PSCI-518: Introduction to PBPK Modeling

Spring 2024

Ian Haworth & Noam Morningstar-Kywi

Course Overview

- Model Building
  - Compound Properties
  - Physiologically Based PK
  - Systemic Model
  - Oral Absorption Model
- Model Application
  - Modeling Clinical Scenarios
  - Modeling to Answer Questions

Project Overview

- Each group is assigned 1 drug
- Groups will use their drug in all in-class and post-class activities
- Part 1 (weeks 1-11): Build a PBPK model for drug
- Part 2 (weeks 12-15): : Use model to answer clinically-relevant questions

- Deliverables:
  - Weekly one-page reports
  - Midpoint group presentations
  - Final individual presentation
  - Final report

Session Structure

5 min:	5-minute question
20 min:	Weekly report presentations
15-20 min:	Didactic Lecture
20-30 min:	GastroPlus Activity
Remainder:	Group Work

Post Class: One-page weekly report (Due each Monday 11:59pm)

Online: Video tutorials on GastroPlus features will be posted on blackboard as needed

Ground Rules

- Students in groups will work together on project, but each is expected to complete GastroPlus activities individually, and to be able to answer questions on this work
- During group presentations, all students will be expected to speak
- Each class will start with a brief in-person quiz (one question related to the report from the previous week, free response, 5 minutes). This will be followed by presentations of the report.

Midazolam

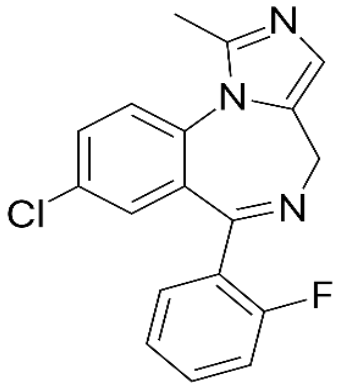


Table 1. Molecular properties of midazolam

MW (g/mol)	325.78
LogP	2.7
Permeability (10^{-4} cm/s)	4.57
pKa	6.04
F_{up} (Fraction unbound plasma)	4.4%
CYP3A4 Km (µM)	3.0
CYP3A4 V_{max} (nmol/min/mg)	1.035

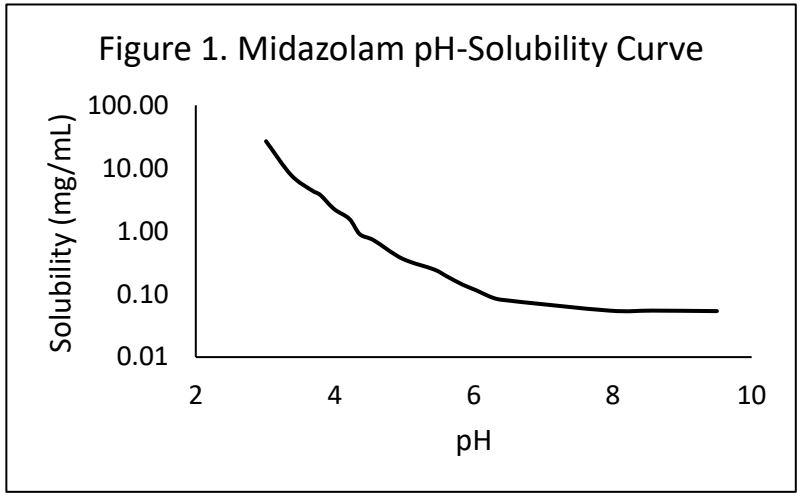


Figure 1. Aqueous solubility of midazolam across a range of pH values.

