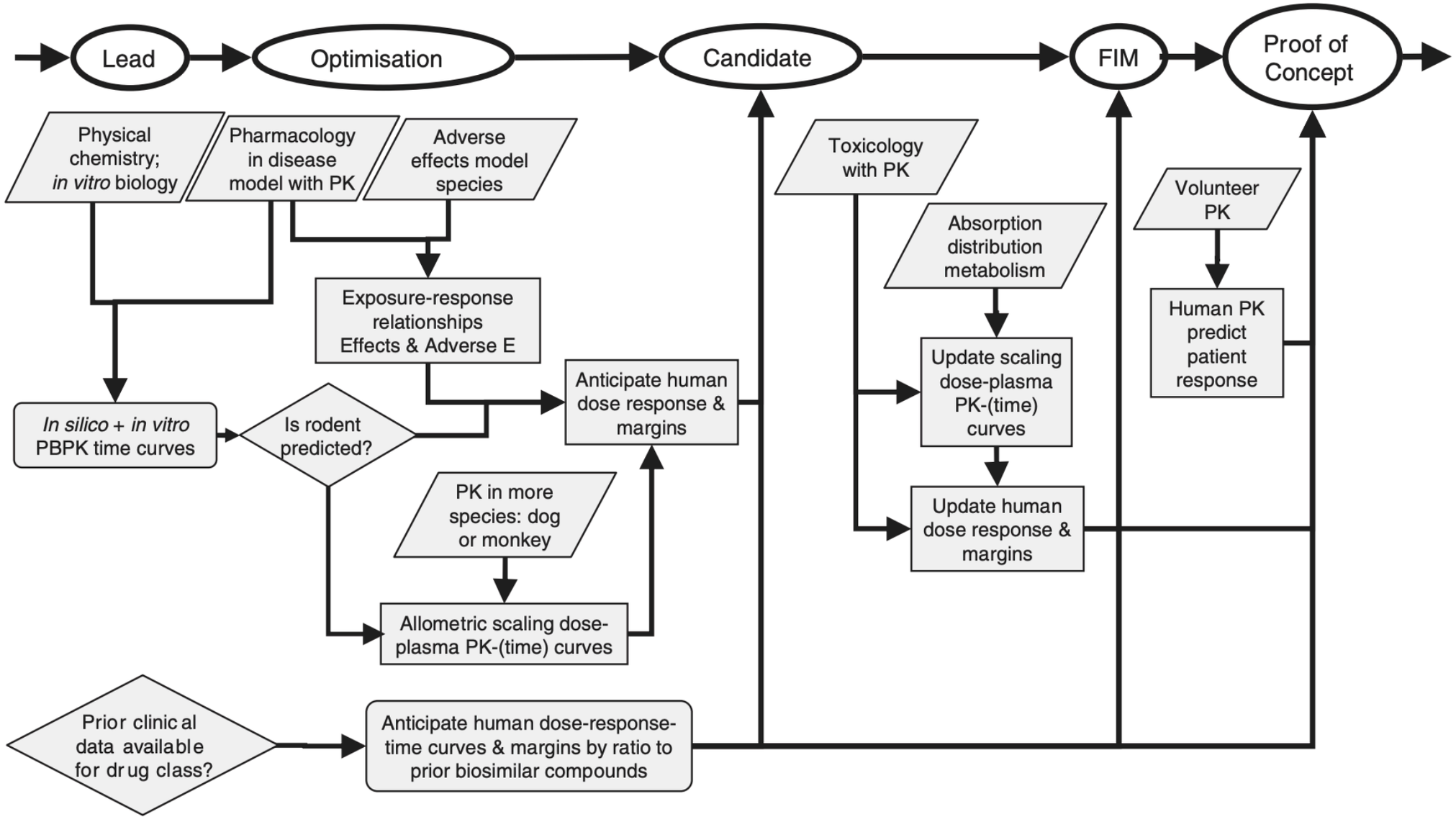
Human Dose Projections in Drug Discovery



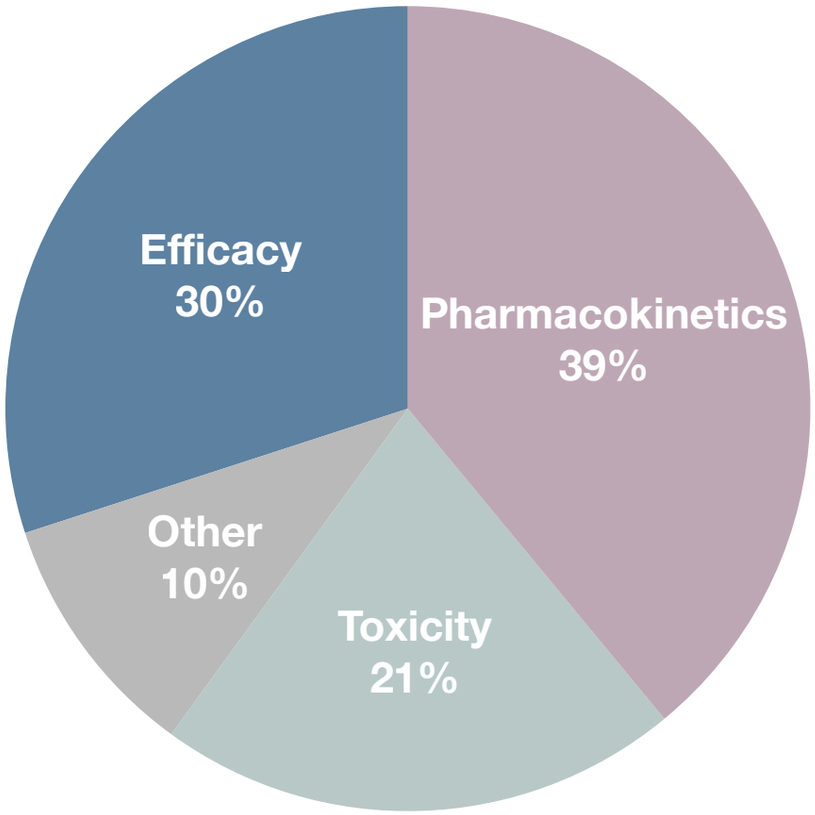
Nick Intermaggio

Literature Group Meeting

11/15/2022

Evolution of Clinical Trial Attrition

Key Drivers of Attrition



– prior to 1997 –

poor understanding of metabolism

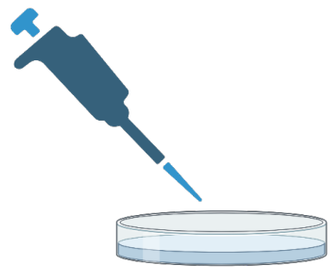
labor intensive clearance models

lack of in vivo PK

Integration of

Pharmacokinetics/Drug Metabolism

(PK/DM) *in to Drug Discovery*



high throughput

in vitro clearance

prioritize compounds

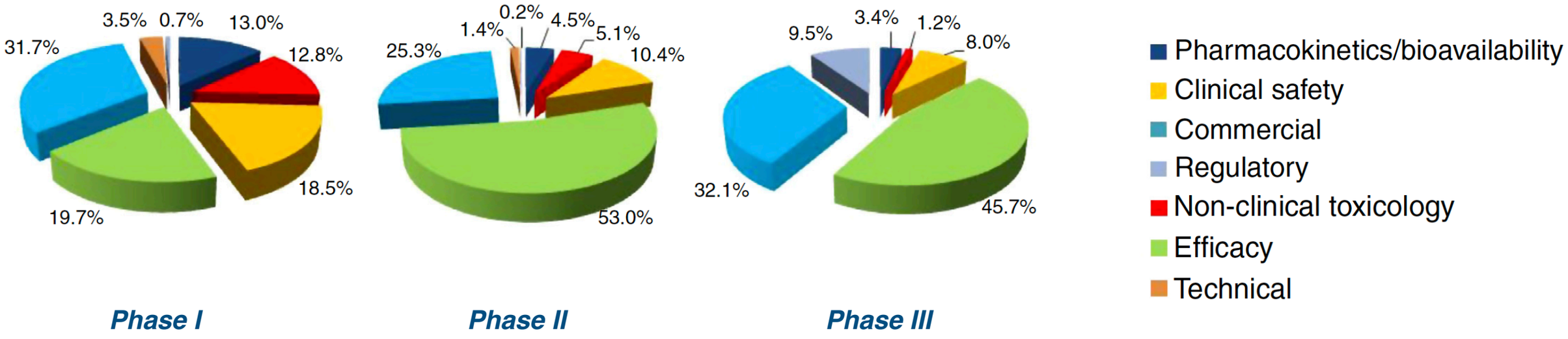
by in vivo PK

ADME models for

physiochemical properties

Waterbeemd, Van. D. et. al. *Nat. Rev. Drug. Disc.*. **2003**, *2*, 192.

Attrition from 2006 – 2010: An Efficacy Crisis



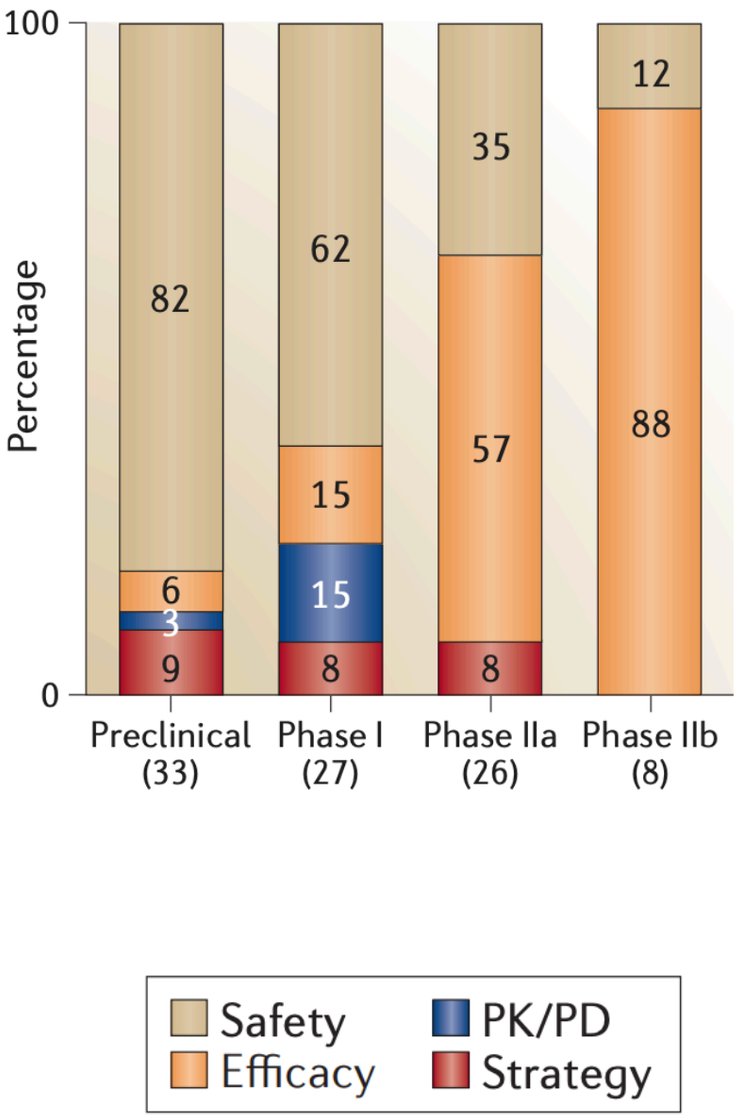
Phase I ***Phase II*** ***Phase III***

Failure to demonstrate efficacy is now the dominant driver of attrition

Bayliss et. al. *Drug. Disc. Today* **2016**, *0, 1*.

Lessons Learned From AstraZeneca's Pipeline

AstraZeneca



40%

"good failures"

clearly demonstrate

pharmacological engagement

therapeutic hypothesis has

been tested with confidence

Therapeutic hypothesis:

Modulation of a particular biological pathway

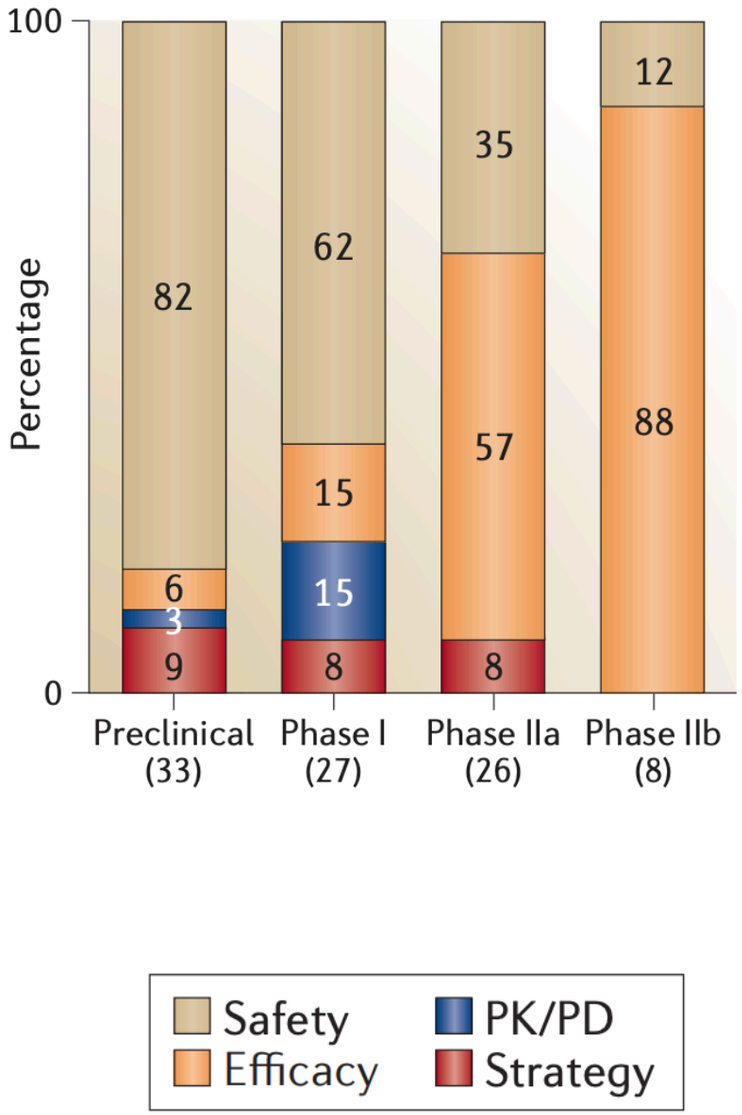
by a novel therapeutic agent will result

in improvement of a given disease state

Cook et. al. *Nat. Rev. Drug. Disc.* **2014**, 13, *419*.

