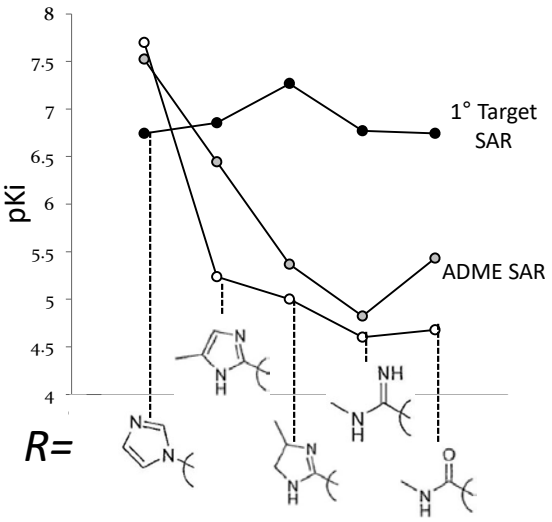
ADME SAR

○ CYP1A2

○ CYP3A4



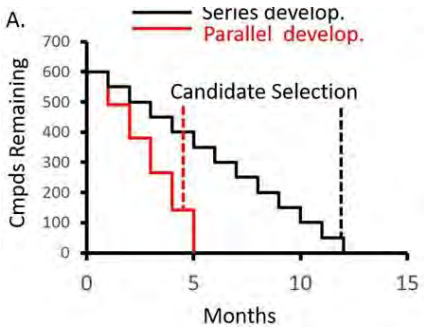
IGF-1R Inhibitor 3-(1H-benzoyl [d]imidazole-2-yl) pyridin-2 (1H)

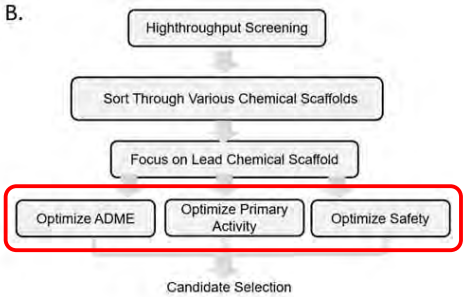


From Velaparthi et al (2007) Bioorg. Med. Chem. Lett. 17:3072

17

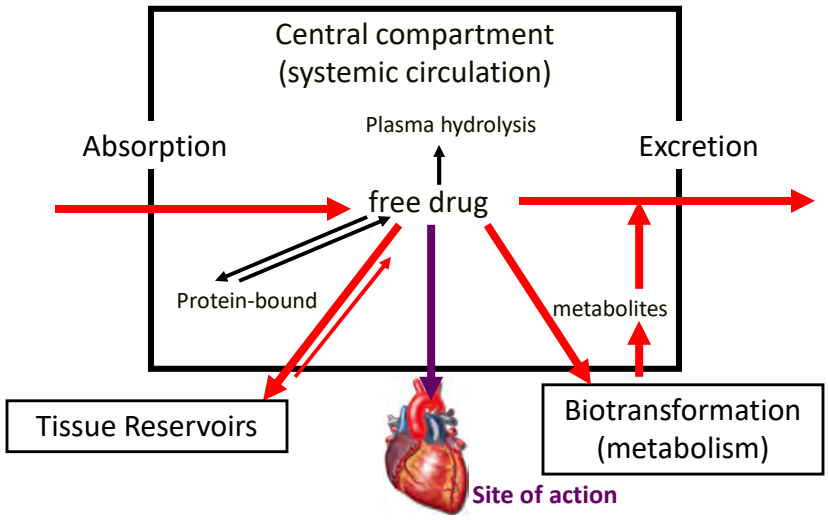
Series vs Parallel Development





18

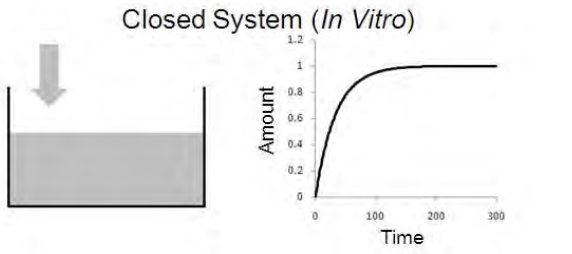
Pharmacokinetics



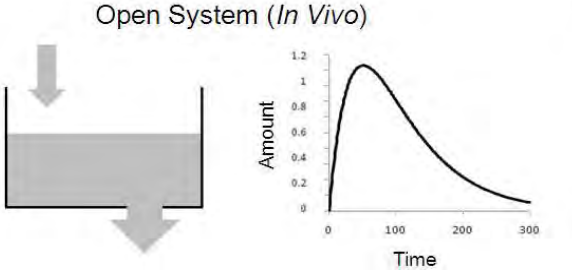
19

A Dichotomy in Drug Discovery……

Drugs are discovered and characterized in these types of systems…



…and used in these types of systems…..



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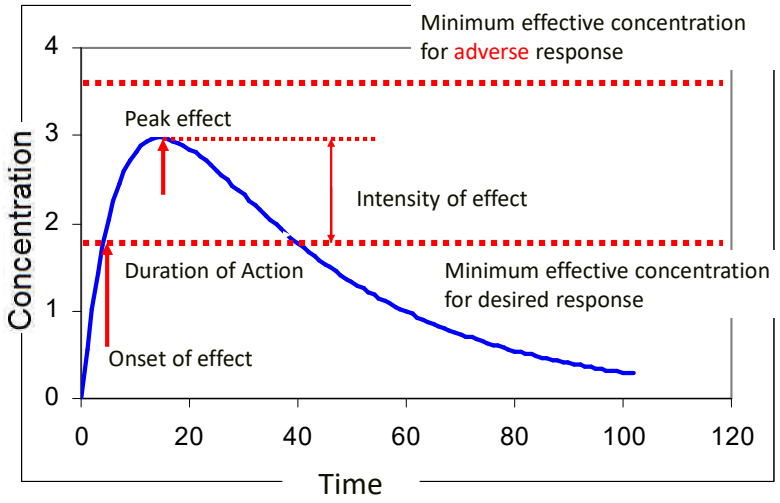
Clinical Pharmacokinetics



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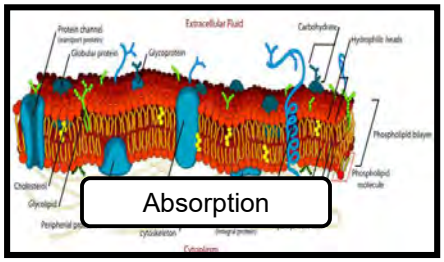