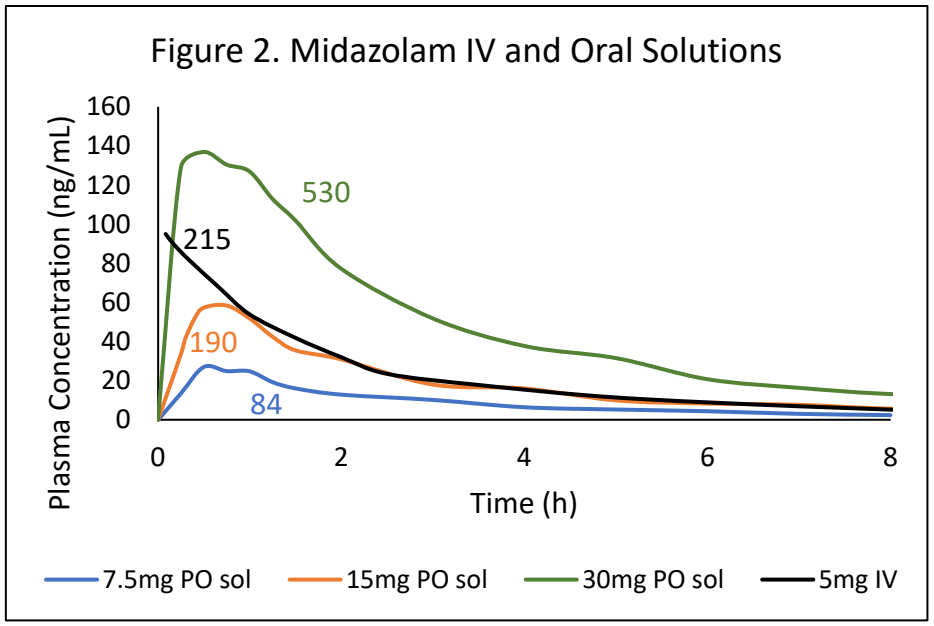


Figure 2. Plasma concentration-time profiles of midazolam after different doses of oral solution (PO) or intravenous formulation (IV). AUCs (ng*h/mL) are shown next to each curve. Oral doses were given in a fasted state.

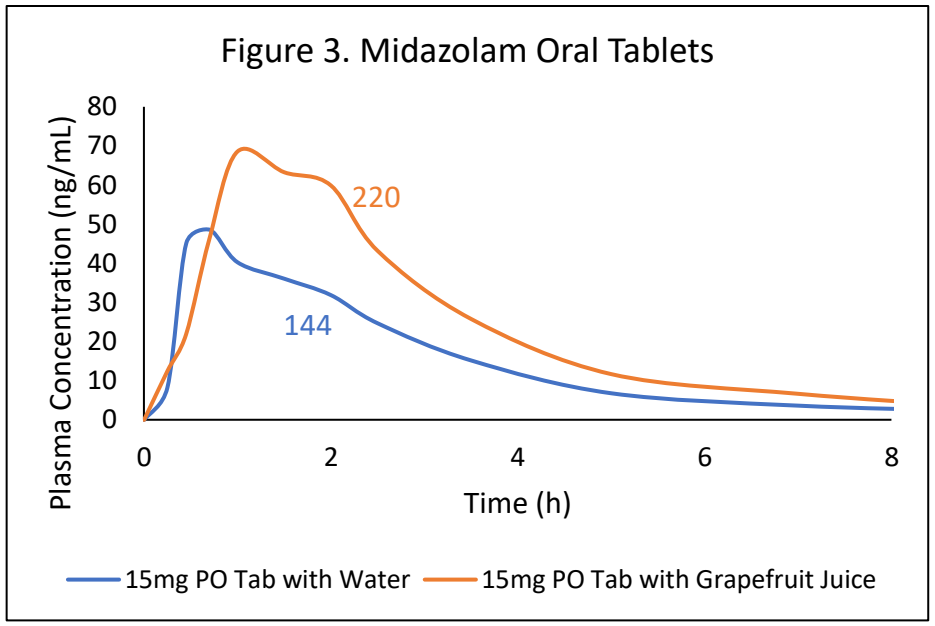


Figure 3. Plasma concentration-time profiles of midazolam after single oral administration (in a fasted state) of 15mg tablets with water or grapefruit juice. AUCs (ng*h/mL) are shown next to each curve.

Table 2. Pharmacokinetic parameters of midazolam for administration of a 15mg oral tablet one hour after a meal.