Lessons Learned From AstraZeneca's Pipeline

AstraZeneca



40%

"good failures"

clearly demonstrate

pharmacological engagement

therapeutic hypothesis has

been tested with confidence

29%

"bad failures"

compound properties

limited dose and exposure

failed to validate or invalidate

therapeutic hypothesis

Cook et. al. *Nat. Rev. Drug. Disc.* **2014**, 13, *419*.

Lessons Learned From AstraZeneca's Pipeline

How can we eliminate "Bad Efficacy Failures"

Guidelines for Drug Candidate Profiles

AstraZeneca

MERCK

Pfizer

gsk

Five "R"s	***TxM Guide***	***Model Based Drug Development***	***"Three Pillars"***

Optimize structure toward a molecule capable of achieving ***sustained target engagement*** *at the site of action for the* ***required duration of time*** *at a* ***clinically acceptable and safe oral dose***

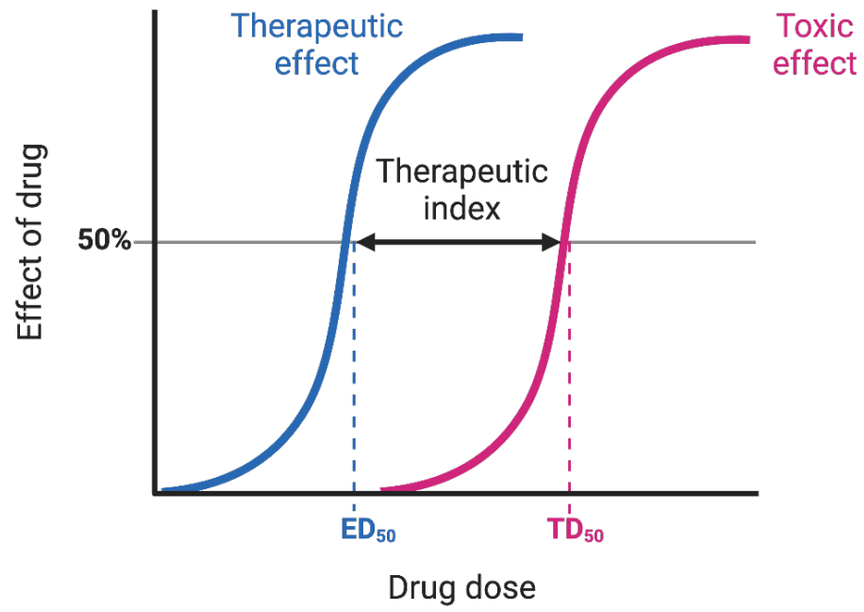
Peters et. al. *Drug. Disc. Today* **2020**, 25, *909*.

What Makes a "Good Dose"?

as low

as possible

1) Safety Considerations



"focusing on low dose requirements is perhaps the most generally effective means of ensuring safety"

Maurer et. al. *Drug. Disc. Today* **2022**, 27, *538.*

What Makes a "Good Dose"?

as low

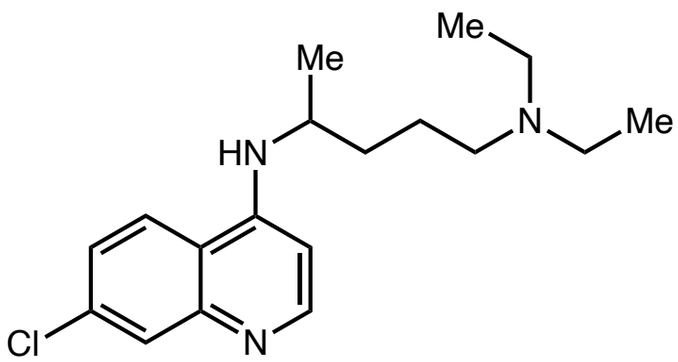
as possible

2) Cost of goods

Most important for

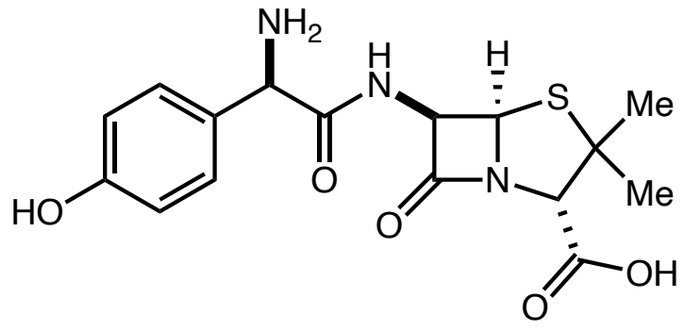
developing ***new anti-infectives***

for the developing world



chloroquine

anti-malarial



amoxicillin

antibiotic

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

What Makes a "Good Dose"?

as low

as possible

3) Patient Compliance

small dose, once a day

is easy to remember

and easy to stick to

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

Getting it Right

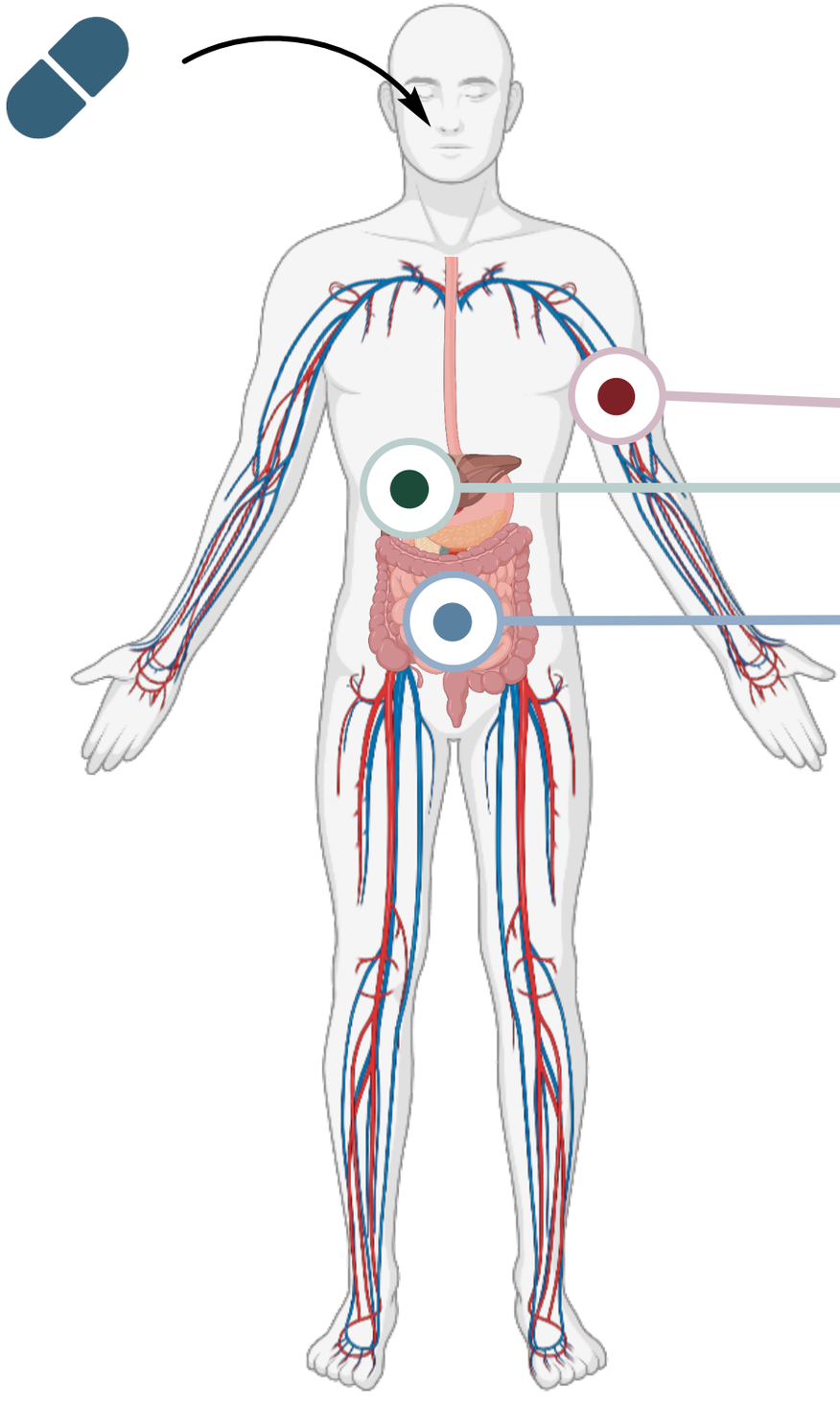
The Right Amount

Test the therapeutic hypothesis

Good Failure	***Bad Failure***
Walk away with no regrets	*Waste of time, money and resources*
Learn something fundamentally New about the disease pathology	*Put patients at risk without furthering Our understanding of the disease*

Bayliss et. al. *Drug. Disc. Today* **2016**, *0, 1*.

How much drug do you actually need?



$F\%$

Oral bioavailability:

Inversely proportional to dose

C_{eff}

Efficacious concentration of drug:

Directly proportional to dose

Cl_T

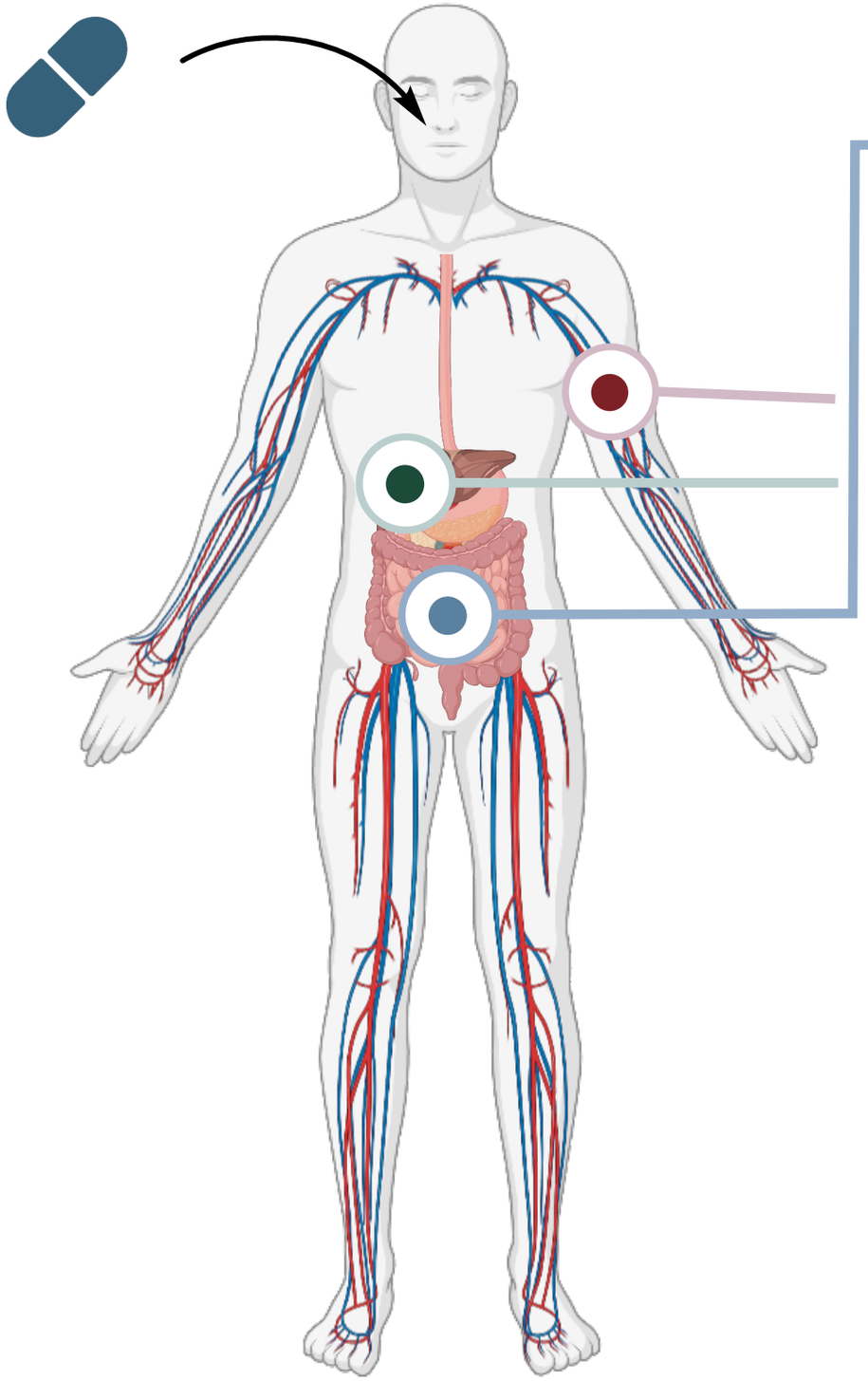
Total clearance:

Directly proportional to dose

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

How much drug do you actually need?