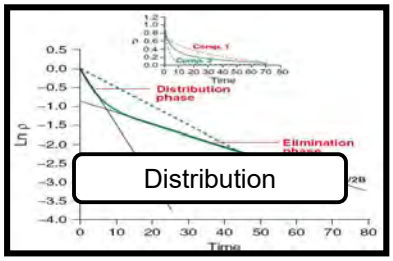

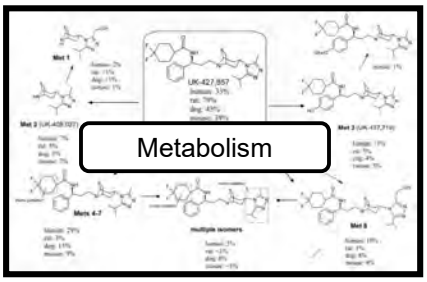

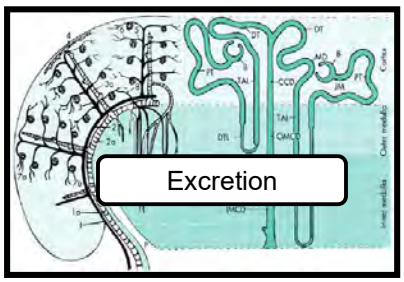

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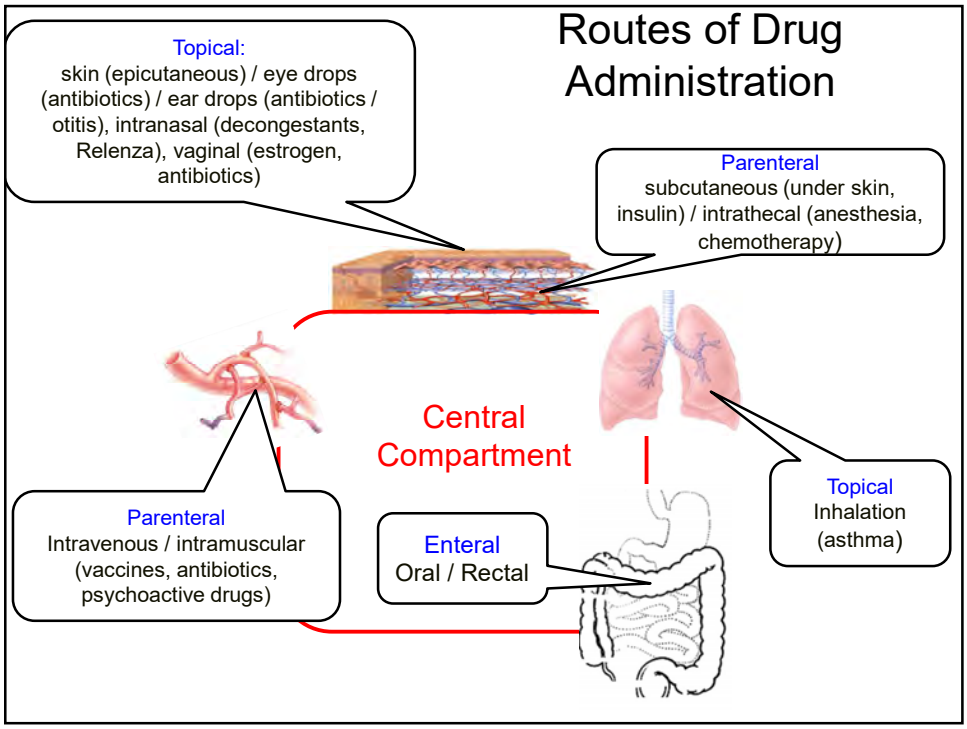
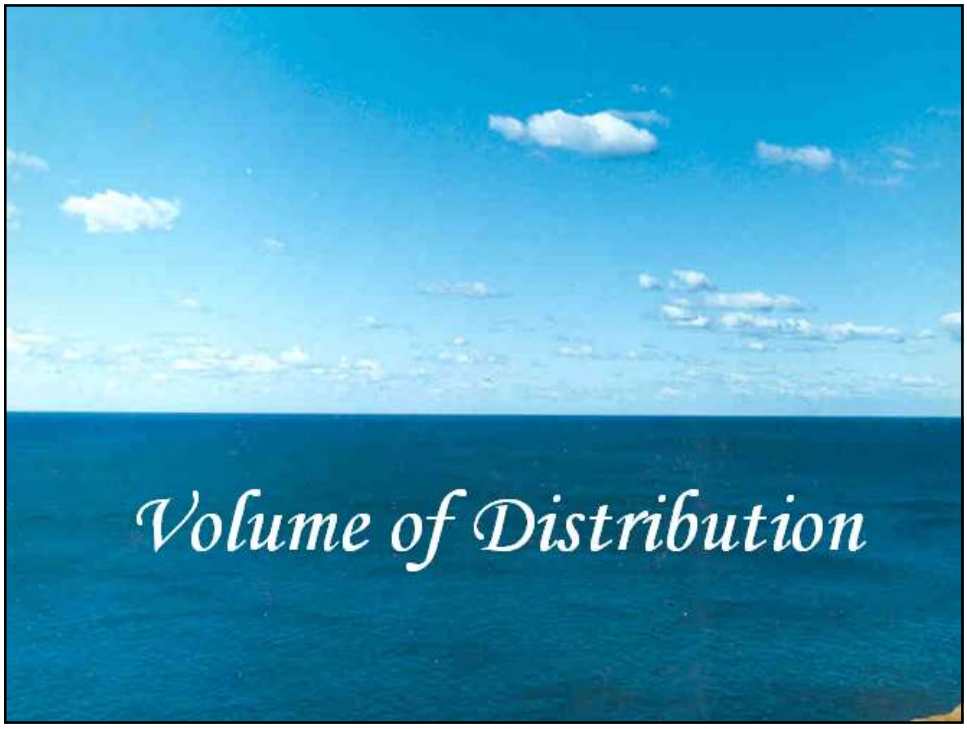
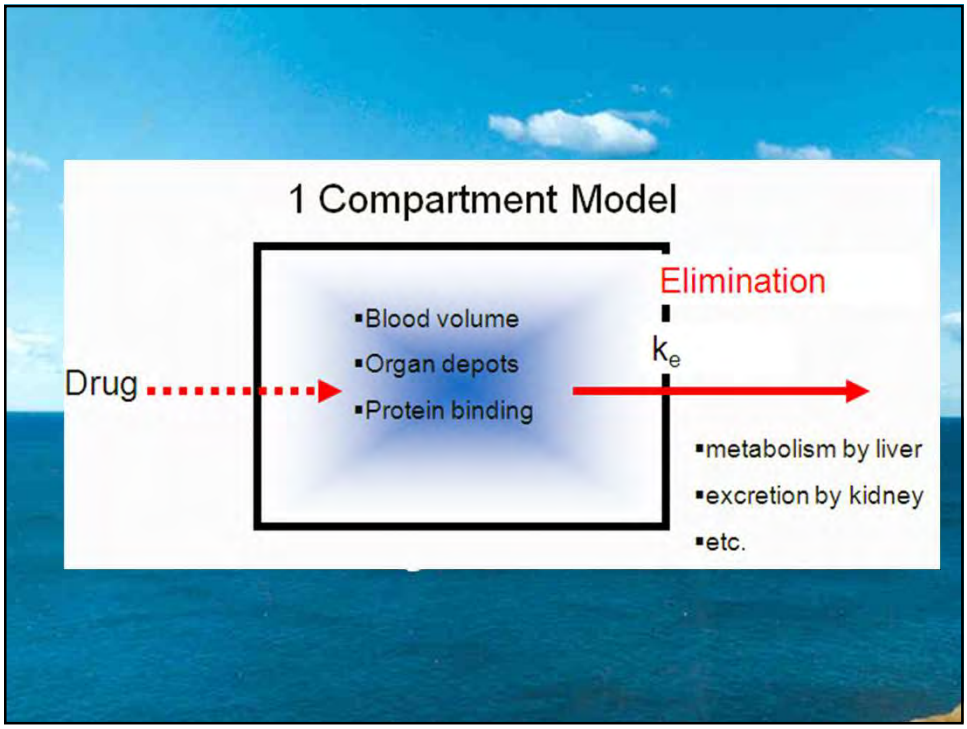

Routes of Drug Administration
Topical:
skin (epicutaneous) / eye drops (antibiotics) / ear drops (antibiotics / otitis), intranasal (decongestants, Relenza), vaginal (estrogen, antibiotics)
Parenteral
subcutaneous (under skin, insulin) / intrathecal (anesthesia, chemotherapy)
Central Compartment
Parenteral
Intravenous / intramuscular (vaccines, antibiotics, psychoactive drugs)
Enteral
Oral / Rectal
Topical
Inhalation (asthma)

23


Volume of Distribution

24


1 Compartment Model
Drug
▪Blood volume
▪Organ depots
▪Protein binding
Elimination
k_e
▪metabolism by liver
▪excretion by kidney
▪etc.

