APTI WEBINARS

# PHARMACOKINETICS MOD. & SIM.

## (PK-Mod&Sim)

Presented by Chandramouli R

# SUMMARY OF CONTENTS

SESSION 1

7 MAY 2020

What this session is ABOUT & NOT ABOUT

Conventional PK

Compartmental Models

How is PK Mod & Sim applied in Drug Development?

ACAT Models

PBPK Models

Software Blackbox - what is under the hood?

Computing resources in PK - Intro & Comparision

**Demo -** say hello to SimBio, WLN, GP

**Demo -** Starting your GP Project - file systems

**Demo -** Predict the fraction absorbed of a drug using *in vitro* properties

# WHAT THIS SESSION IS NOT ABOUT

## WHAT IS OUT OF BOUNDS

- This is NOT a theoretical PK / BP class
- We will NOT be talking PK theory - not more than required
- PK is a crosscutting topic - only computational aspects of PK
- The presentor does not endorse the software titles in any manner

# WHAT THIS SESSION IS ABOUT

## CONTENTS DEALT HERE

- This is a session on applied PK
- Computing aspects of PK will be dealt here
- LecDem sessions on popular PK computing resources (GP, /WINNONLIN /Lixoft/ SimBiology)
- LecDem & a GP case study
- The softwares demoed here have an evaluation and/or an academic license

# PHARMACOKINETICS

deals with the changes in concentration of a drug and its metabolites in the  different body fluids and tissues as a result of the processes of absorption,  distribution, elimination, and metabolism.