C_{max} (ng/mL)	35.7
T_{max} (h)	1.98
AUC (ng*h/mL)	177

Introduction to Modeling and Simulation

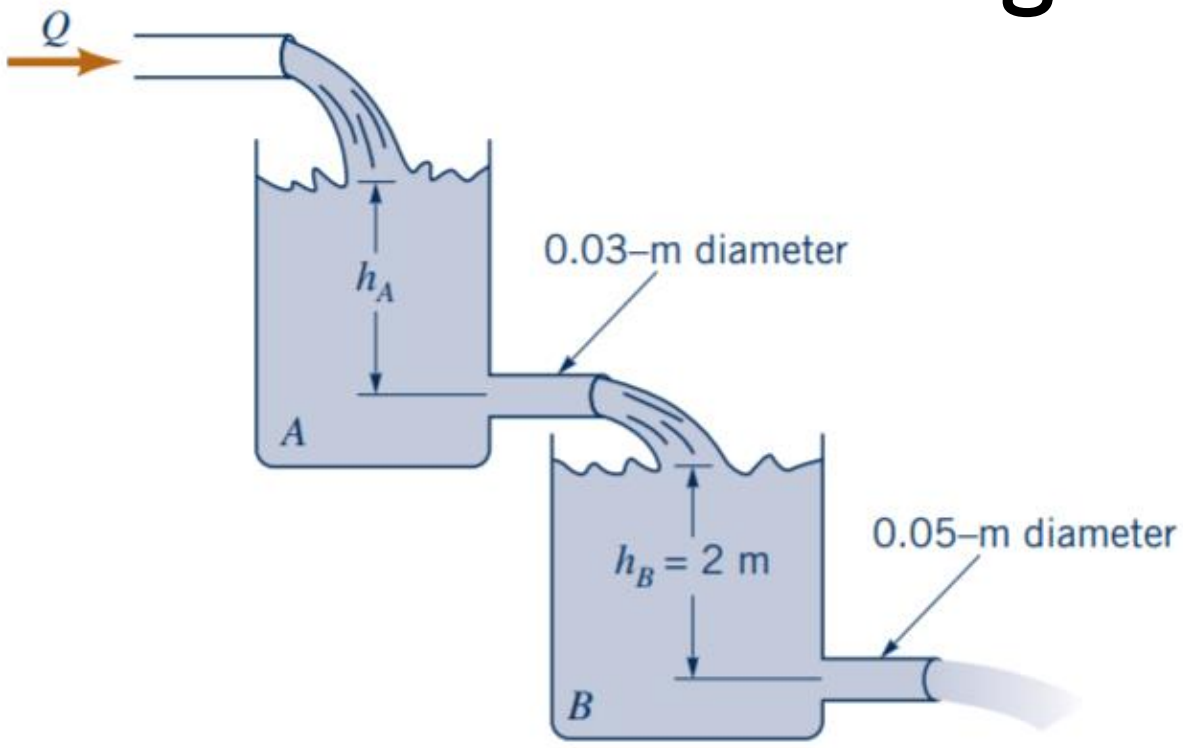
PSCI-599, Spring 2023

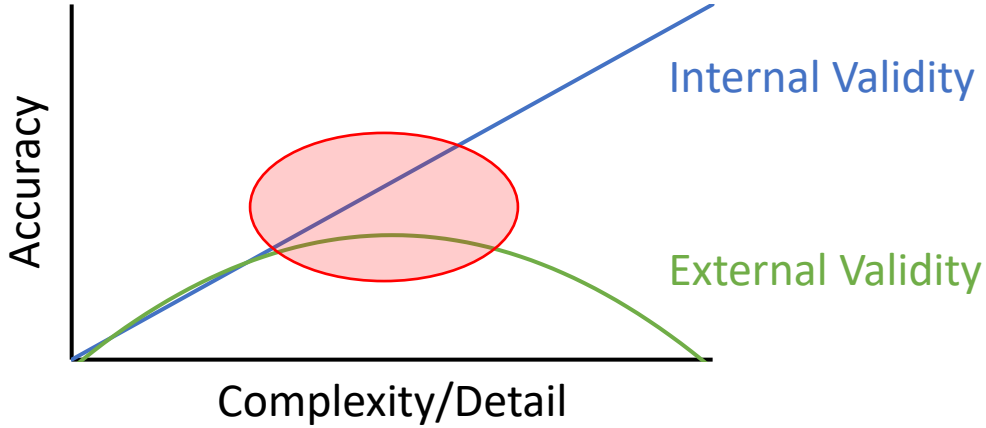
Noam Morningstar-Kywi

What is a Model?