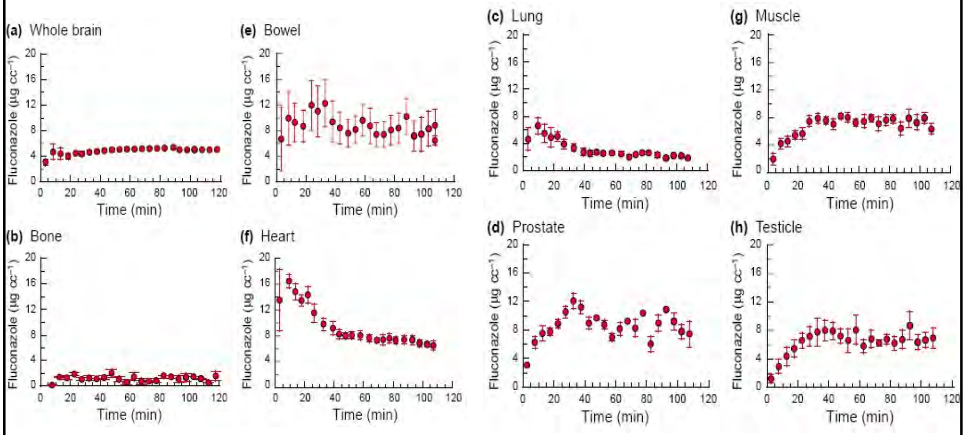
25


47

26

Quantitative PET Scans for PK

^{18}F Fluconazole Distribution with PET Scan



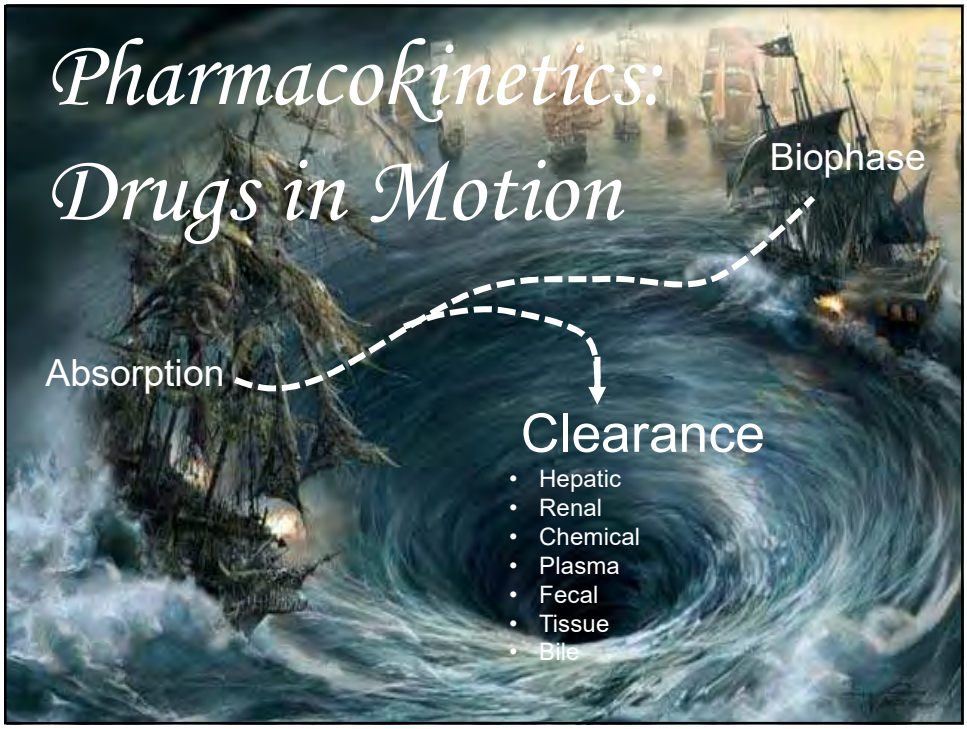
Pien et al (2005) Drug Disc. Today 10:259

27

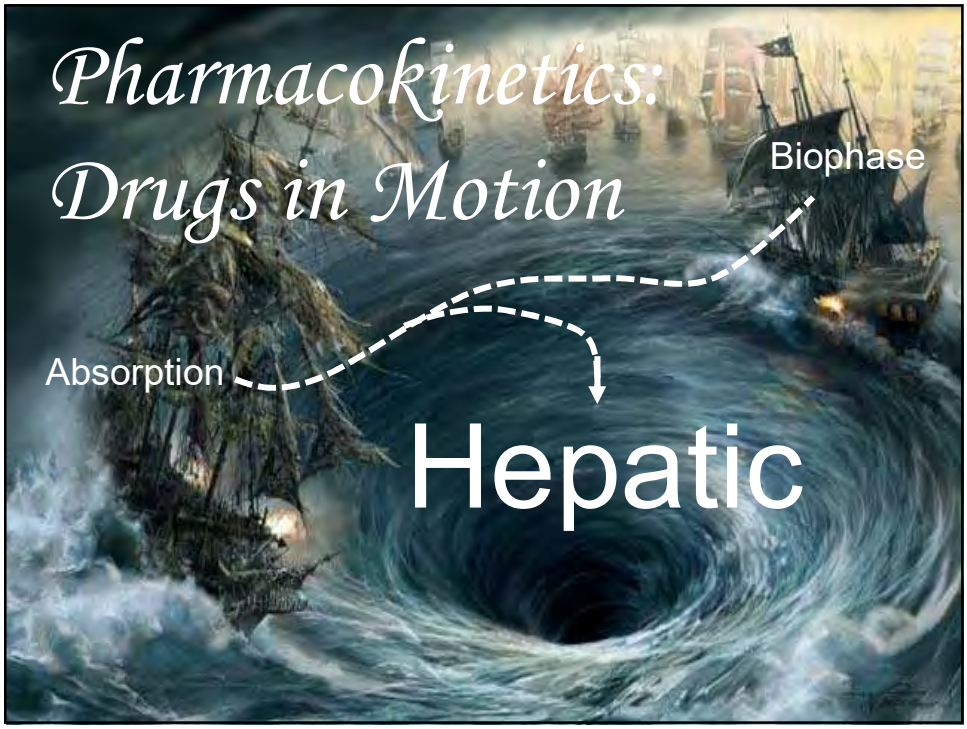
Lecture 6: Development: PK Absorption / Distribution

- The impact of Pharmacokinetics on Drug utility
- The power of medicinal chemistry to modify PK/Safety in early stages of discovery programs
- Influence of druglike properties on drug pK
- Impact of chemical structure on drug disposition in vivo
- The impact of early safety studies

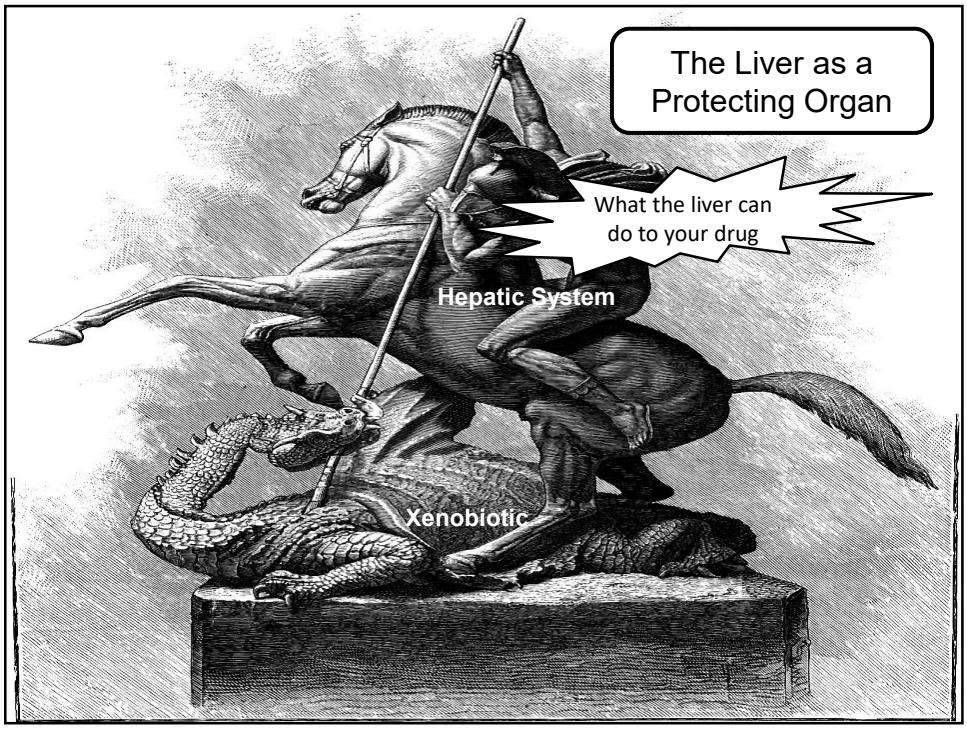
28


Pharmacokinetics:
Drugs in Motion
Biophase
Absorption
Clearance
• Hepatic
• Renal
• Chemical
• Plasma
• Fecal
• Tissue
• Bile

29

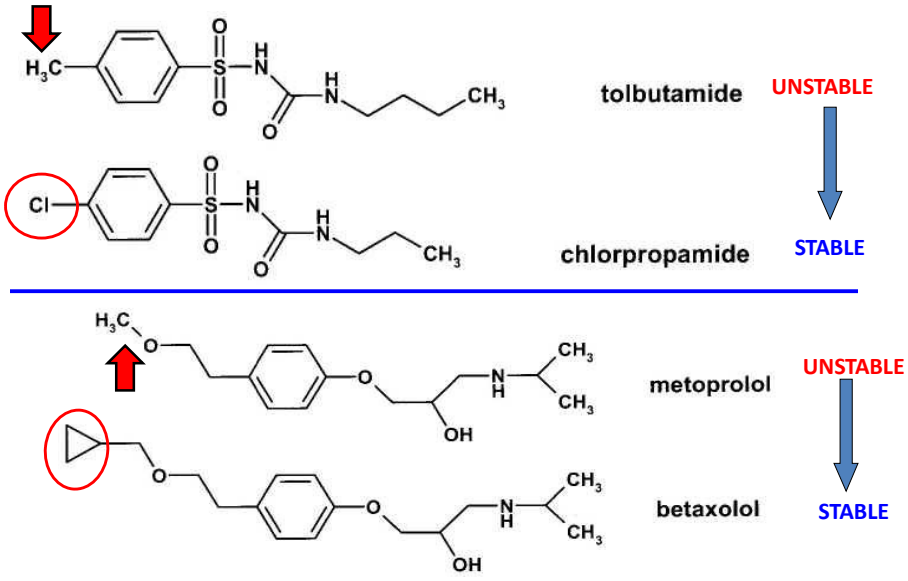

Pharmacokinetics:
Drugs in Motion
Biophase
Absorption
Hepatic

30



31

SAR for Hepatic Metabolism



Manoury et al (1987) J Med. Chem. 30:1003

32

Chemically Addressing PK Issues

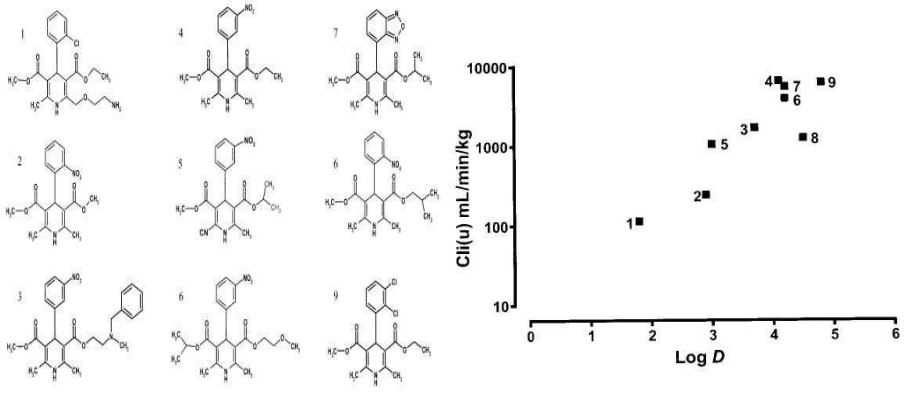
- Structurally affect Physico-Chemical Properties
  - Define relationship between pKa, LogP, PSA that tracks PK problem
  - General effect to address global problem (i.e. absorption)