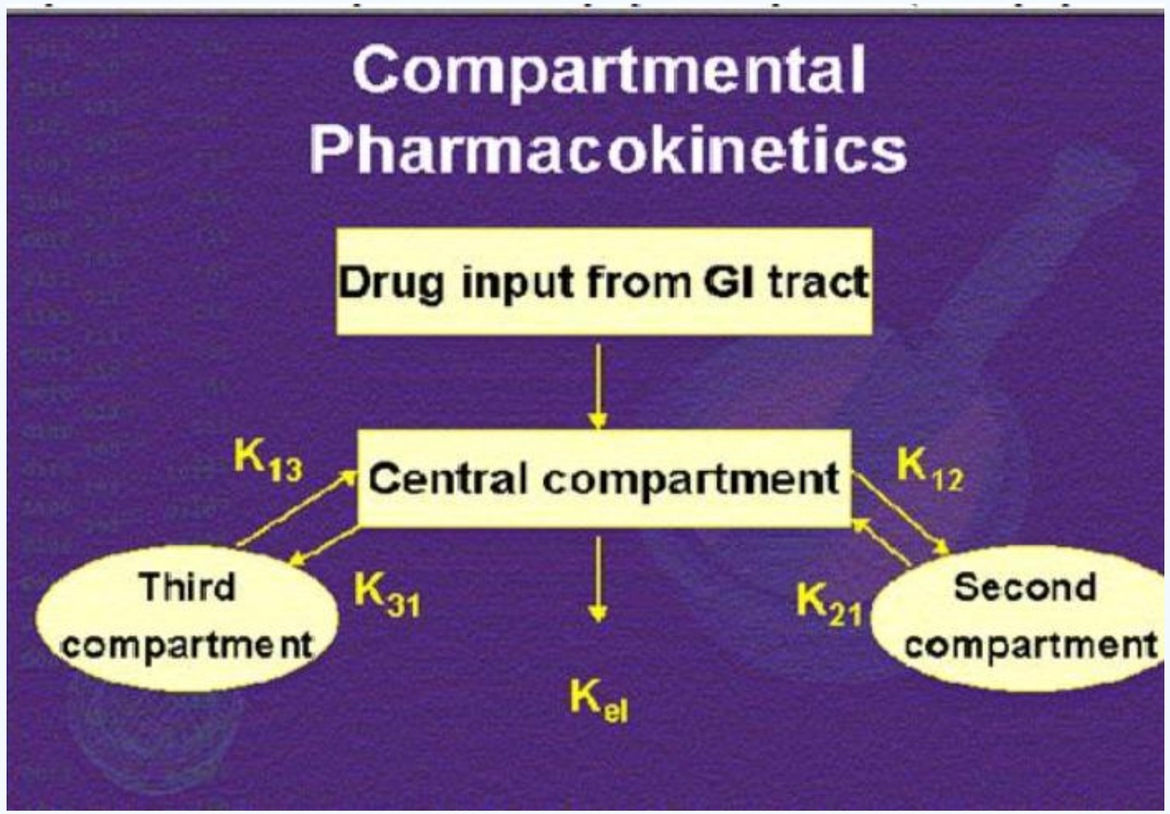
# PHARMACOKINETIC MODEL

**mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species**

# PHARMACOKINETIC SIMULATIONS

**simulation method used in determining the safety levels of a drug during its development**

# Flavours of PK



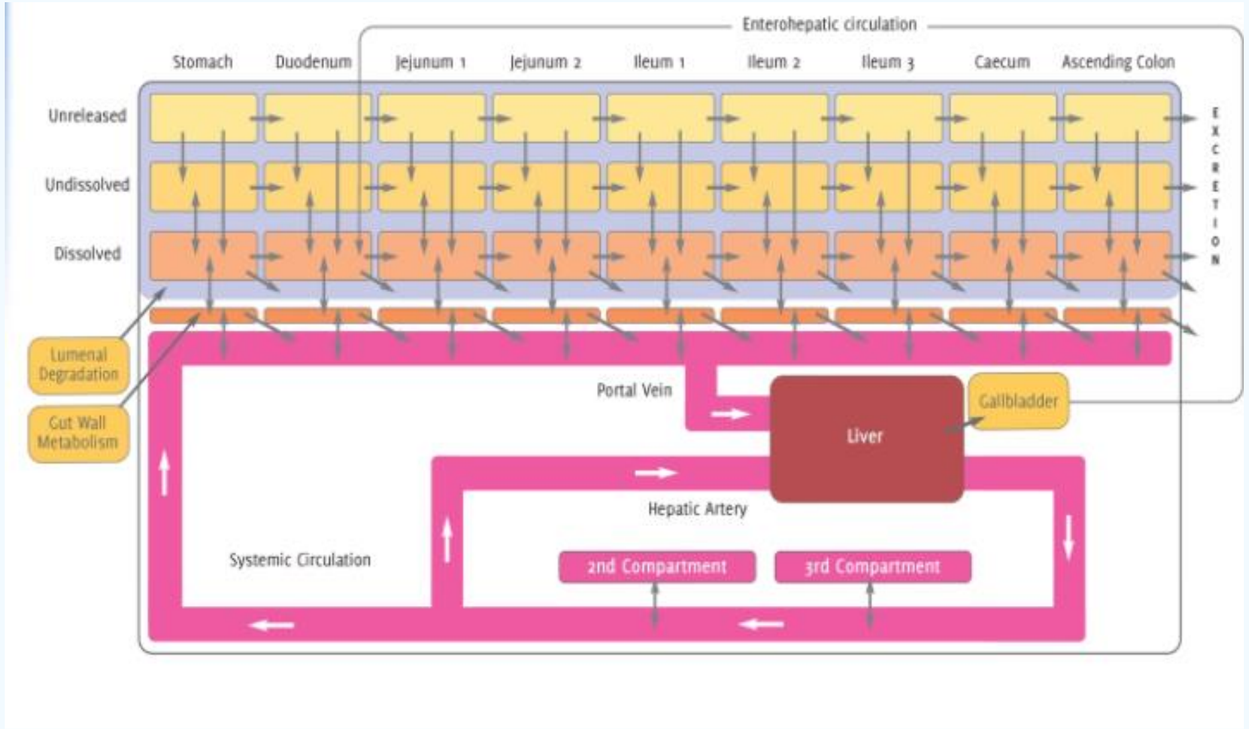

## COMPARTMENTAL

- pharmacokinetics that take place after absorption are defined by the parameters: first pass extraction , clearance , volume of distribution , subject weight, central compartment (1) to peripheral compartment (2) rate constant (K12), and peripheral compartment to central compartment rate constant (K21).
- Or a 3 compartment model

# Flavours of PK

## ADVANCED COMPARTMENTAL ABSORPTION AND TRANSIT MODEL (ACAT)

- Based on the original Compartmental Absorption and Transit (CAT) model published by Yu and Amidon
- GIT as a set of compartments. These compartments correspond approximately to the different segments of the digestive tract – stomach, duodenum, jejunum, ileum, and colon:
- The first compartment represents the stomach, the next seven compartments represent the small intestine, and the final gastrointestinal compartment represents the colon.