Mathematical Model: Using input (x), predict output (y) at time (t)

Modeling and Simulation



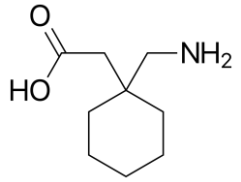


Nomenclature

- **Model**: Description of a system using mathematical equations
  - Inputs: values assigned to model parameters (independent variables)
  - Outputs: Results calculated with equations using inputs (dependent variables)
- **Simulation**: Integration of model over time to produce series of results
- **Prediction**: Specific model output for a given input
  - Accuracy depends on quality of inputs, certainty of model

Modeling and Simulation in Drug Design

Compound Structure



ADMET Predictor

Compound Properties

Physiologic Properties

PK Properties

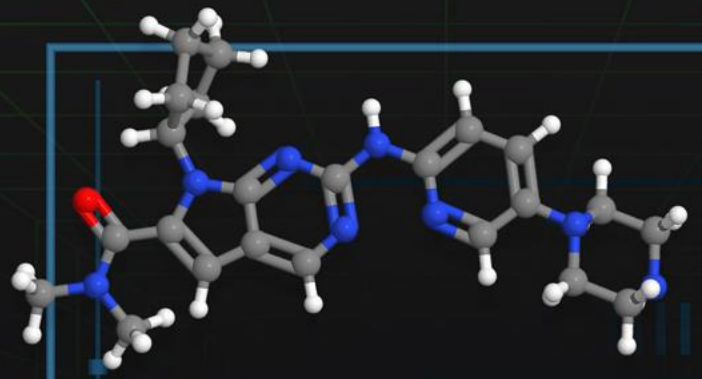
GastroPlus

In vitro & in vivo experiments

Simulate (Predict):

- Dissolution and Absorption
- Bioavailability
- Systemic Disposition
- Minimum Effective Dose
- Maximum Safe Dose
- First-in-Human Dose
- Therapeutic Effect
- Drug-Drug Interactions (DDIs)
- …and more

What goes into a simulation?