- Distinct Site-Directed structural change
  - Block formation of a distinct metabolite
  - Reduce affinity for transport process (i.e. P-gp)

33

Log D and Hepatic Clearance

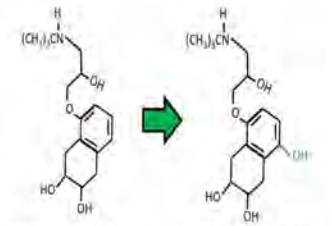
(Susceptibility to Metabolism)



Smith et al (2006) Pharmacokinetics and Metabolism in Drug Design

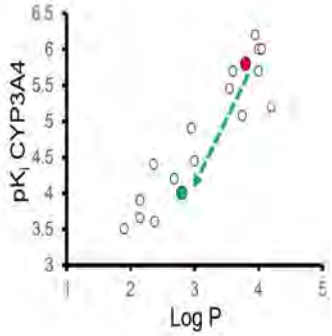
34

Modifying Druglike Character to Eliminate a Hazardous Side Effect



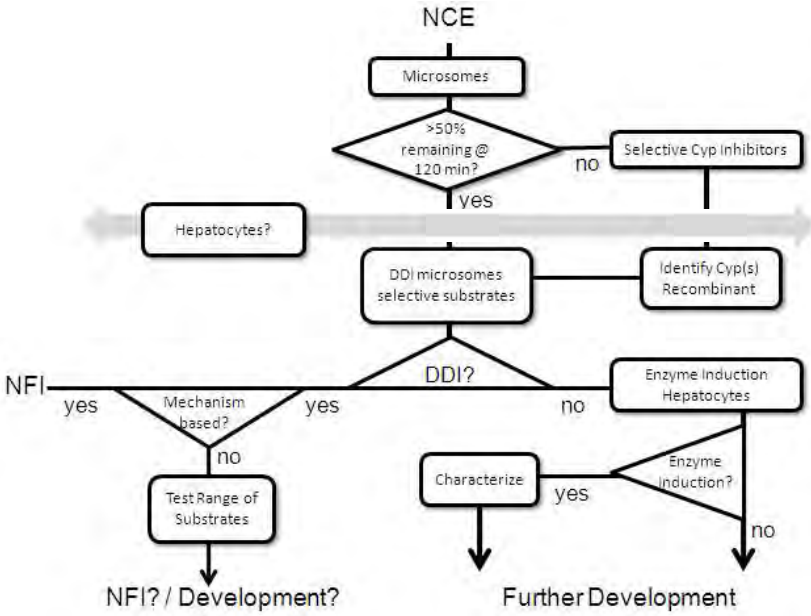
Fragments	π
11 carbons	5.5
1 phenyl	2
2 IMHB	1.3
1 amine	-1
1 ether	-1
3 alcohols	-3
Log P	3.8

Fragments	π
11 carbons	5.5
1 phenyl	2
2 IMHB	1.3
1 amine	-1
1 ether	-1
4 alcohols	-4
Log P	2.8

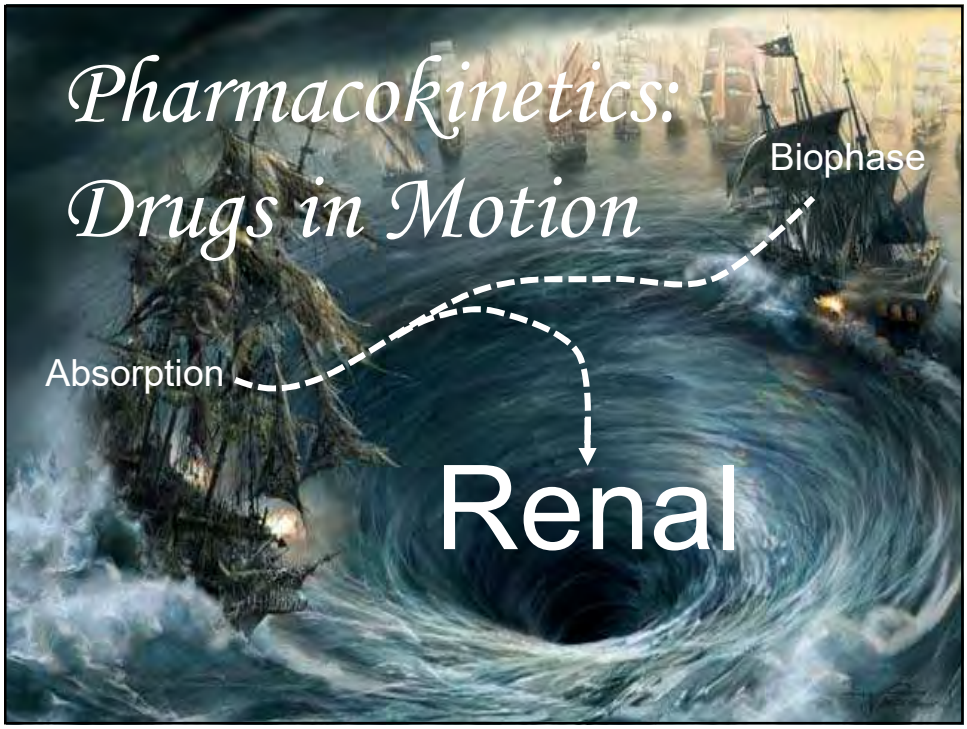


35

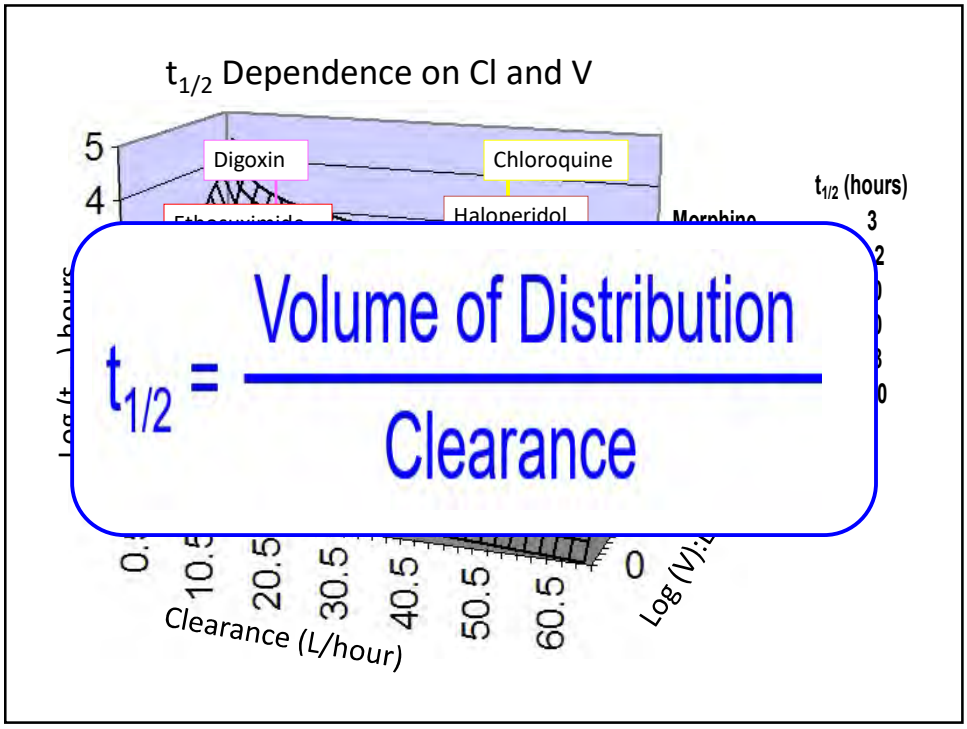
Decision Tree for Assessing In Vitro Hepatic Effects