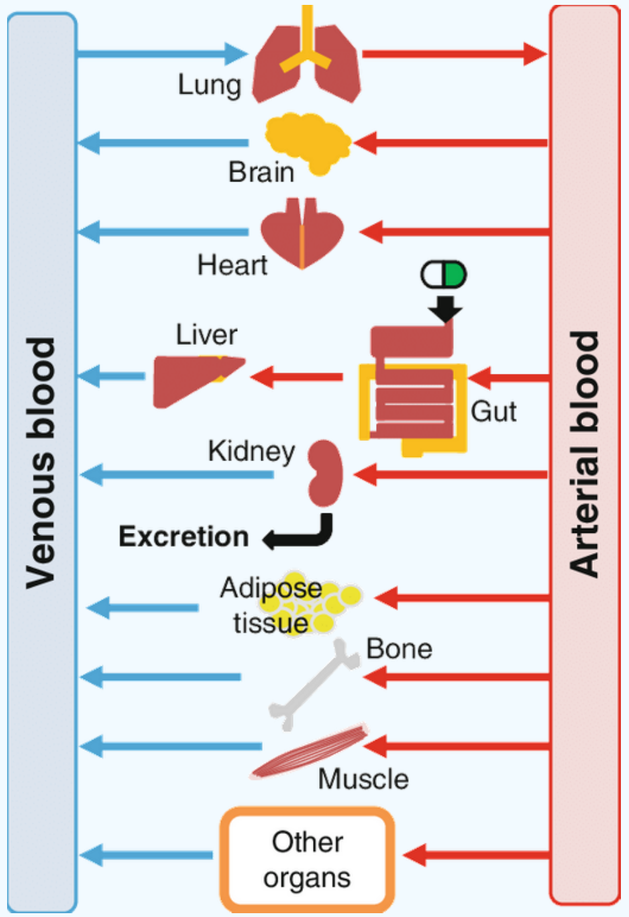



Yu and Amidon (1999).

# Flavours of PK

## PHYSIOLOGICALLY-BASED PHARMACOKINETICS (PBPK)

- PBPK treats the distribution and clearance of a drug on the basis of the drug's interaction individually with all of the organs.
- PBPK has traditionally been considered difficult to parameterize due to the need for estimates or measurements of tissue:plasma partition coefficients (Kps) and tissue protein binding (fut) values.
- In the past 10 years, these problems have been solved through *in silico* estimates based on tissue composition of neutral lipids, phospholipids, and water

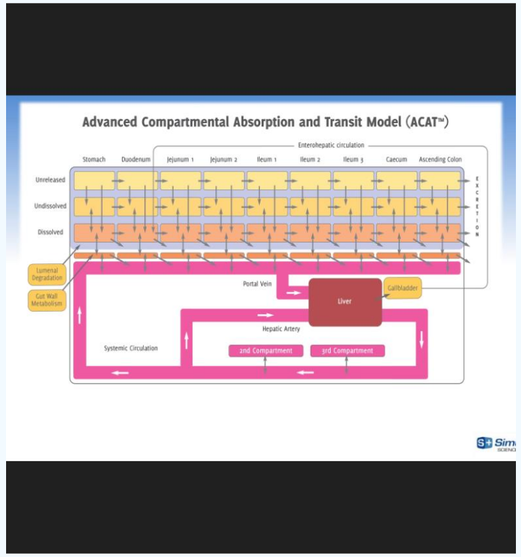



(Poulin, 2000, 2001, 2002, Rodgers, 2005, 2006, 2007).