$F\%$ — ***Predicted from preclinical data***

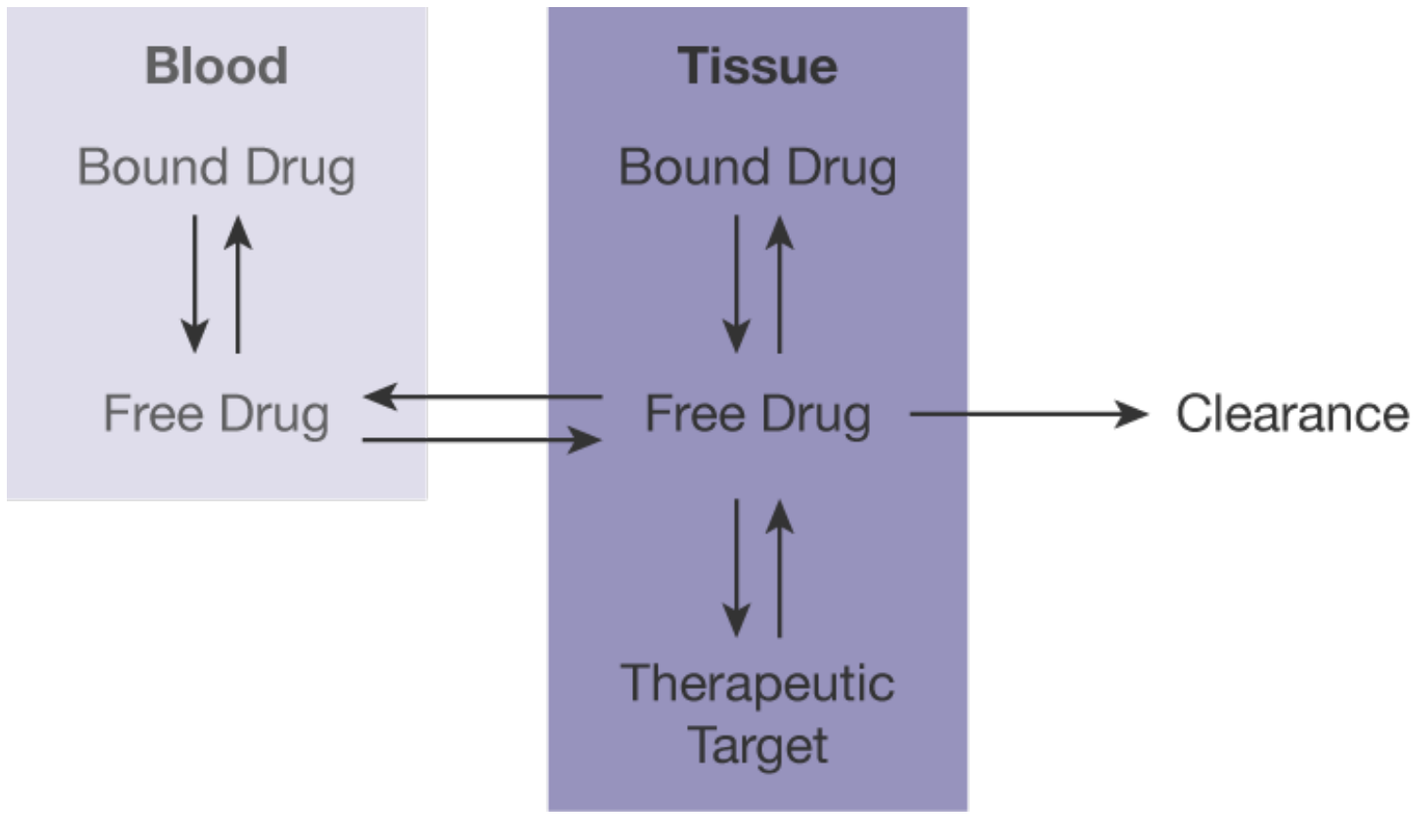
C_{eff} — ***Predicted from preclinical data***

Cl_T — ***Predicted from preclinical data***

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Free Drug Hypothesis



Assumption #1

Free diffusion

through biomembranes

Assumption #2

Only free drug is

Able to elicit pharmacological

Effects or be cleared from the body

Correct for

C_{eff} Cl_T → $C_{eff,u}$ $Cl_{,u}$

Plasma protein binding

Smith et. al. *Nat. Rev. Drug. Disc.* **2010**, *9*, 929.

Defining an Efficacious Concentration

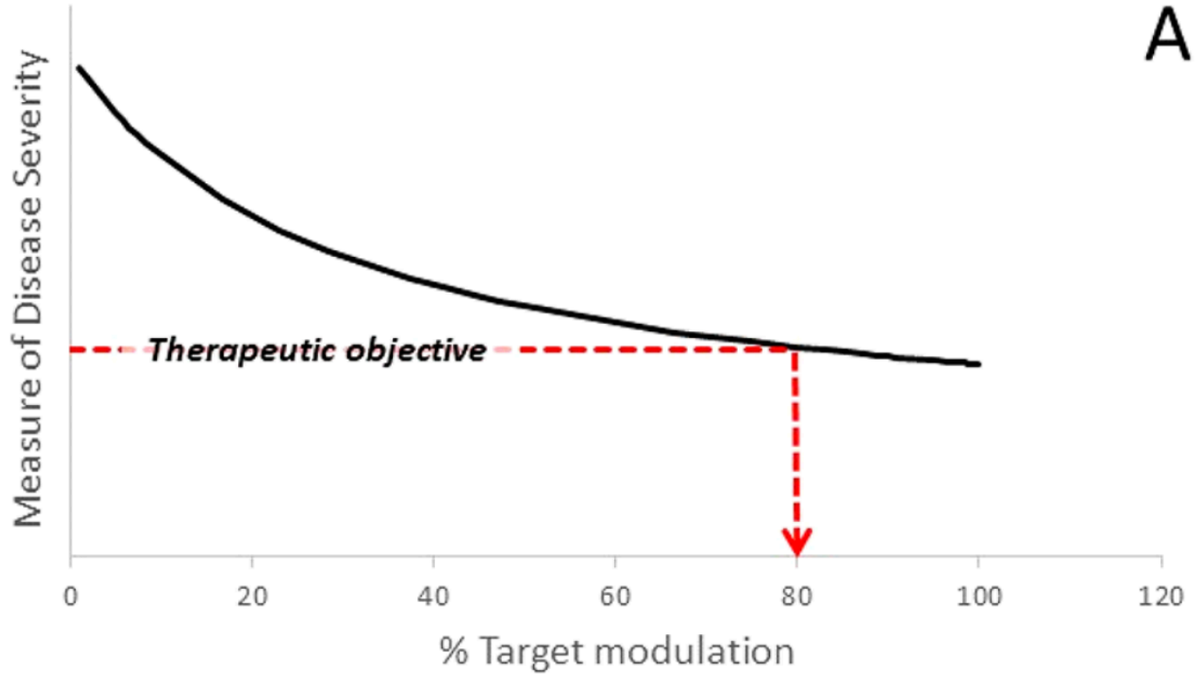
$$C_{eff,u} \propto \frac{IC_{50} * (coverage\ multiple)}{f_u}$$

Coverage multiple:

How high does [Drug] have to be with Respect to IC_{50}?

Well defined targets:

Leverage previous clinical data



Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

Pharmacodynamic experiments

What information do we have?

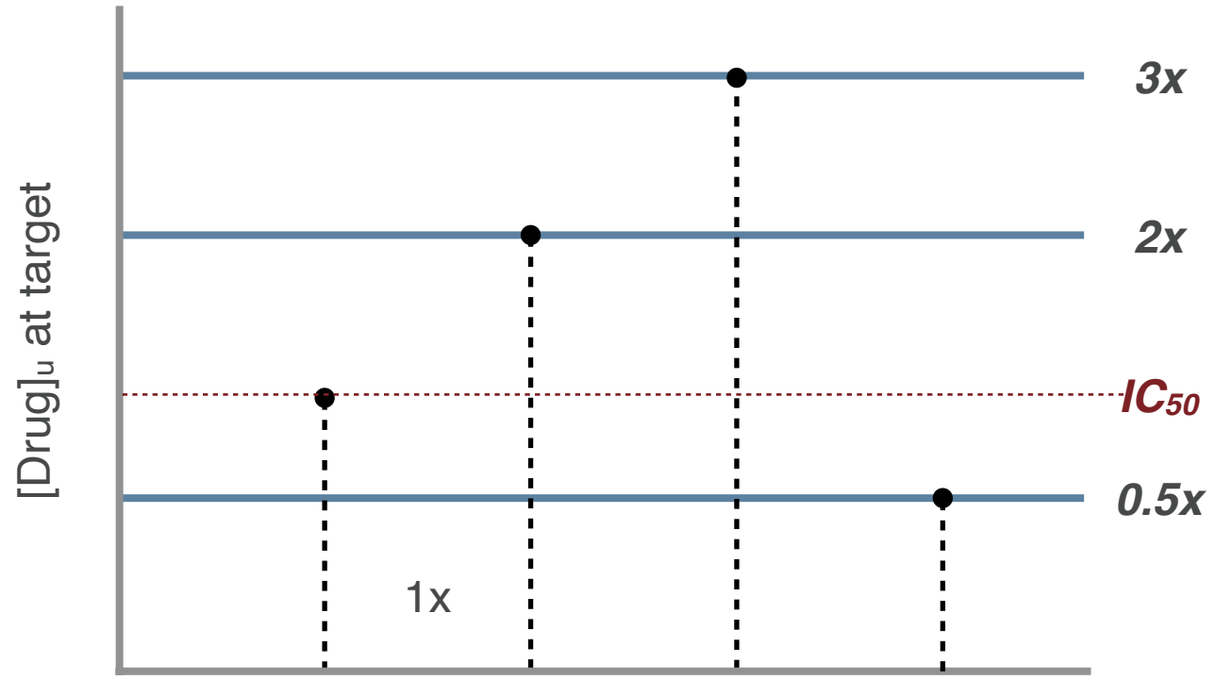
Animal IC_{50}

Human IC_{50}

Animal Efficacy model

Step 1: Define $C_{eff,u,animal}$

Relate efficacy in animal model back to in vitro animal potency



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

What information do we have?

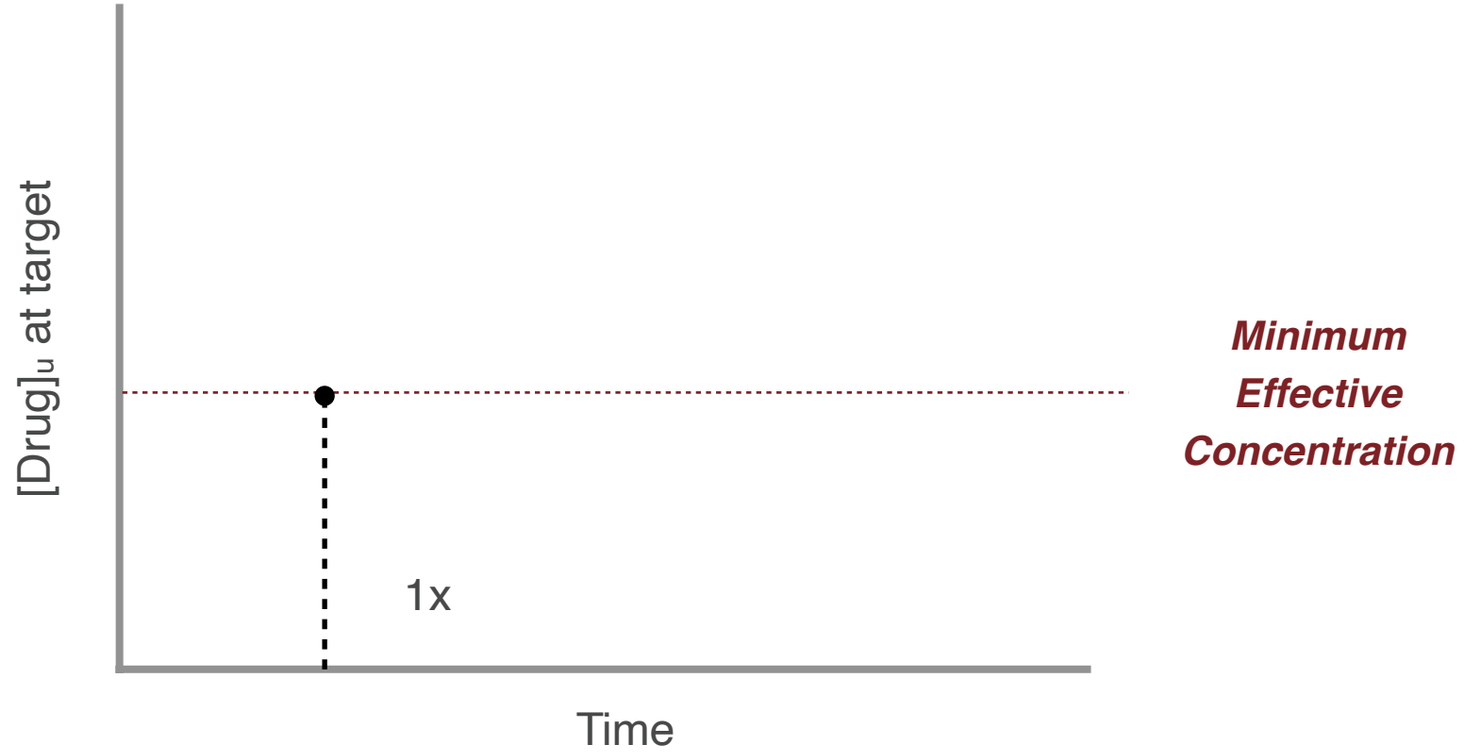
Animal IC_{50}

Human IC_{50}

Animal Efficacy model

Step 2: Define efficacy driver

Coverage multiple = 1x



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

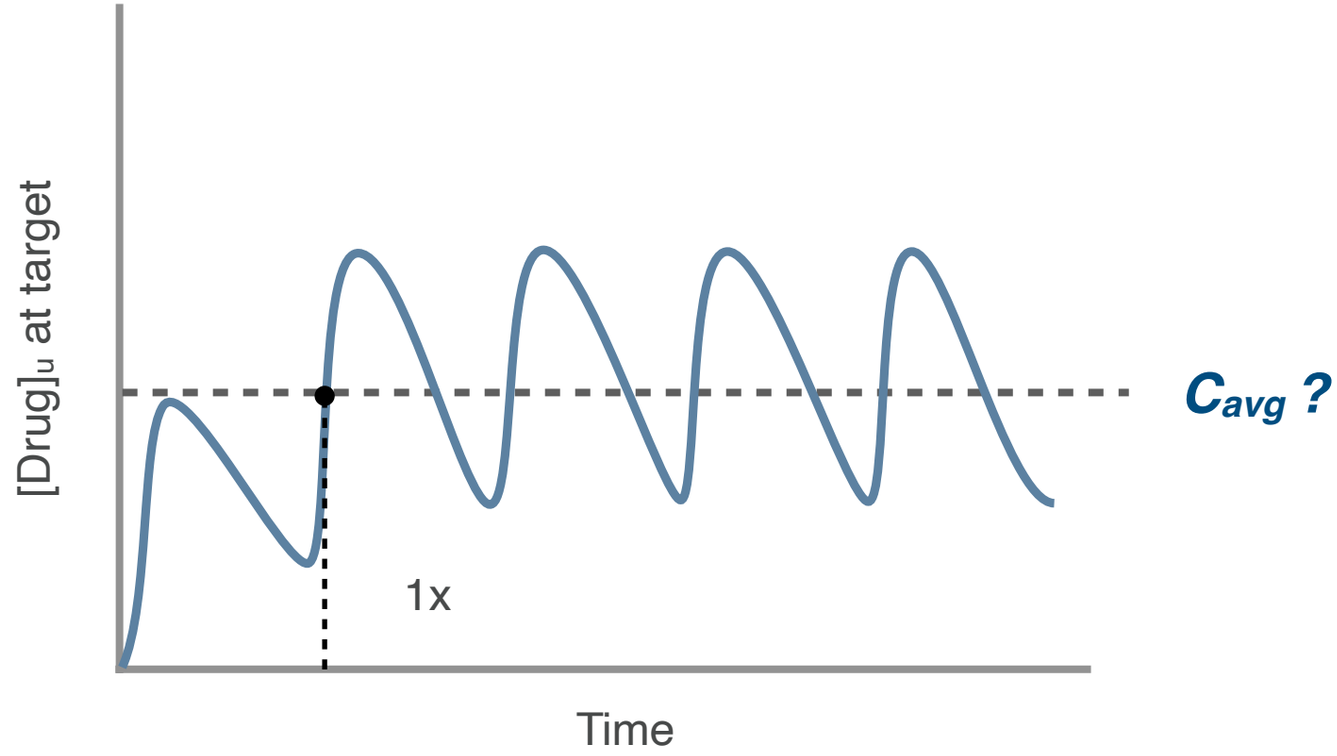
What information do we have?