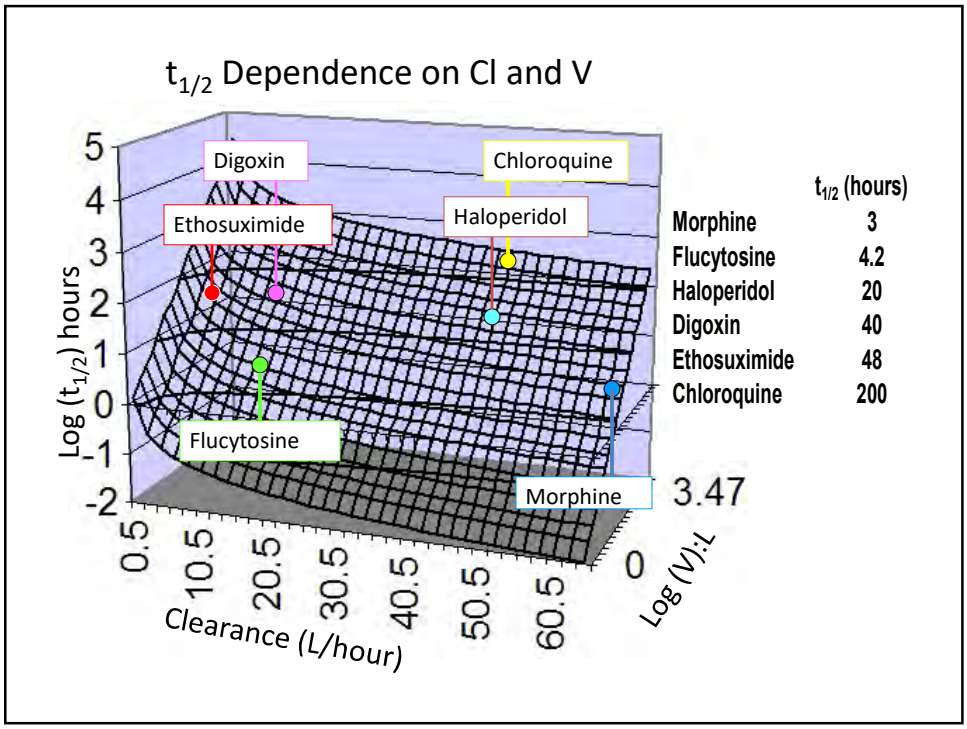
36


Pharmacokinetics:
Drugs in Motion
Biophase
Absorption
Renal

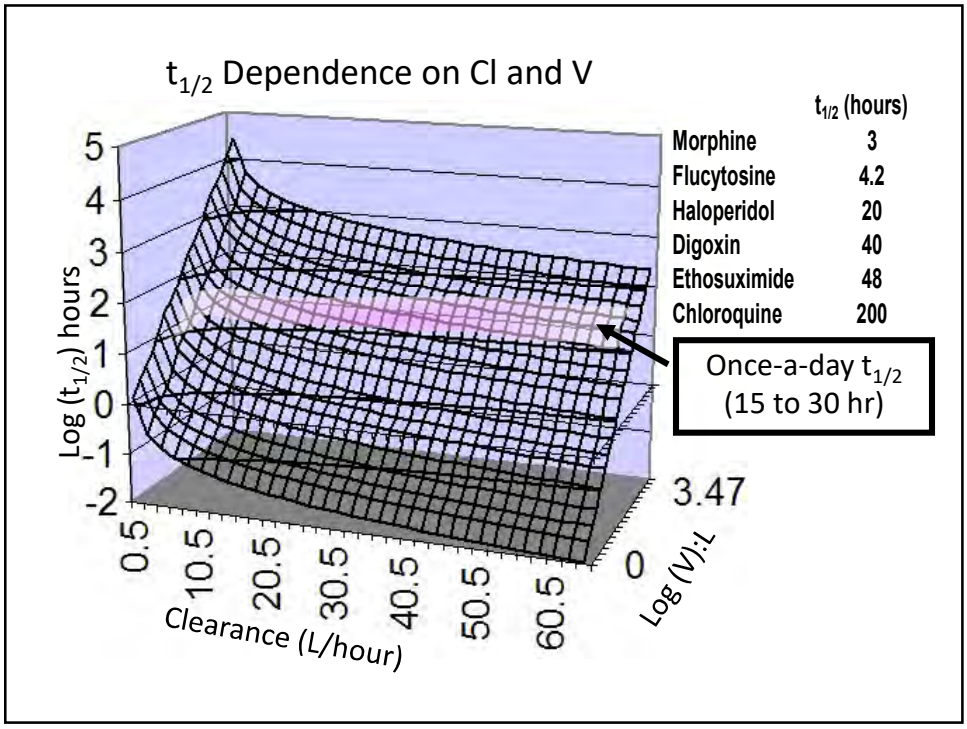
37


$t_{1/2}$ Dependence on Cl and V
Digoxin
Chloroquine
Haloperidol
Morphine
$t_{1/2}$ (hours)
Clearance (L/hour)
$t_{1/2} = \frac{\text{Volume of Distribution}}{\text{Clearance}}$

38

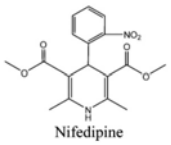

$t_{1/2}$ Dependence on Cl and V
Digoxin
Chloroquine
Ethosuximide
Haloperidol
Flucytosine
Morphine
Log ($t_{1/2}$) hours
5
4
3
2
1
0
-1
-2
0.5
10.5
20.5
30.5
40.5
50.5
60.5
Clearance (L/hour)
3.47
0
Log (V):L
$t_{1/2}$ (hours)
Morphine 3
Flucytosine 4.2
Haloperidol 20
Digoxin 40
Ethosuximide 48
Chloroquine 200

39


$t_{1/2}$ Dependence on Cl and V
Log ($t_{1/2}$) hours
5
4
3
2
1
0
-1
-2
0.5
10.5
20.5
30.5
40.5
50.5
60.5
Clearance (L/hour)
3.47
0
Log (V):L
$t_{1/2}$ (hours)
Morphine 3
Flucytosine 4.2
Haloperidol 20
Digoxin 40
Ethosuximide 48
Chloroquine 200
Once-a-day $t_{1/2}$
(15 to 30 hr)

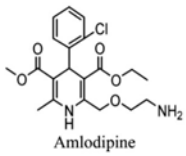
40

Manipulation of Dosing with Acid-Base Character of Molecules



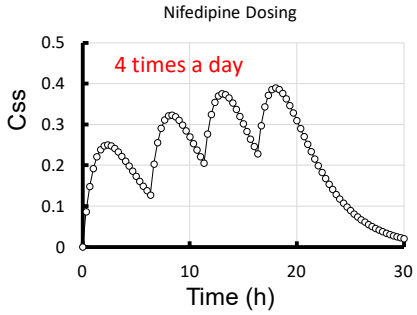
Neutral

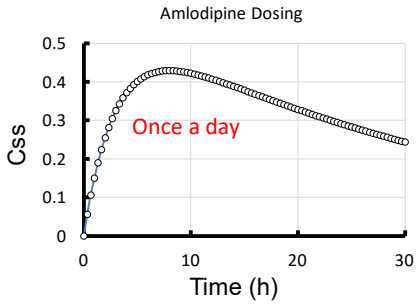
- LogP=2.9
- V_d=0.79 L/kg
- CL=7.3 mLm^{-1}kg^{-1}
- $t_{1/2}$= 1.9 h



Base

- LogP=3.3
- V_d=17 L/kg
- CL=7.0 mLm^{-1}kg^{-1}
- $t_{1/2}$= 34 h



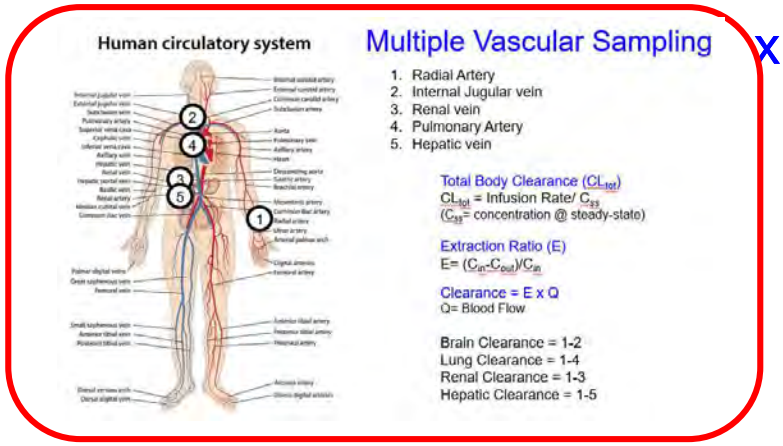


41

Methods to Delineate Complex In Vivo PK Mechanisms

- Multiple Vascular Access
- Pattern Recognition
- Co-addition of Tool Molecules
- Knockout of PK processes