Compound

Formulation

Pharmacokinetics

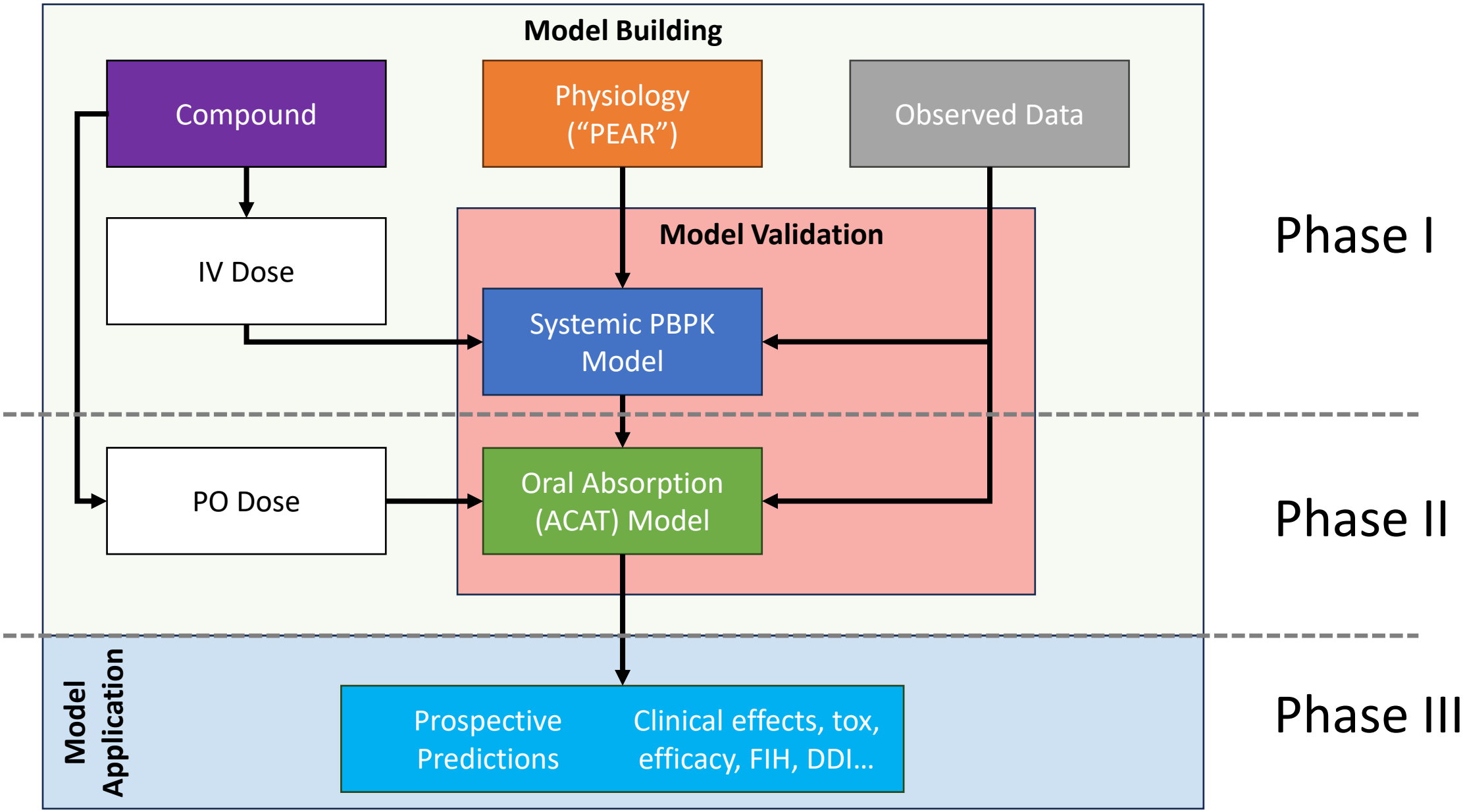
Absorption
Distribution
Metabolism
Elimination