- ***Animal IC_{50}***
- ***Human IC_{50}***
- ***Animal Efficacy model***

Step 2: Define efficacy driver

Coverage multiple = 1x

but when?



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

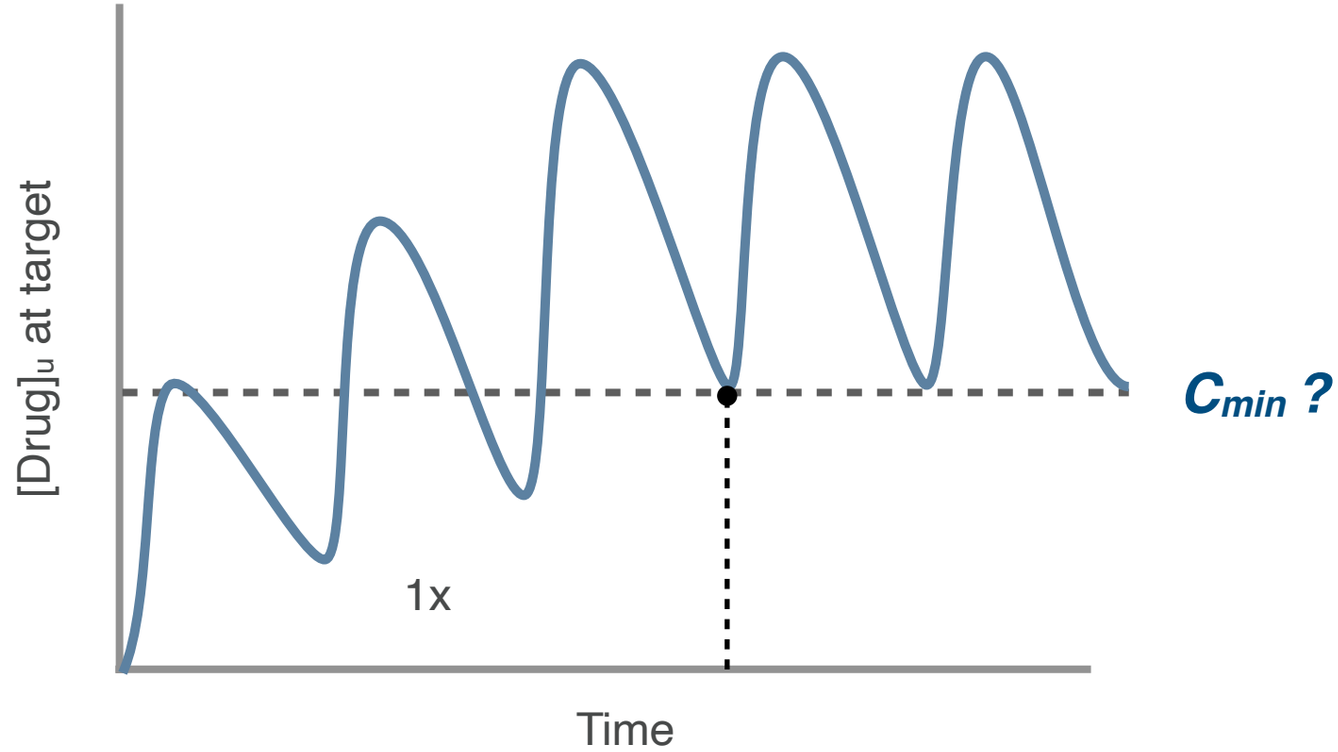
Pharmacodynamic experiments

What information do we have?

- ***Animal IC_{50}***
- ***Human IC_{50}***
- ***Animal Efficacy model***

Step 2: Define efficacy driver

What duration of target engagement?



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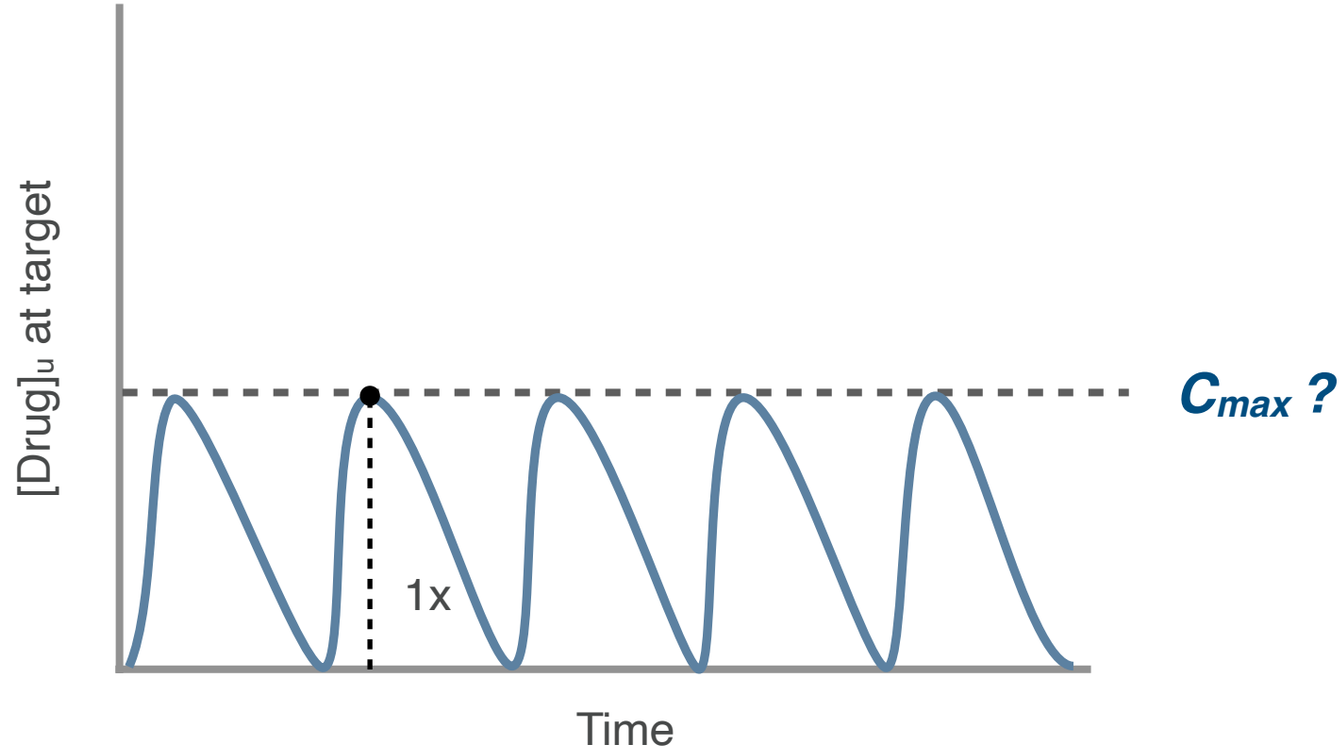

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

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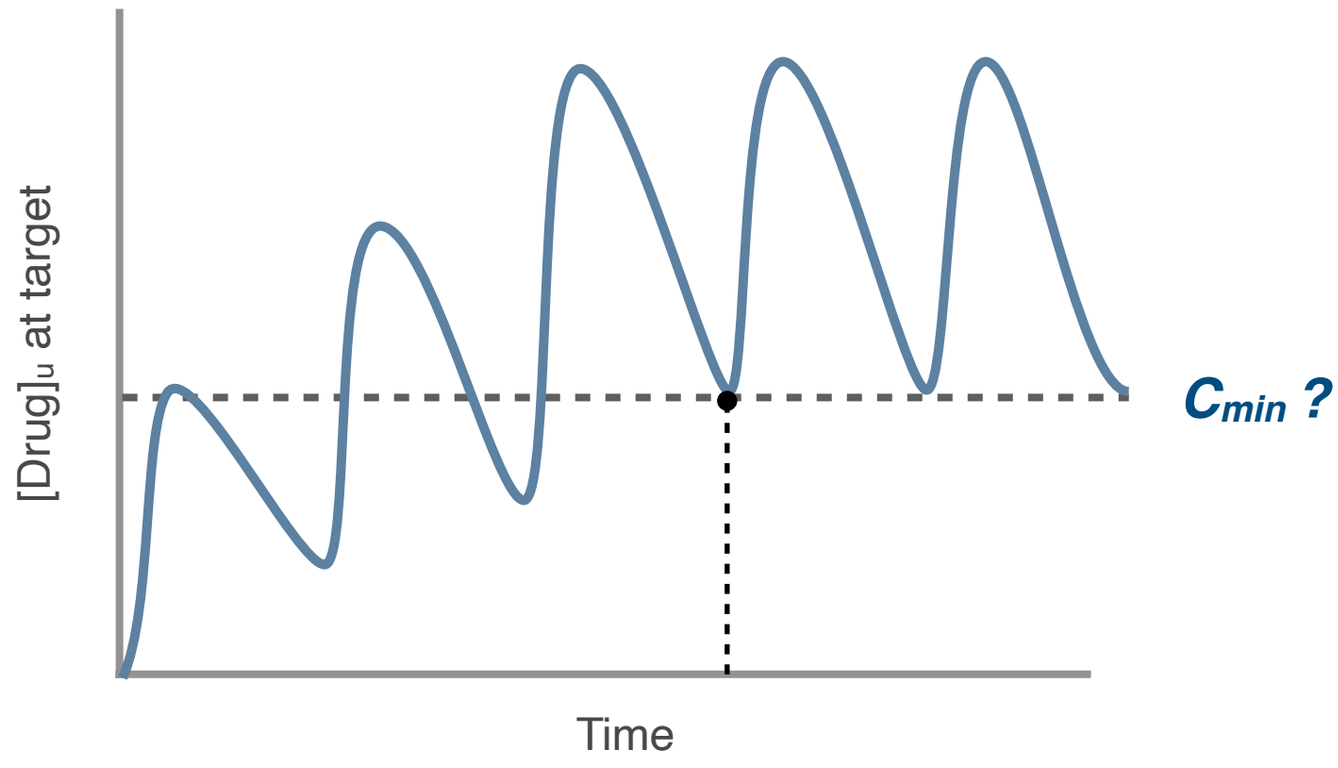
Animal IC_{50}

Human IC_{50}

Animal Efficacy model

C_{min} driven efficacy:

[Drug] must be at or above MEC throughout duration of treatment



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

What information do we have?

Animal IC_{50}

Human IC_{50}

Animal Efficacy model

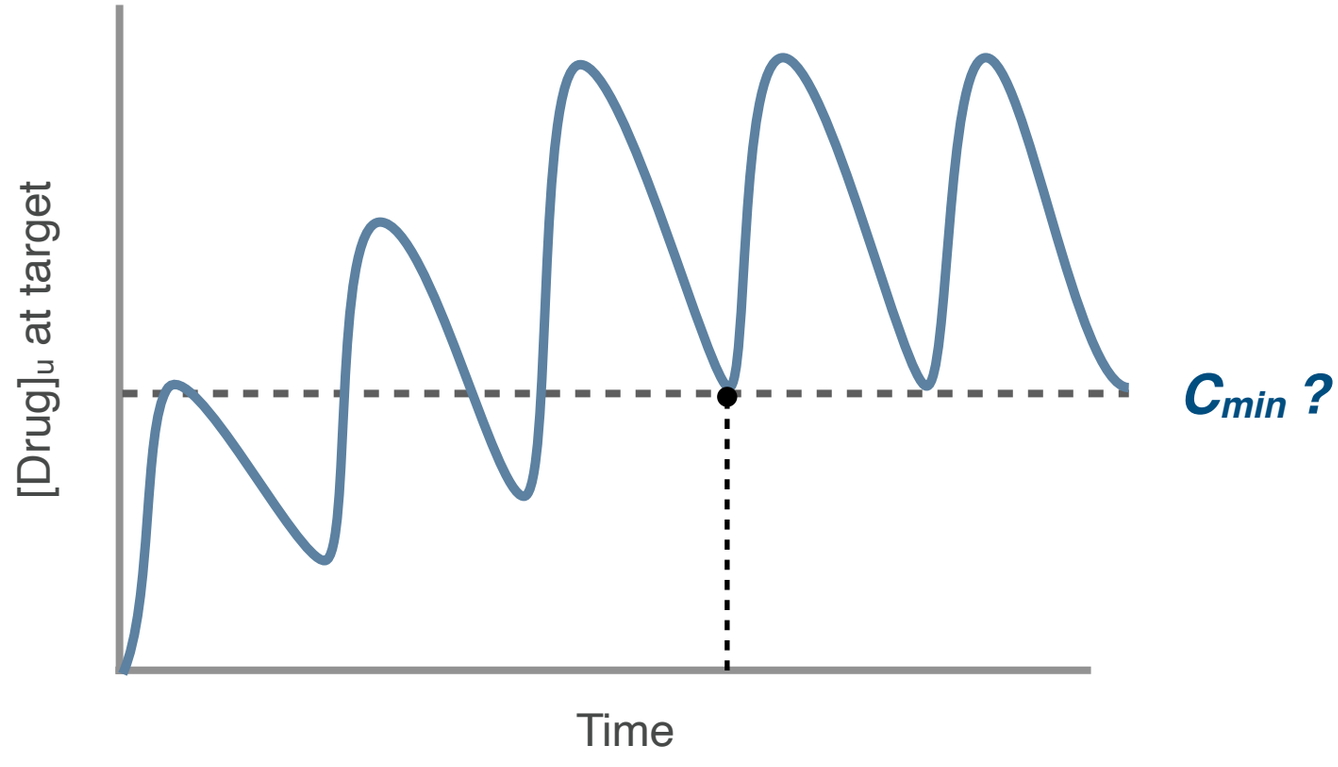
C_{min} driven efficacy:

[Drug] must be at or above MEC throughout duration of treatment

Highest required dose

Higher risk for toxicity

Best chance of testing hypothesis



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

What information do we have?