42



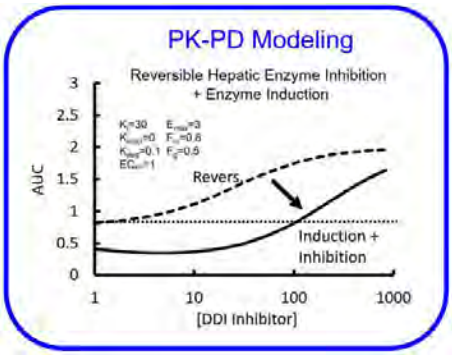
- Knockout of PK processes

43

Methods to Delineate Complex In Vivo PK Mechanisms

- Multiple Vascular Access
- Pattern Recognition
- Co-addition of Tool Molecules
- Knockout of PK processes

44

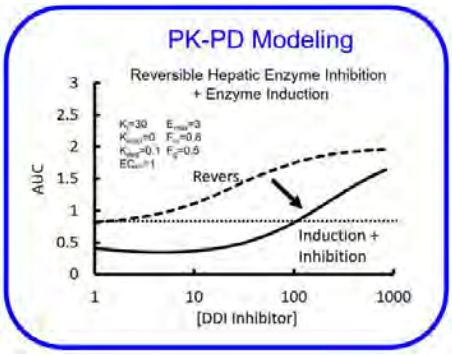


elineate Complex
Mechanisms

cess

- Pattern Recognition
- Co-addition of Tool Molecules
- Knockout of PK processes

45



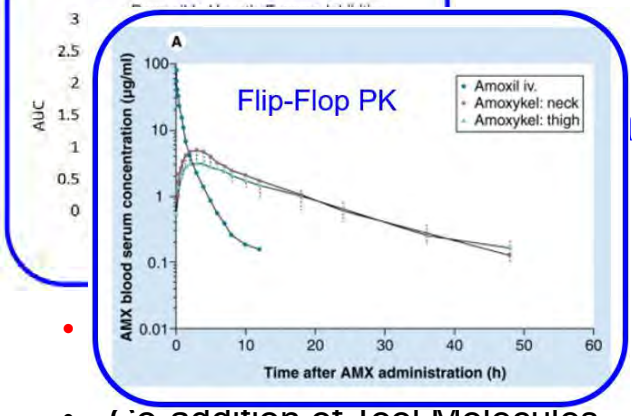
elineate Complex
Mechanisms

cess

- Pattern Recognition
- Co-addition of Tool Molecules
- Knockout of PK processes

46

PK-PD Modeling

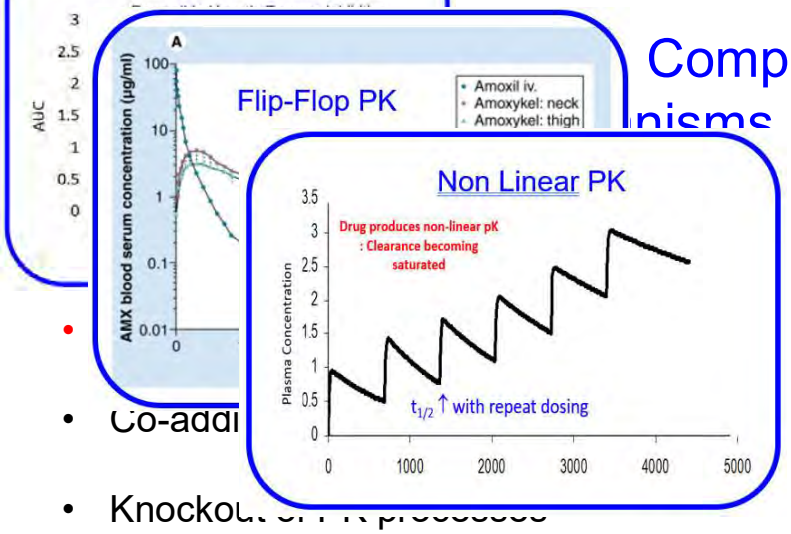


Complex nisms

- Co-addition of Tool Molecules
- Knockout of PK processes

47

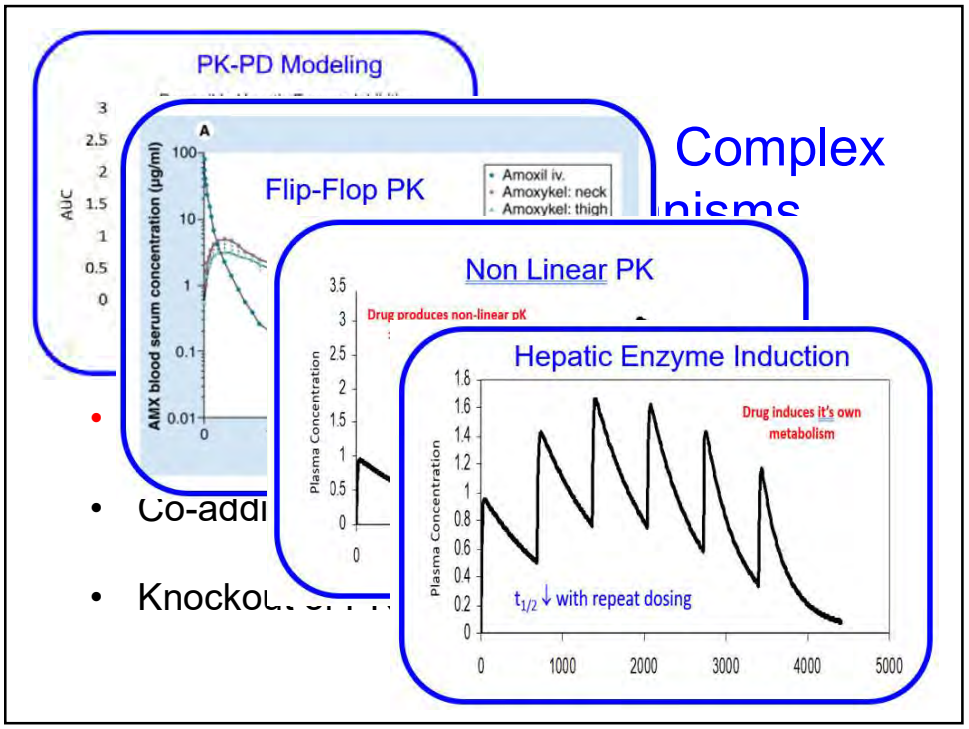
PK-PD Modeling



Complex nisms