Dose

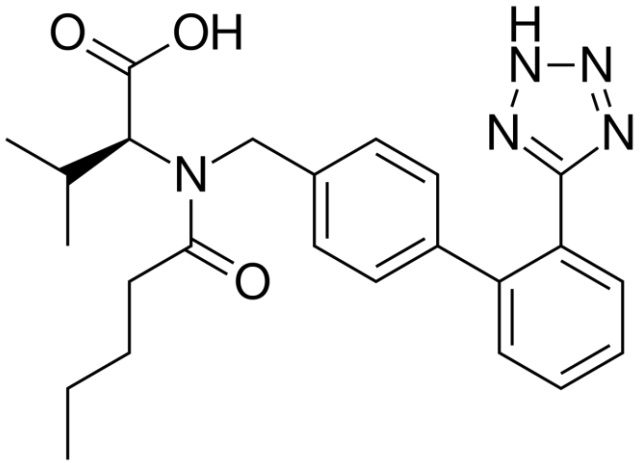
Schedule

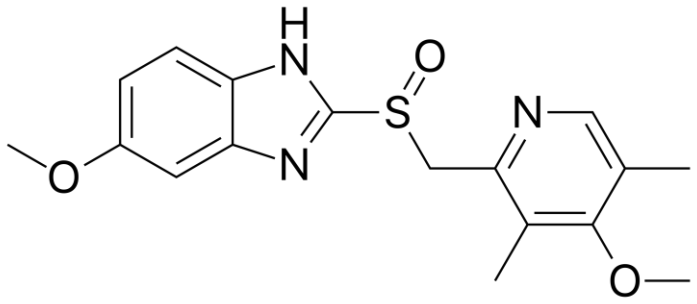
Physiology

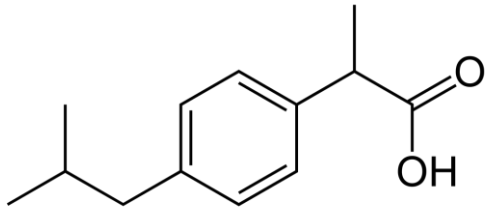
Model Building and Application

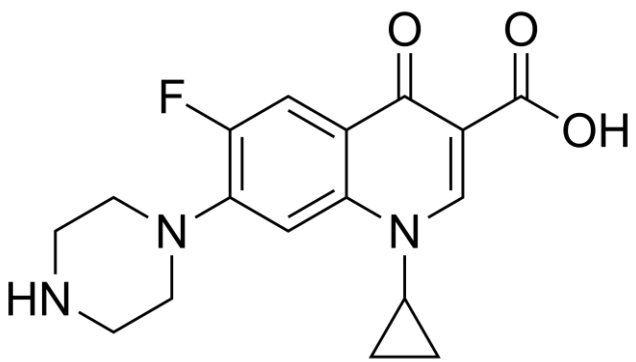


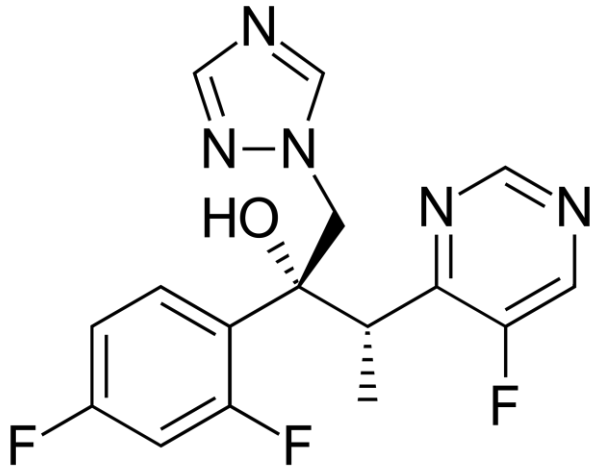
Think about the properties of your drug

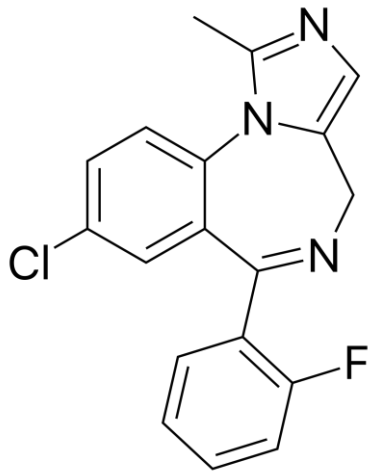












More Nomenclature (for this course)

Predicted:
Properties predicted by ADMET Predictor (not measured) → model inputs

Experimental data:
Properties measured in an experiment → model inputs

Simulated / Results:
Results of simulation → model output

Observed:
Pharmacokinetic data from clinical study → model validation

GastroPlus Terms

ADMET Predictor (AP) → Uses machine-learning models to predict physicochemical and physiomolecular properties of drugs

GastroPlus (GP) → Runs simulations on drug pharmacokinetics using drug and physiologic properties as inputs

Project = **Drug Database (.mdb)** → database of "Drug Records" containing information on compound, dosing, physiology, and kinetics

Drug Record → Stores information for a single drug-dose-physiology configuration. Each drug record can run a unique simulation.

Different Drug Records are used for different compounds, but also for different doses of same compound, and so on. A Drug Database consists of multiple Drug Records.

Support Files → Method for inputting additional data, such as observed Cp-time profiles. Each Drug Record can have its own set of support files.

GastroPlus Activities

Demo then Group Work

- Create project, import structure (ADMET Predictor)
- Run simulation, examine results
- Copy drug record, add experimental data
- Run simulation on ‘new’ record
- Compare results, discuss