# Generations of PK

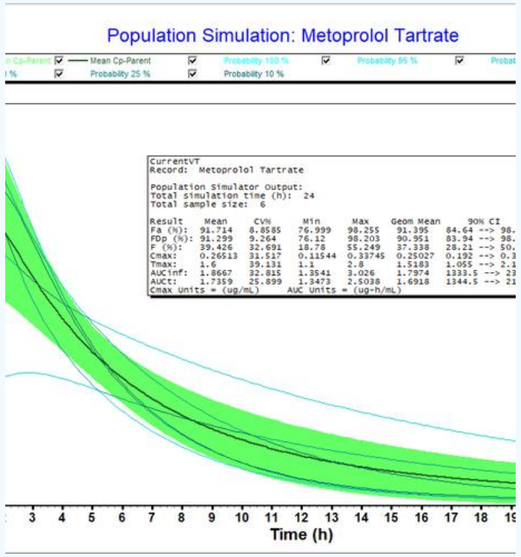
## 1 G

based on Blackbox and emperical models, lesser development of AMs




## 2 G

Compartmental & ACAT models, based on better mathematical models and Bio and cheminformatics support




## 3 G

PBPK models & sim - better computational and statistical prowess

# DD APPLICATIONS OF PK-MOD&SIM

## WHY IS IT IMPORTANT TO US?

# DRUG DEVELOP. APPLICATIONS OF PK-MOD&SIM

## WHY IS IT IMPORTANT TO US?

**Model & simulate** gastrointestinal, ocular and nasal and pulmonary absorption,  pharmacokinetics, and optionally, pharmacodynamic effects, for drugs dosed in humans and animals

**Model & predict Absorption** net fraction of the dose that is absorbed into the apical membrane of  the epithelial cells in the gastrointestinal tract, in keeping with the modern definition of absorption by the U.S. Food and Drug Administration (USFDA).

# DRUG DEVELOP. APPLICATIONS OF PK-MOD&SIM

## WHY IS IT IMPORTANT TO US?

(Ring 2011, Poulin 2011a, Poulin 2011b, Vuppugalla 2011, Jones 2011b, Parrott 2005, De Buck 2007, Gibson 2009, Jones 2011)

Drug companies are now building **PBPK models** for all new candidate drugs **early in the discovery and development cycles**

These models can be parameterized using *in silico* (distribution) and *in vitro* (intrinsic clearance) methods and can provide a “ballpark” **estimate of the human plasma concentration vs. time profile prior to *in vivo* testing in animals**

**successful methods for scale-up from animals**

**early estimate of local organ tissue concentrations** which can be tied to pharmacodynamic models

# DRUG DEVELOP. APPLICATIONS OF PK-MOD&SIM

## WHY IS IT IMPORTANT TO US? - F&D

Predict the fraction absorbed of a drug **using *in vitro***

***properties*** *(dose, dosage form, solubility, dose particle radius, dose particle density, diffusion coefficient, logP (or logD at a specified pH), and permeability)*

Predict the fraction absorbed for a **new compound** (solubility @ pH, estimated in vivo human effective permeability (Peff) and logP)

Predict Fa using **in vivo data in other species and in vitro data**

**simulate the behavior of different dosage forms,** including iv bolus**,** iv infusion, tablet, capsule, solution, suspension, and several forms of controlled release modified release (MR), delayed release (DR) and time release (TR).

# DRUG DEVELOP. APPLICATIONS OF PK-MOD&SIM

## WHY IS IT IMPORTANT TO US? - F&D

Modeling **Enterohepatic circulation**

Modeling Administration in **oral cavity**

Modeling in **special populations** - Geriatric, pregnancy, pediatric or obseity

# COMPUTING IN PK-MOD &SIM

they are basically ODE solvers

# CHOOSING YOUR SOFTWARE

## CONSIDERATIONS

### EASE OF USE

Learning curves
Coding / Markup
I/O
File systems

### SUPPORT

Popularity
User base
Documentation
File Exchanges

### REGULATORY

Reg. Approval
File format submission
21 CFR 11 Compliance

### COST

Lic. Vs. Free
Add-ins cost
Open Source
Your requirements

*Certara Phoenix WinNonlin* and add-ins | Lic.

★★★


*Simulations Plus - Gastro Plus 9* & several add-ins | Lic.

★★★★

*SimBiology* Model, simulate, and analyze biological systems | Lic.

★★★★

*IEEE STELLA Architect* | Free

★★★

PK-Sim
PBPK modeling & simulation
MoBi
Biological modeling & simulation

Open Systems Pharmacology Suite | Free

★★★

Several Github forks in R Project | Free

★★

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# QUESTIONS? COMMENTS?

## LET US KNOW!


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