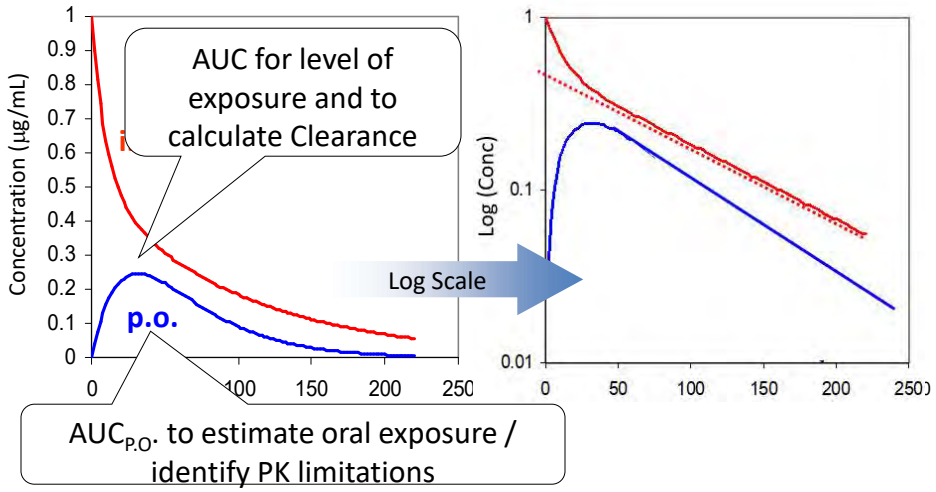
- Co-addi
- Knockou

48

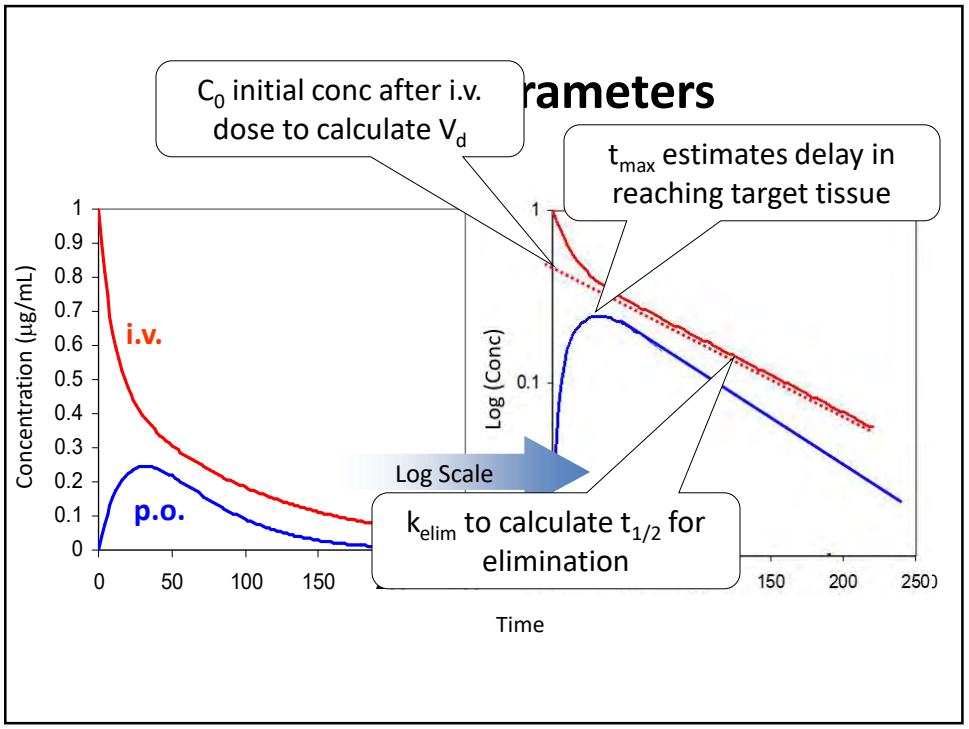


49

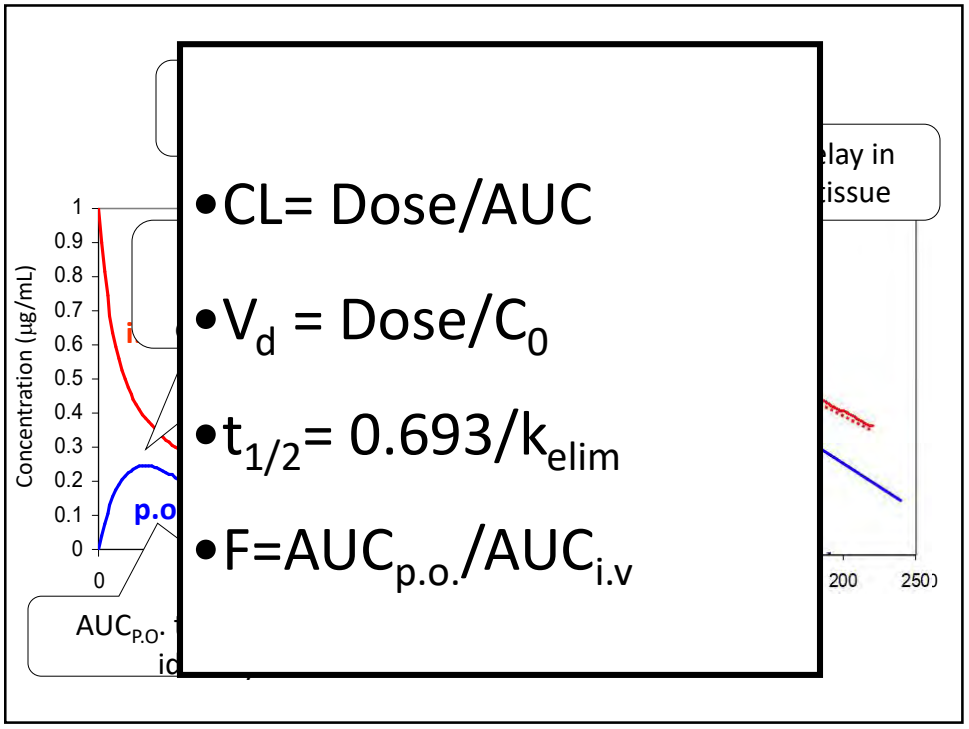
In Vivo PK Parameters



50


rameters
C_0 initial conc after i.v. dose to calculate V_d
t_{max} estimates delay in reaching target tissue
Concentration (µg/mL)
i.v.
p.o.
Log (Conc)
Log Scale
k_{elim} to calculate $t_{1/2}$ for elimination
Time

51


Concentration (µg/mL)
p.o
$AUC_{P.O.}$
•CL= Dose/AUC
•V_d = Dose/C_0
•$t_{1/2}$= 0.693/k_{elim}
•F=$AUC_{p.o.}$/$AUC_{i.v}$

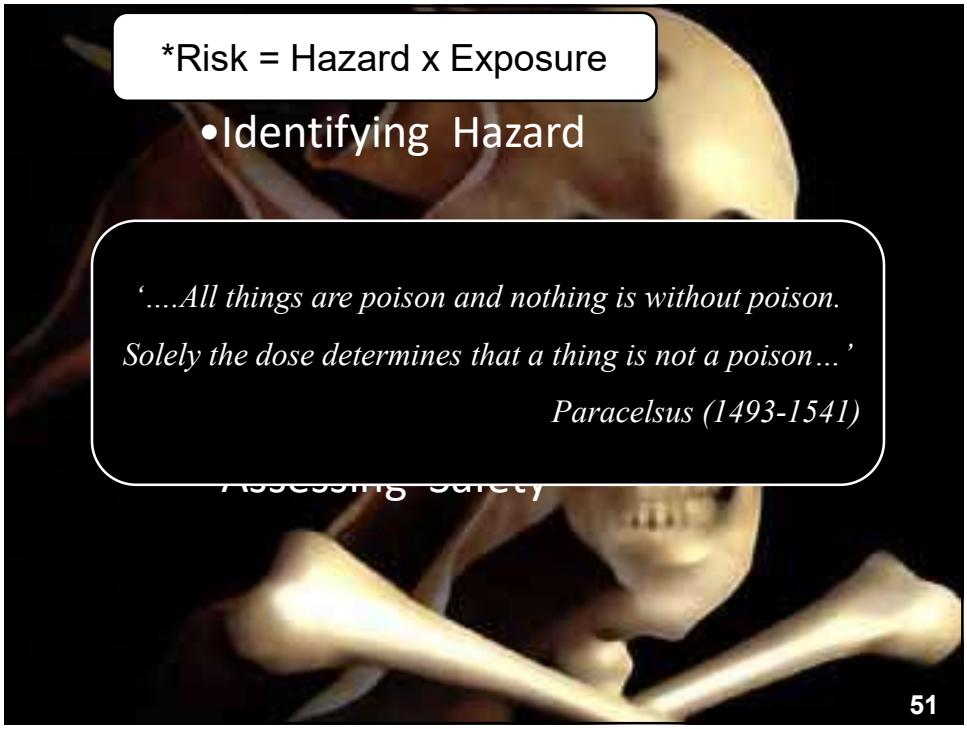
52


Pharmacokinetics
for Pharmacologic
Safety Testing

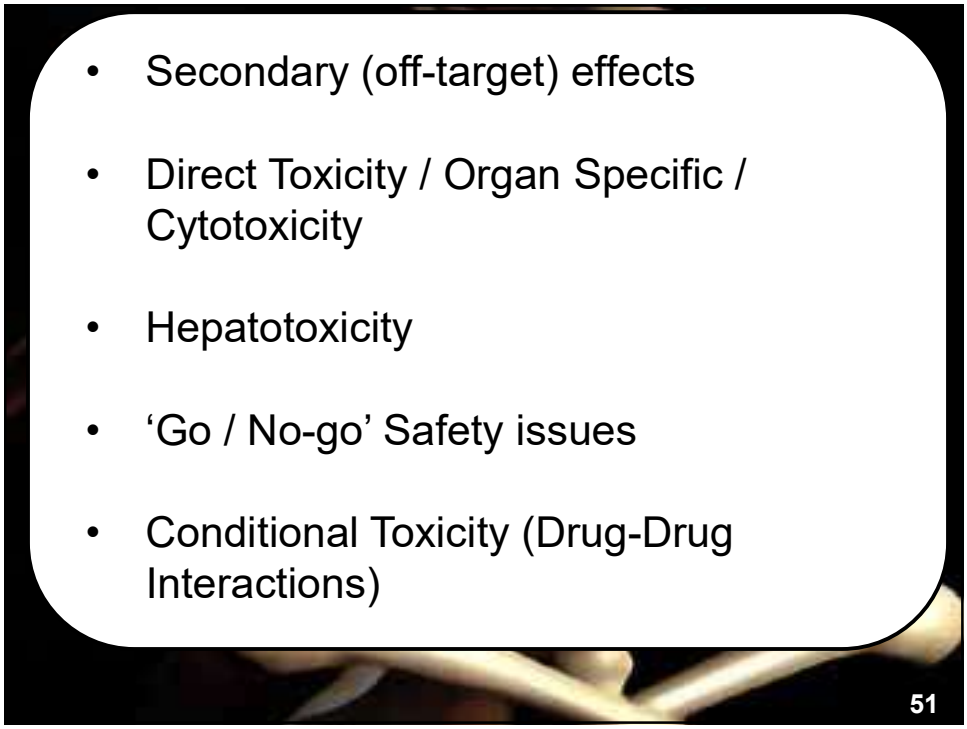
53


*Risk = Hazard x Exposure
•Identifying Hazard
•Defining Risk*
•Safety Pharmacology Assays
•Assessing Safety
51