Animal IC_{50}

Human IC_{50}

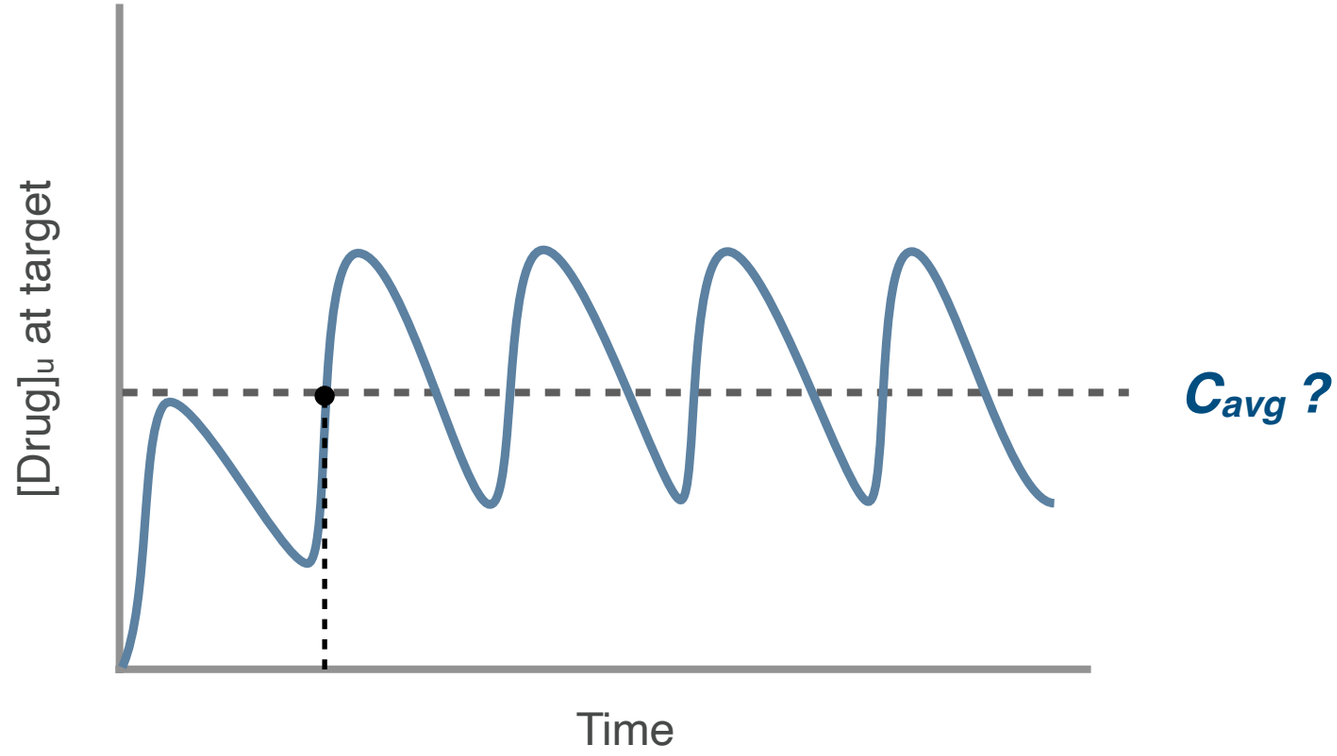
Animal Efficacy model

C_{avg} driven efficacy:

driven by total drug exposure (AUC). Dropping below MEC is tolerated

Medium required dose

Must be confident in assignment to have confidence in testing hypothesis



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

What information do we have?

- ***Animal IC_{50}***
- ***Human IC_{50}***
- ***Animal Efficacy model***

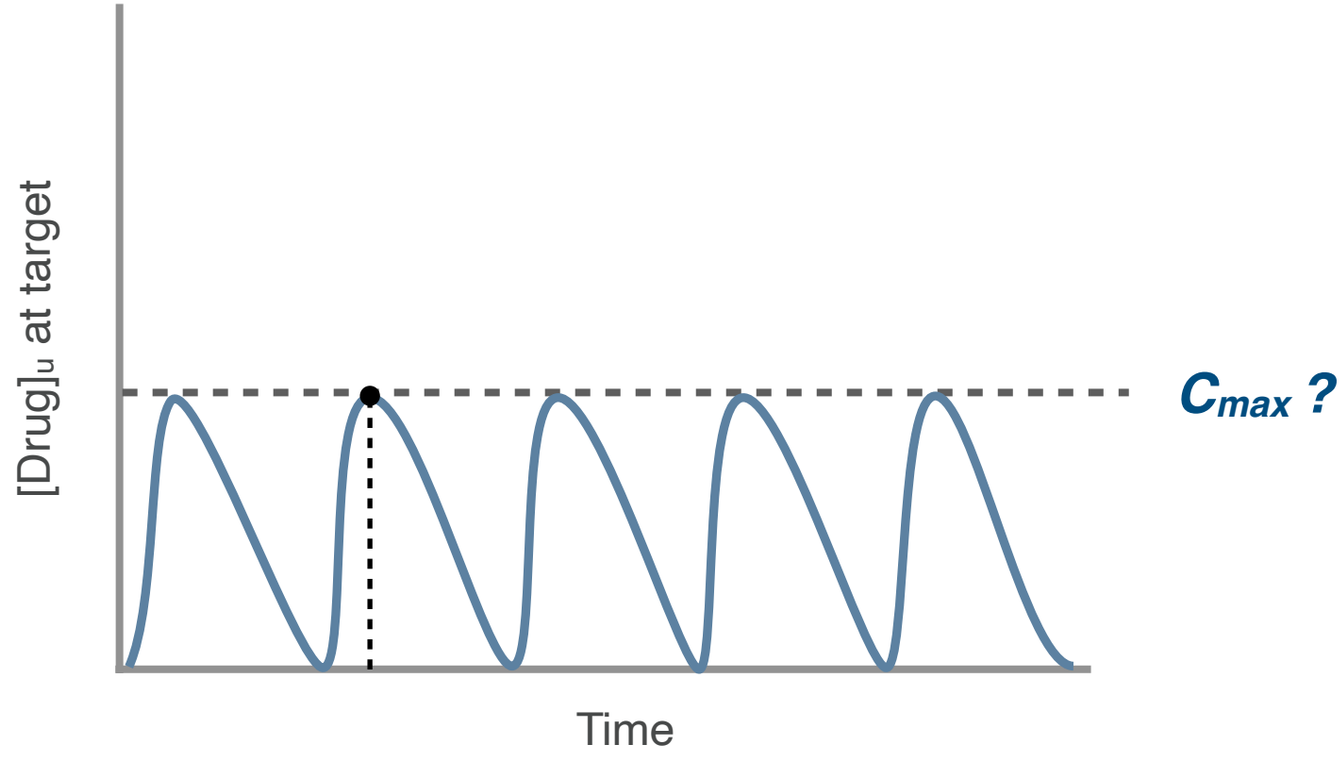
C_{max} driven efficacy:

Efficacy driven by peak exposure periods

Lowest required dose

Not common driver of efficacy

More often invoked for tox studies



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

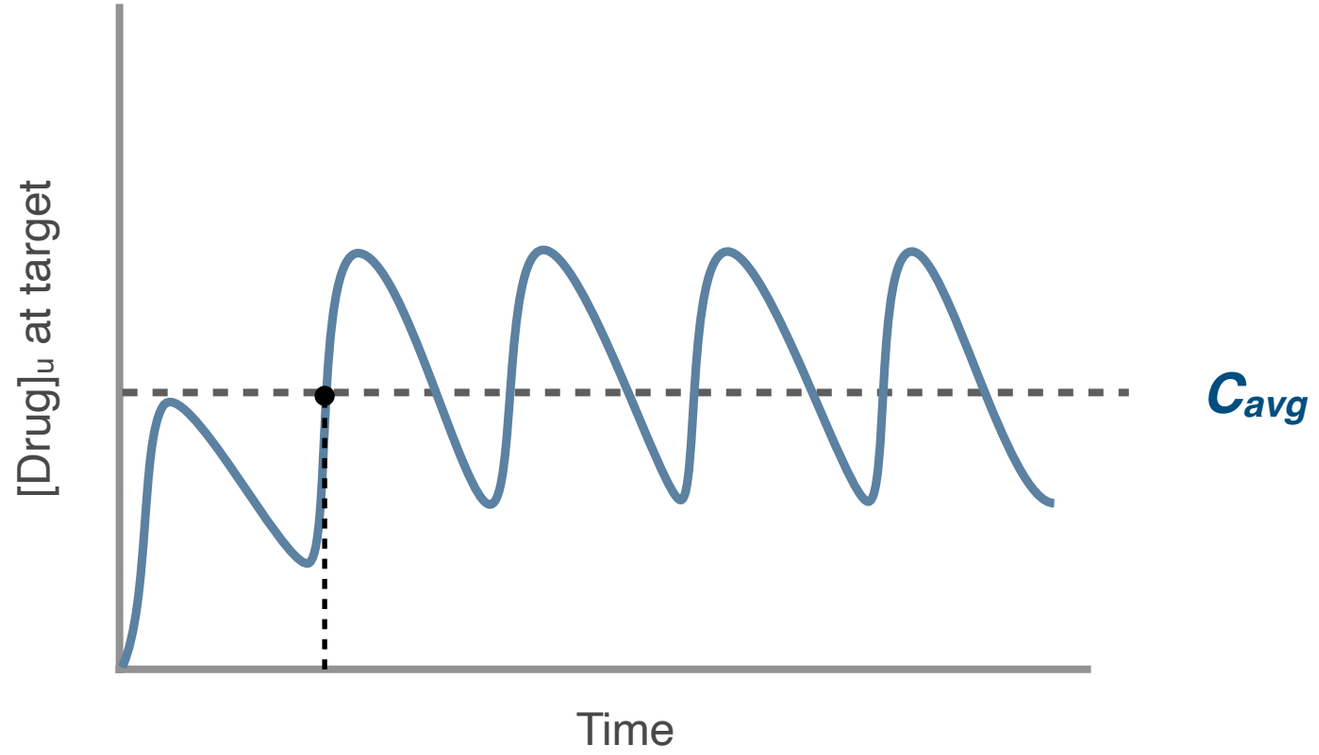
What information do we have?

Animal IC_{50}

Human IC_{50}

Animal Efficacy model

Step 3: Assume coverage multiple at chosen [Drug] (C_{avg}) will translate to humans



Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Pharmacodynamic experiments

What information do we have?

$$coverage\ multiple = \frac{C_{eff,u,animal,avg}}{in\ vitro\ IC_{50,animal}}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

Pharmacodynamic experiments

What information do we have?

$$C_{eff,u,h} = \frac{IC_{50,human} * coverage\ multiple}{f_{u,human}}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

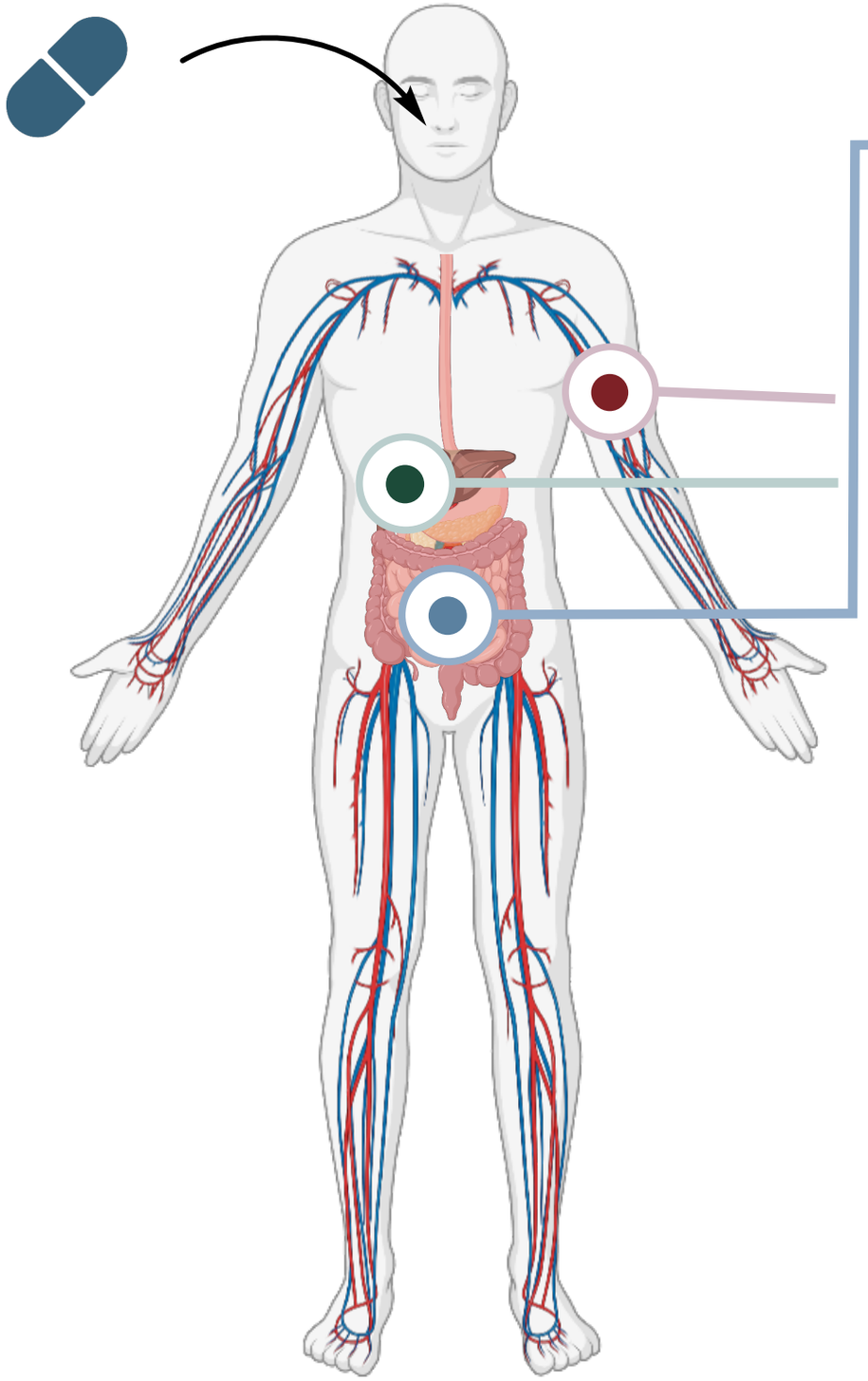
Pharmacodynamic experiments

What information do we have?

$$C_{eff,u,h} = IC_{50,human} * \left(\frac{C_{eff,u,animal}}{IC_{50,animal}}\right) * \left(\frac{1}{f_{u,human}}\right)$$

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

How much drug do you actually need?



$F\%$ — ***Predicted from preclinical data***

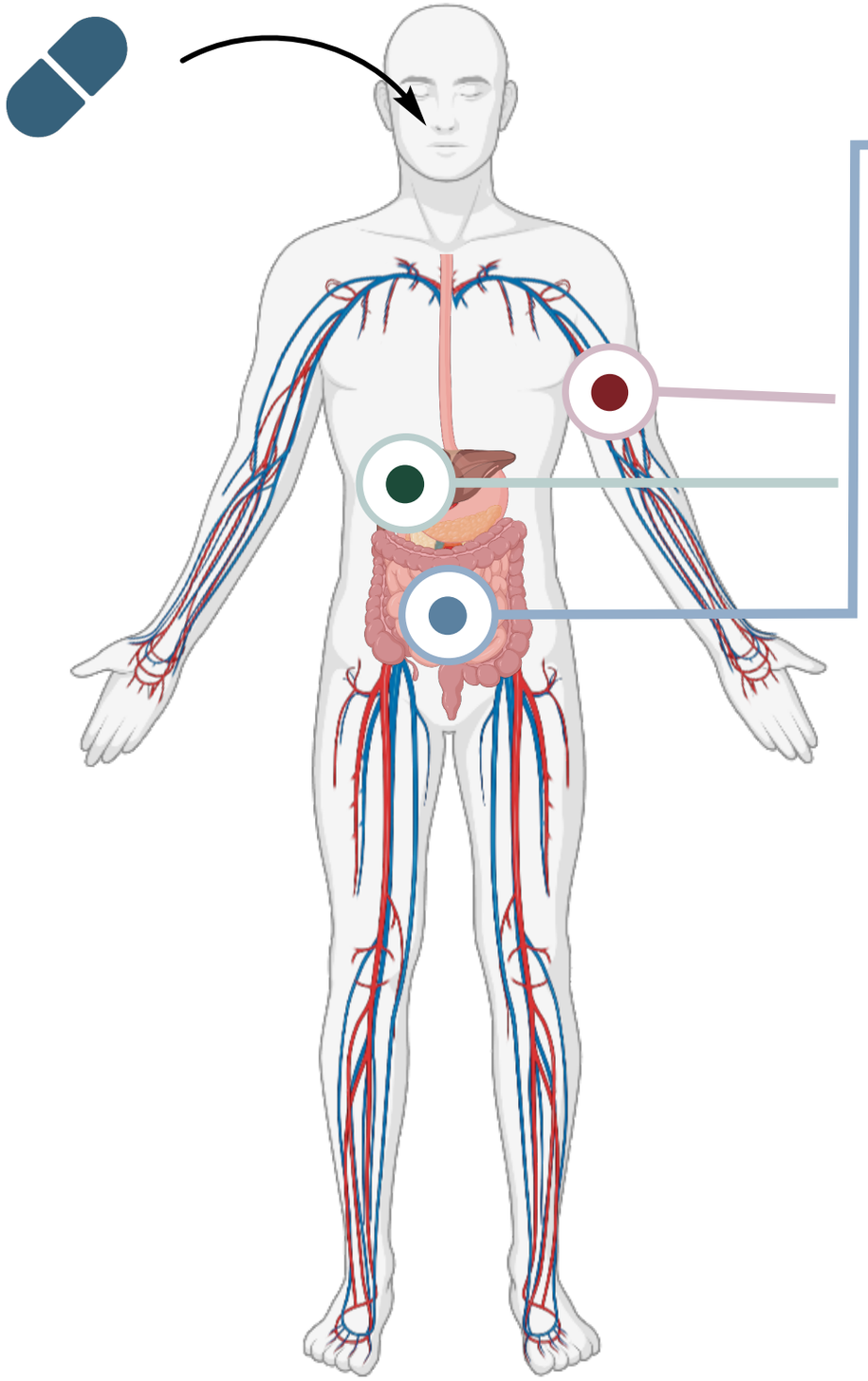
C_{eff} — ***Predicted from preclinical data***

Cl_T — ***Predicted from preclinical data***

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

How much drug do you actually need?



F% — ***Predicted from preclinical data***

C_{eff}

$$IC_{50,human} * \left(\frac{C_{eff,u,animal}}{IC_{50,animal}}\right) * \left(\frac{1}{f_{u,human}}\right)$$

Cl_T — ***Predicted from preclinical data***

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.

Projecting Human Clearance: 3 Methods

In vitro – in vivo correlation (IVIVC)

Multispecies Allometric Scaling

Single Species Allometric Scaling

Smith et. al. *J. Med. Chem.* **2019**, 62*,* 2245*.;* Sodhi, J. K. et. al. *J. Med. Chem.* **2021**, *64*, 3546

Scaling Intrinsic Clearance through IVIVC

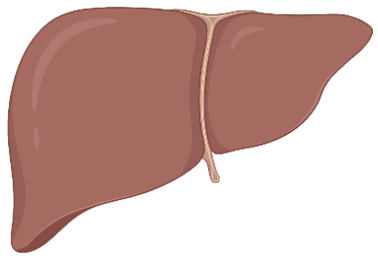
In vitro – in vivo correlation (IVIVC)

Generally ***most preferred method***

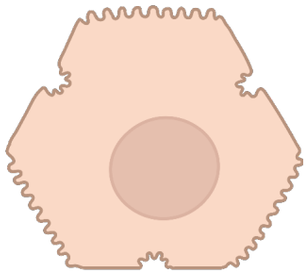
Fast *turnaround time*

Direct ***calculation from in vitro data***

Generally only applicable to CYP450 clearance

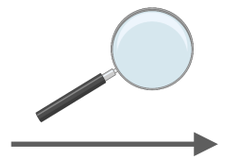


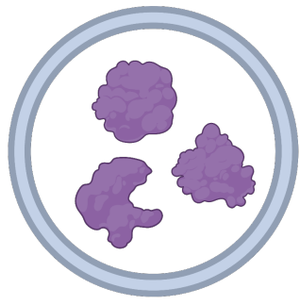
Liver



Hepatocyte

In-tact liver cell containing metabolizing enzymes and membrane transporters



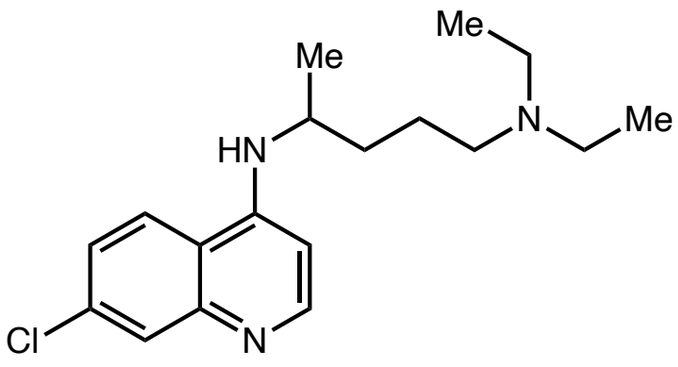


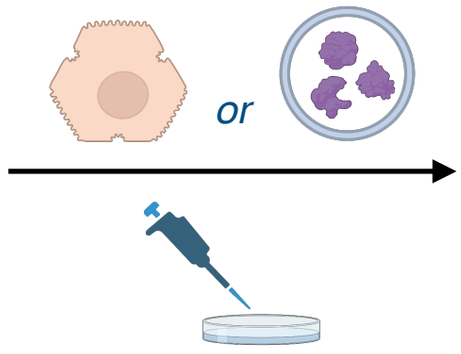
Microsome

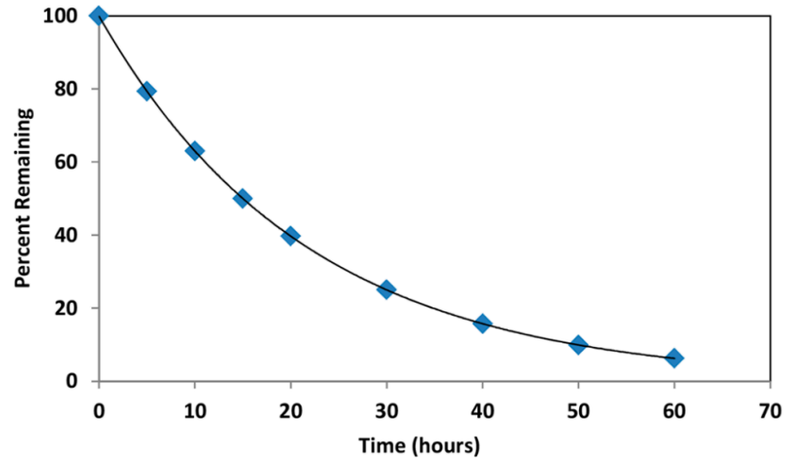
“vesicle - like” molecules, high concentration of CYP 450 Enzymes

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.; Sodhi, J. K. et. al. *J. Med. Chem.* **2021**, *64*, 3546

Scaling Intrinsic Clearance through IVIVC







$$Cl_{int,u,in\ vitro} = \frac{\ln(2)}{t_{\frac{1}{2}}} * \frac{V_{inc}}{cell\ number\ or\ [protein]} * \frac{1}{f_{u,inc}}$$

Intrinsic ability of hepatocyte or microsome to remove the drug

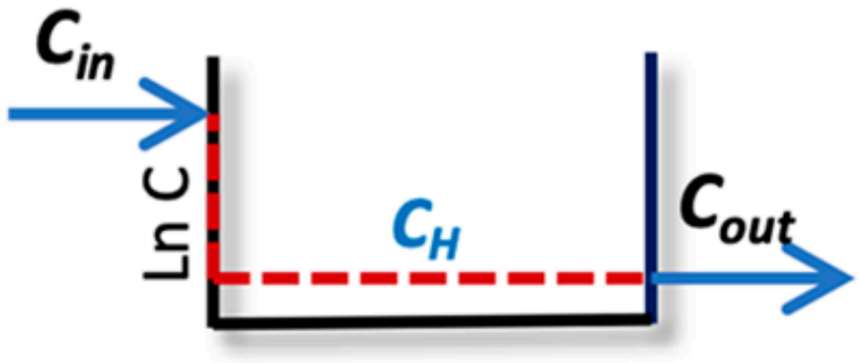
In the absence of organ blood flow or protein binding

$$Cl_{int,u,in\ vivo} = Cl_{int,u,in\ vitro} * \frac{\#\ enzymes\ or\ cells\ in\ whole\ liver}{\#\ enzymes\ or\ cells\ in\ incubation}$$

Predicted unbound clearance In vivo

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.; Sodhi, J. K. et. al. *J. Med. Chem.* **2021**, *64*, 3546

Applying the Well Stirred Model



Assumptions:

Free passive diffusion

Drug is evenly distributed throughout liver

Enzymes are evenly distributed throughout liver

$$Cl_{Hepatic,total} = \frac{Q_H * f_{u,blood} * Cl_{int,u,in\ vivo}}{Cl_{int,u,in\ vivo} * (Q_H + f_{u,blood})}$$

Total in vivo hepatic clearance predicted from in vitro data

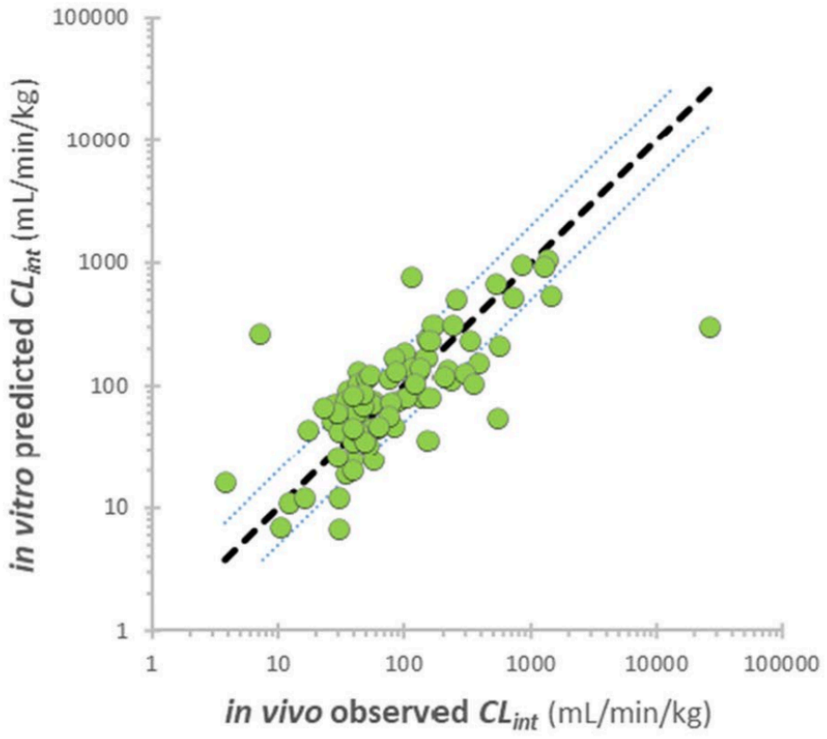
Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.; Sodhi, J. K. et. al. *J. Med. Chem.* **2021**, *64*, 3546