54

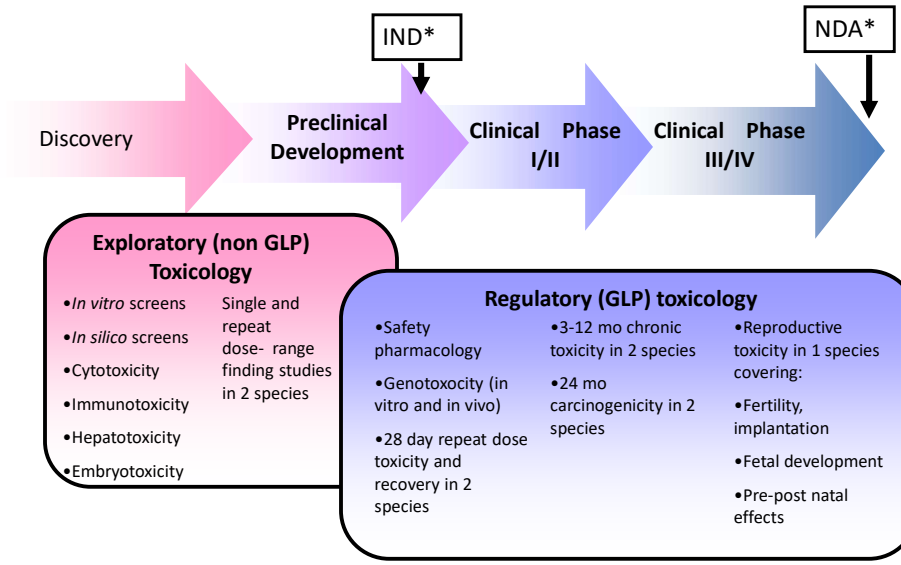

*Risk = Hazard x Exposure
•Identifying Hazard
'....All things are poison and nothing is without poison.
Solely the dose determines that a thing is not a poison…'
Paracelsus (1493-1541)
51

55


• Secondary (off-target) effects
• Direct Toxicity / Organ Specific / Cytotoxicity
• Hepatotoxicity
• 'Go / No-go' Safety issues
• Conditional Toxicity (Drug-Drug Interactions)
51

56

Safety Assessment



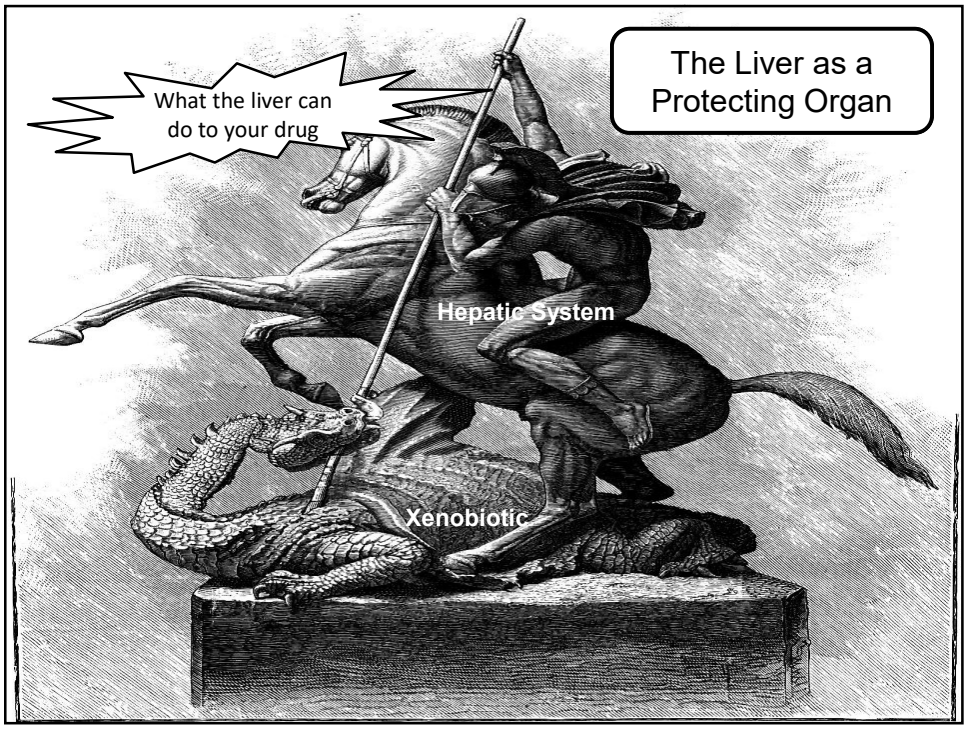
*Investigational New Drug: Application to conduct clinical trials
*New Drug Application: Application to market drug

57

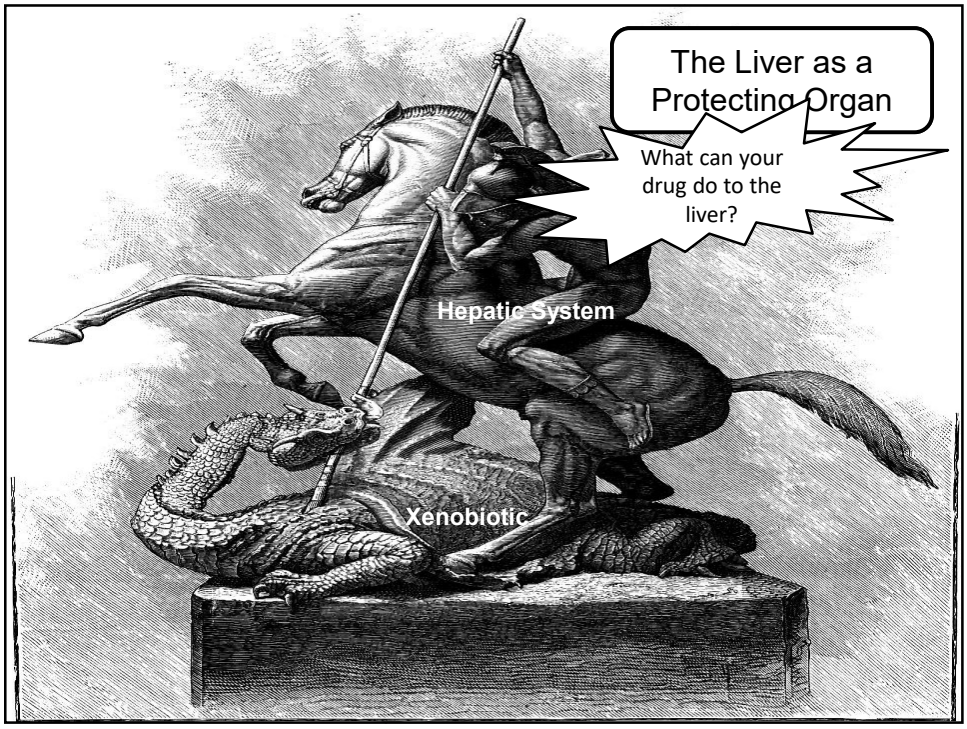
'Off-Target' Drug Effects

- Receptors
- Enzymes
- Transporters
- DNA
- Gene
- Cell processes
- Behavior
- Cardiovascular
- Gastrointestinal
- Endocrine function
- Mutation
- Tumorigenesis
- Reproductive function
- Histology

58


The Liver as a Protecting Organ
What the liver can do to your drug
Hepatic System
Xenobiotic

59


The Liver as a Protecting Organ
What can your drug do to the liver?
Hepatic System
Xenobiotic

60

Drug-Induced Hepatoxicity

Intrinsic Hepatotoxicity:

Occurs in all individuals in a dose-dependent, and thus predictable, manner

61

Drug-Induced Hepatoxicity

Safety Pharmacology Trivia

Drug-induced liver injury most frequent cause of withdrawal of approved drug

62

What registrants will gain from this Course:

- Information to prevent inadequate PK from derailing a promising new drug candidate
- Strategies to enhance the utility of a new drug candidate
- An understanding of the basic principles of pharmacokinetics and early safety pharmacology to support subsequent program development of new compounds

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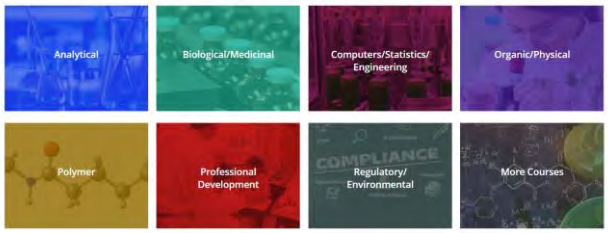
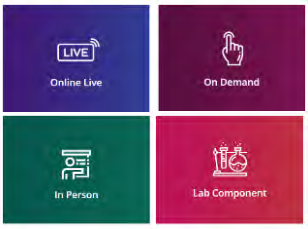


Course Formats



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6