Checking for positive in vitro in vivo correlation (IVIVC)

Perform predictions for at least 2 preclinical species and compare calculated total clearance to real in vivo data

Mouse

Rat



If in vitro data for preclinical species ***predicts in vivo clearance within 2x*** *human* ***in vitro data can be scaled to Predict human clearance***

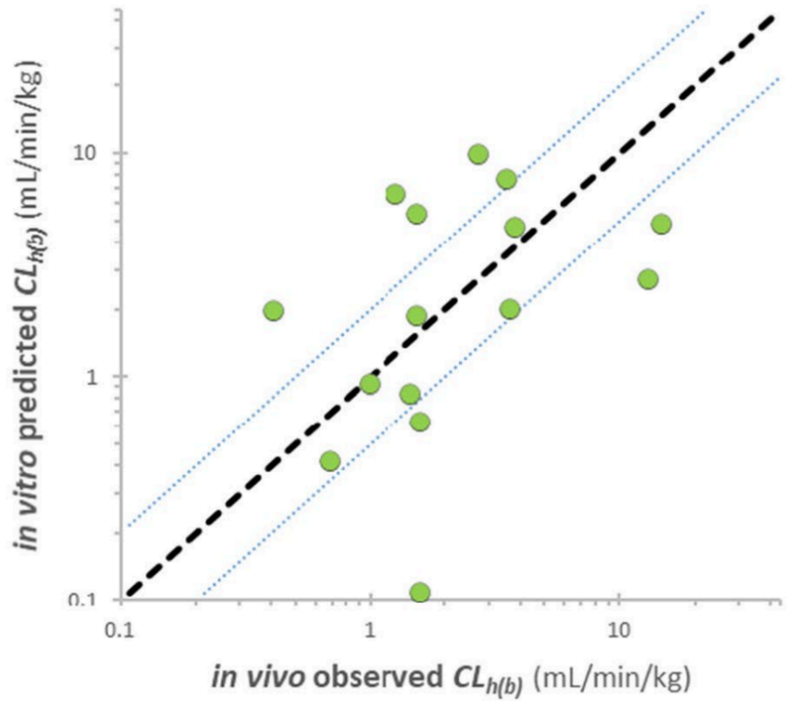
Tess, D. A. et. al. *Pharmaceutical Research* **2022**, 39, *1615.*

Checking for positive in vitro in vivo correlation (IVIVC)

Perform predictions for at least 2 preclinical species and compare calculated total clearance to real in vivo data

Mouse

Rat

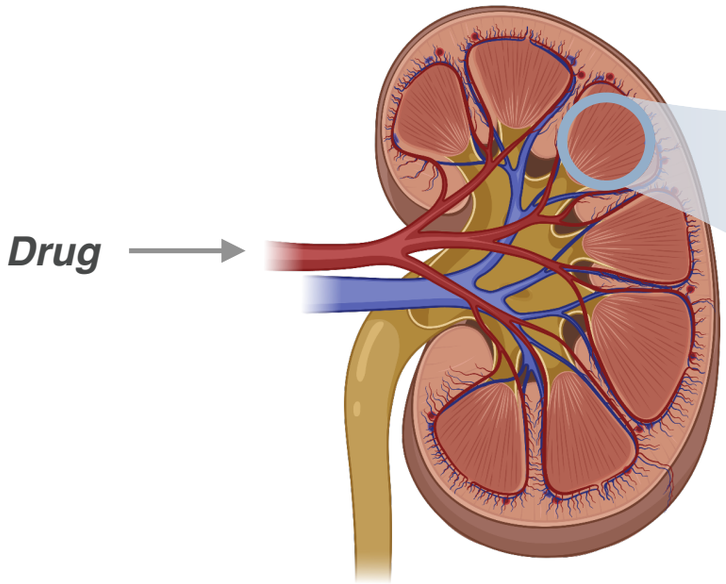


*If in vitro data fails to predict in vivo data within 2 fold **IVIVC cannot be used***

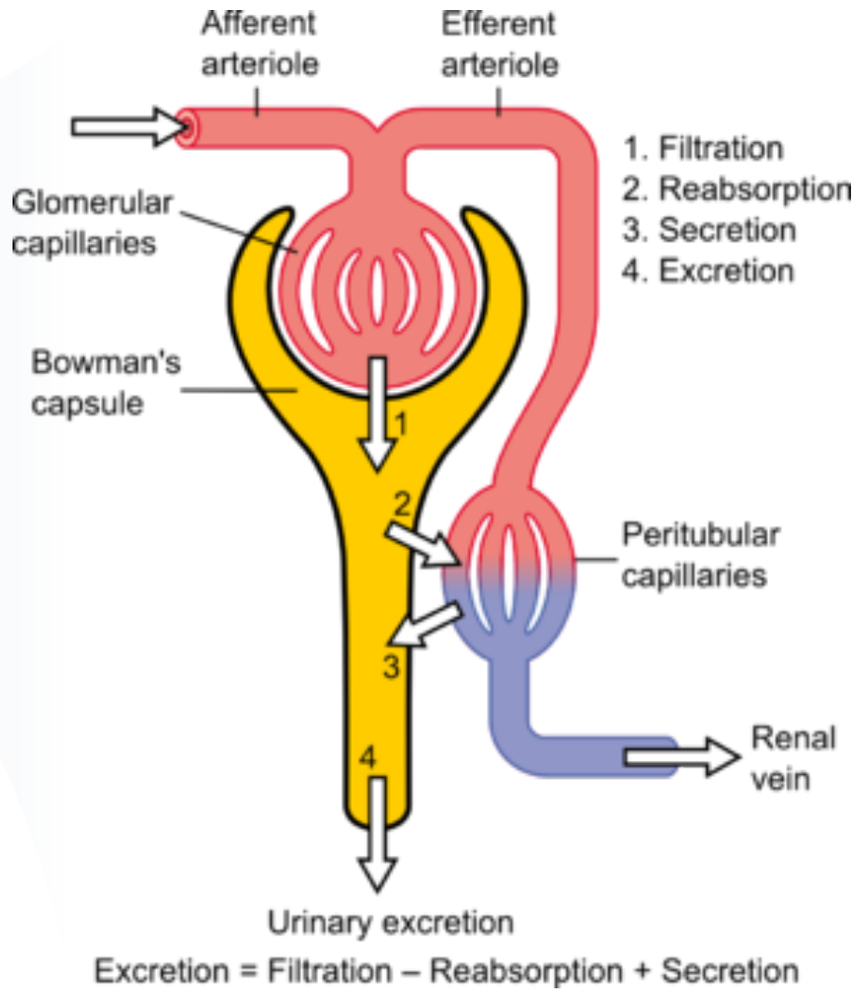
*Indicative of alternate mechanism of clearance i.e. **Renal or Biliary clearance***

Tess, D. A. et. al. *Pharmaceutical Research* **2022**, 39, *1615.*

Clearance in the Kidney



Kidney



Renal Clearance

Passive clearance via rate of glomerular filtration (GFR)

polar and poorly permeable compounds

Clearance ***bounded by flow rate***

Can we relate flow rate between species?

$$Cl_{r,u} = f_{u,blood} * GFR$$

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.

Interspecies Allometry

Multispecies

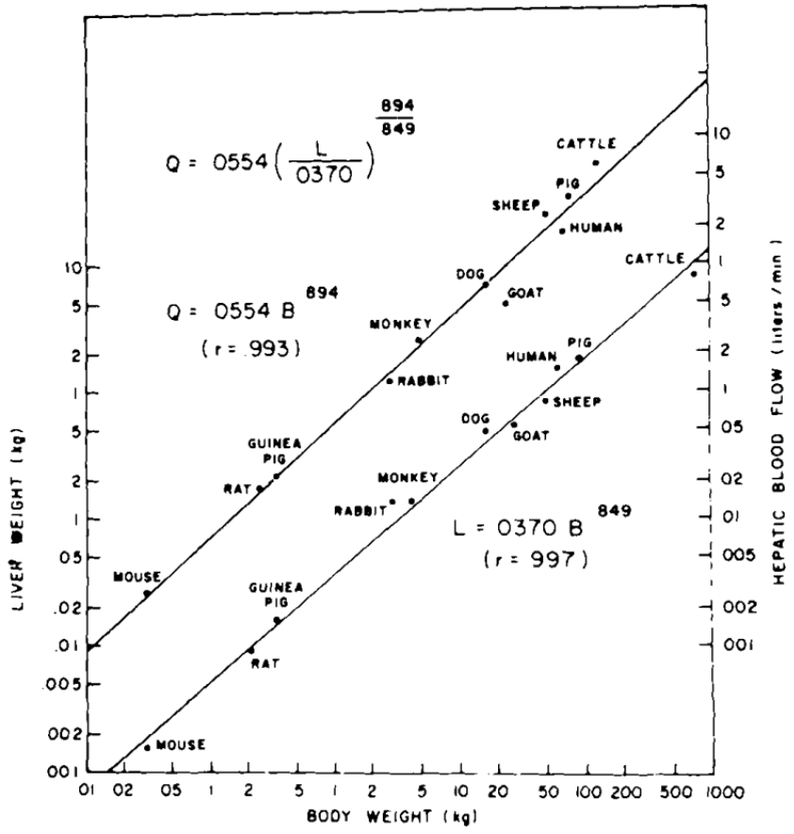
Allometric Scaling

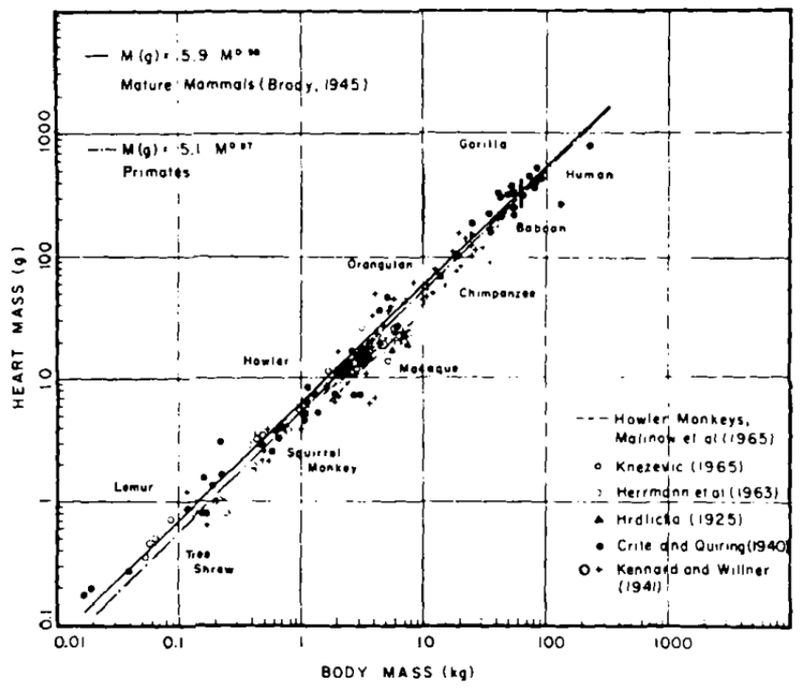
$$X_{phys} = a * (body\ weight)^b$$

$$\log(X_{phys}) = ab * \log(body\ weight)$$

X_{phys} – physiological parameter

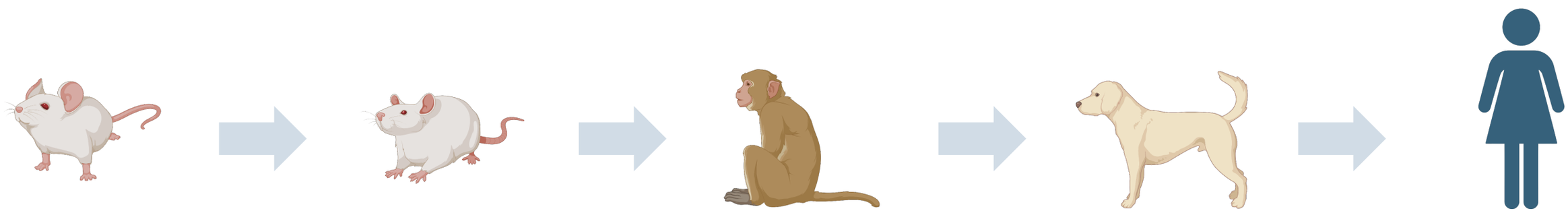
"a" and "b" – correction factors

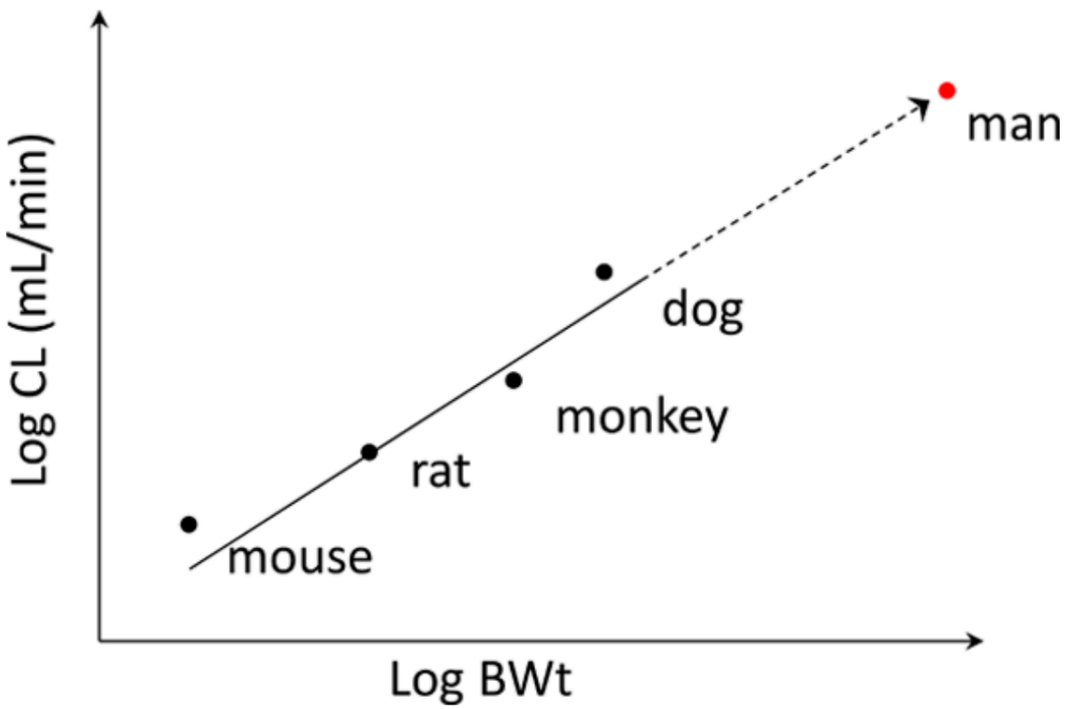




Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.; Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513; Mordenti, J. *J. Pharma. Sci.* **1896**, *75*, 1028

Allometric Scaling of Clearance





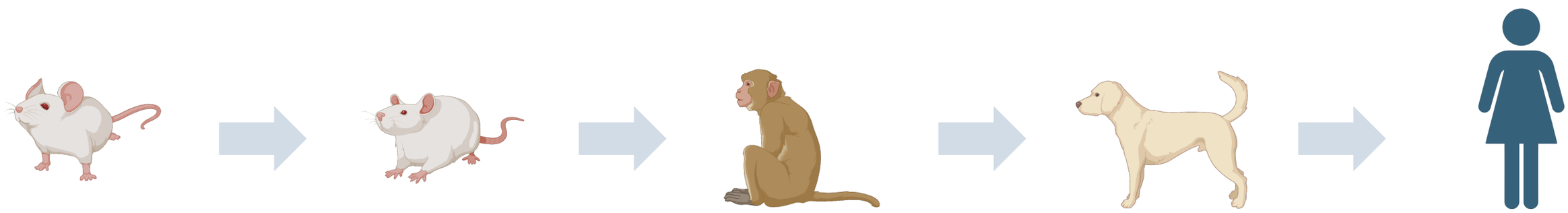
Allometric Scaling for Human PK

$$\log(Cl) = ab * \log(body\ weight)$$

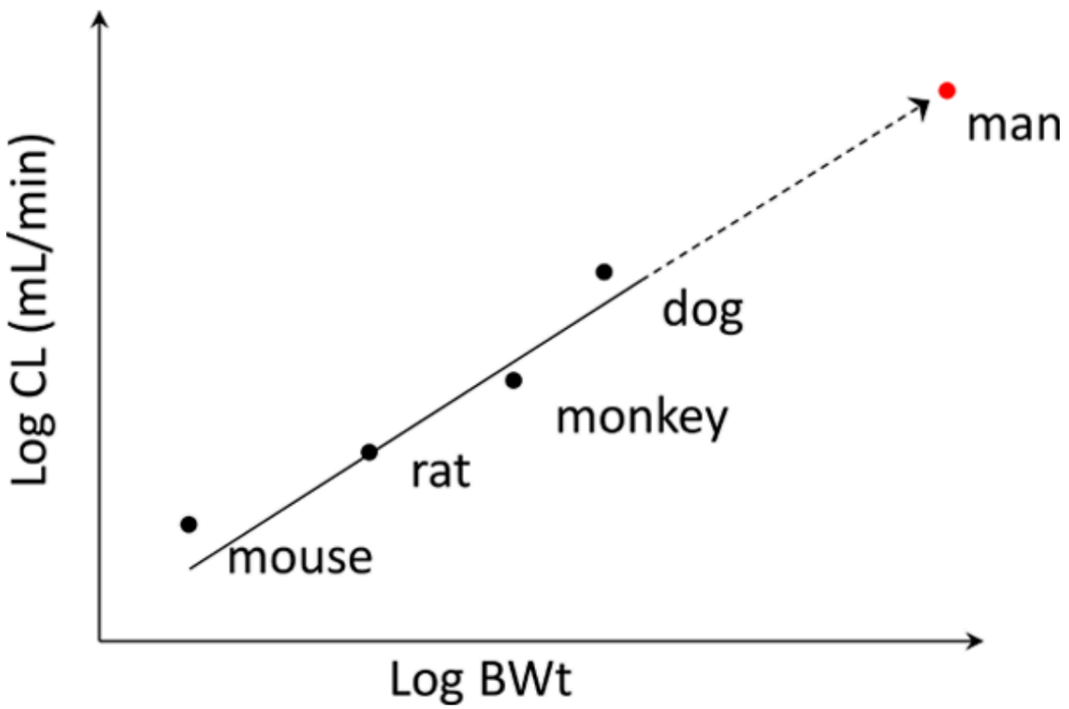
correction factors "a" and "b" are adjusted to correct for error

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.; Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

Allometric Scaling of Clearance



Mouse *Rat* *Monkey* *Dog* *Human*



Allometric Scaling for Human PK

Oldest method for prediction of human PK

Preferred for compounds with renal or biliary clearance

Labor intensive and expensive

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.*;* Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

Projecting Human Clearance: 3 Methods

In vitro – in vivo correlation (IVIVC)

Multispecies Allometric Scaling

Single Species Allometric Scaling

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.*;* Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

Single Species Scaling

Single Species

Allometric Scaling

Rat

Human

$$Cl_{human} = Cl_{animal} * \left(\frac{BW_{human}}{BW_{animal}}\right)^{0.75}$$

Single Species Scaling for Human PK

Assumes exponential factor of 0.67 - 0.75

Low cost but imposes more uncertainty

controversial yet widely employed

Smith et. al. *J. Med. Chem.* **2019**, 62, 2245.*;* Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

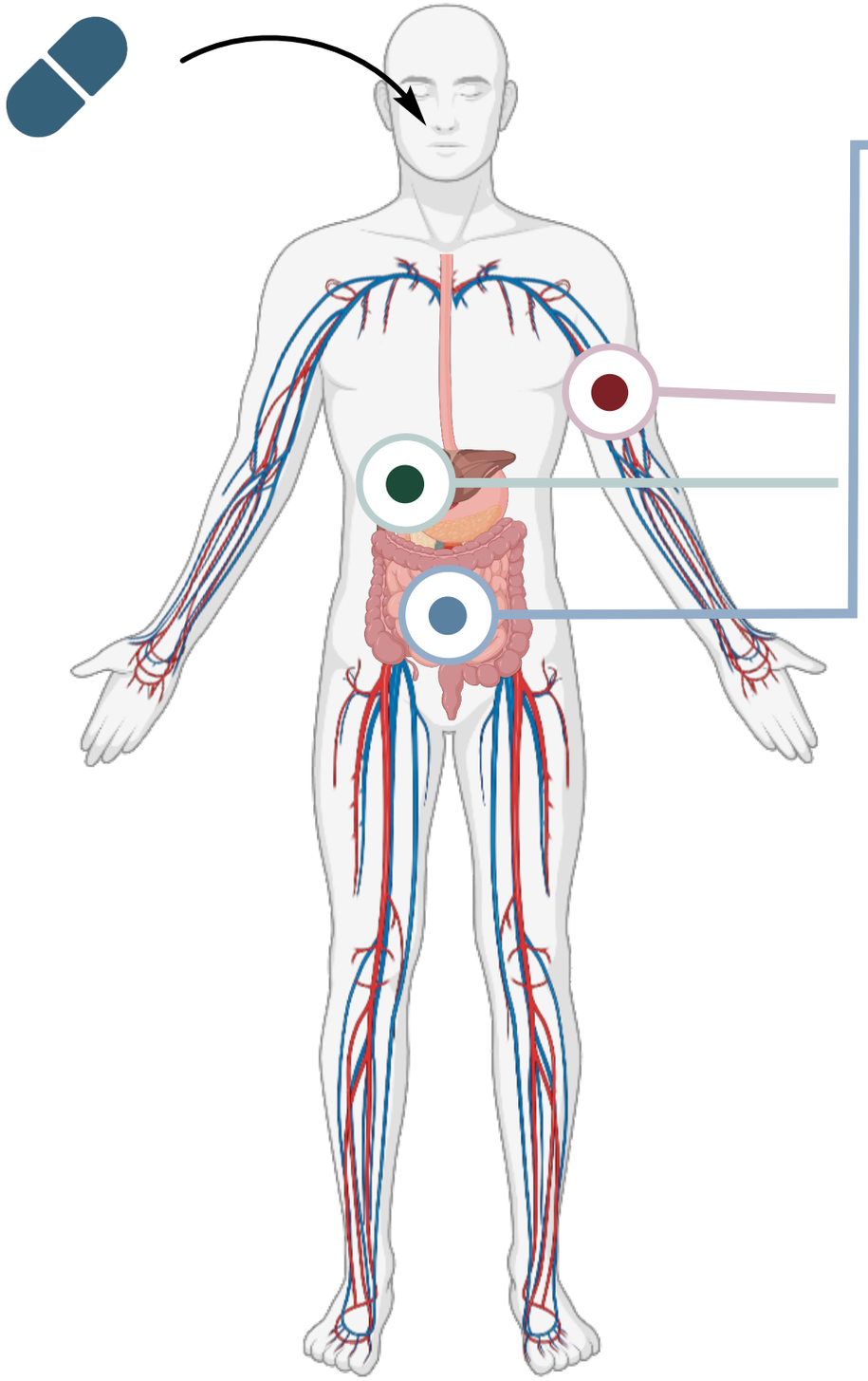
Projecting Human Clearance: 3 Methods

In vitro – in vivo correlation (IVIVC)

Multispecies Allometric Scaling

Single Species Allometric Scaling

How much drug do you actually need?



F% — ***Predicted from preclinical data***

C_{eff}

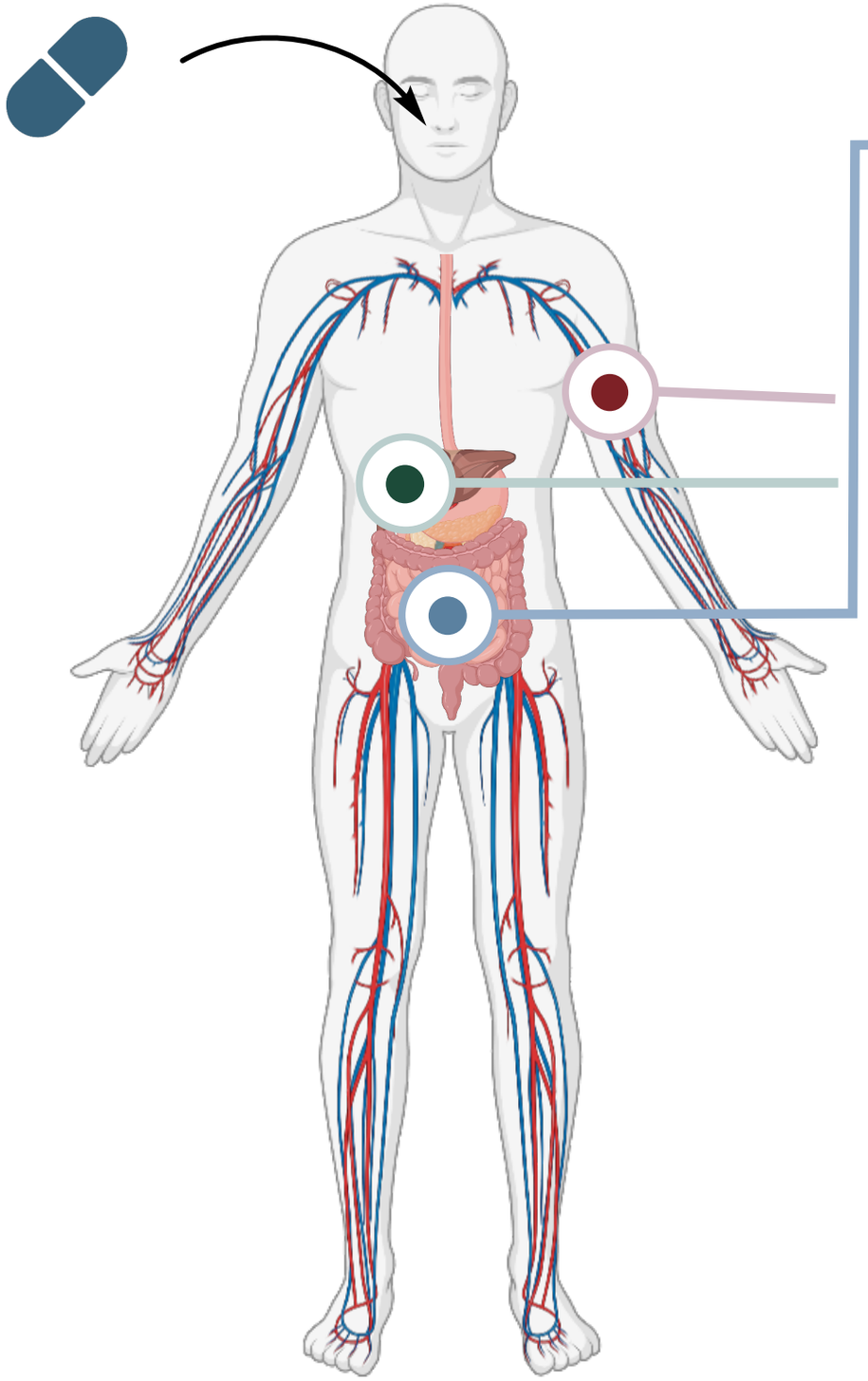
$$IC_{50,human} * \left(\frac{C_{eff,u,animal}}{IC_{50,animal}}\right) * \left(\frac{1}{f_{u,human}}\right)$$

Cl_T — ***Predicted from preclinical data***

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Devery III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Flowers II, R. A.; Stephenson, C. R. J. *Chem. Sci.* **2015**, *6*, 537.

How much drug do you actually need?



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Cl_T

$$\frac{Q_H * f_{u,blood} * Cl_{int,u,in\ vivo}}{Cl_{int,u,in\ vivo} * (Q_H + f_{u,blood})}$$

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Devery III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Flowers II, R. A.; Stephenson, C. R. J. *Chem. Sci.* **2015**, *6*, 537.

Predicting Oral Bioavailability from Preclinical Species

F%

Oral Bioavailability

Determined allometrically

Often Single Species Scaling

calculation ***dependent on clearance mechanism***

Hepatic clearance and high E_h

$$F\% = f_a * f_g * \left(1 - \frac{Cl_h}{Q_h}\right)$$

Assumptions:

*(f_a*f_g) = is consistent across species*

Clearance prediction is accurate

Renal/biliary/other clearance mechanism

$$F\% = f_a * f_g$$

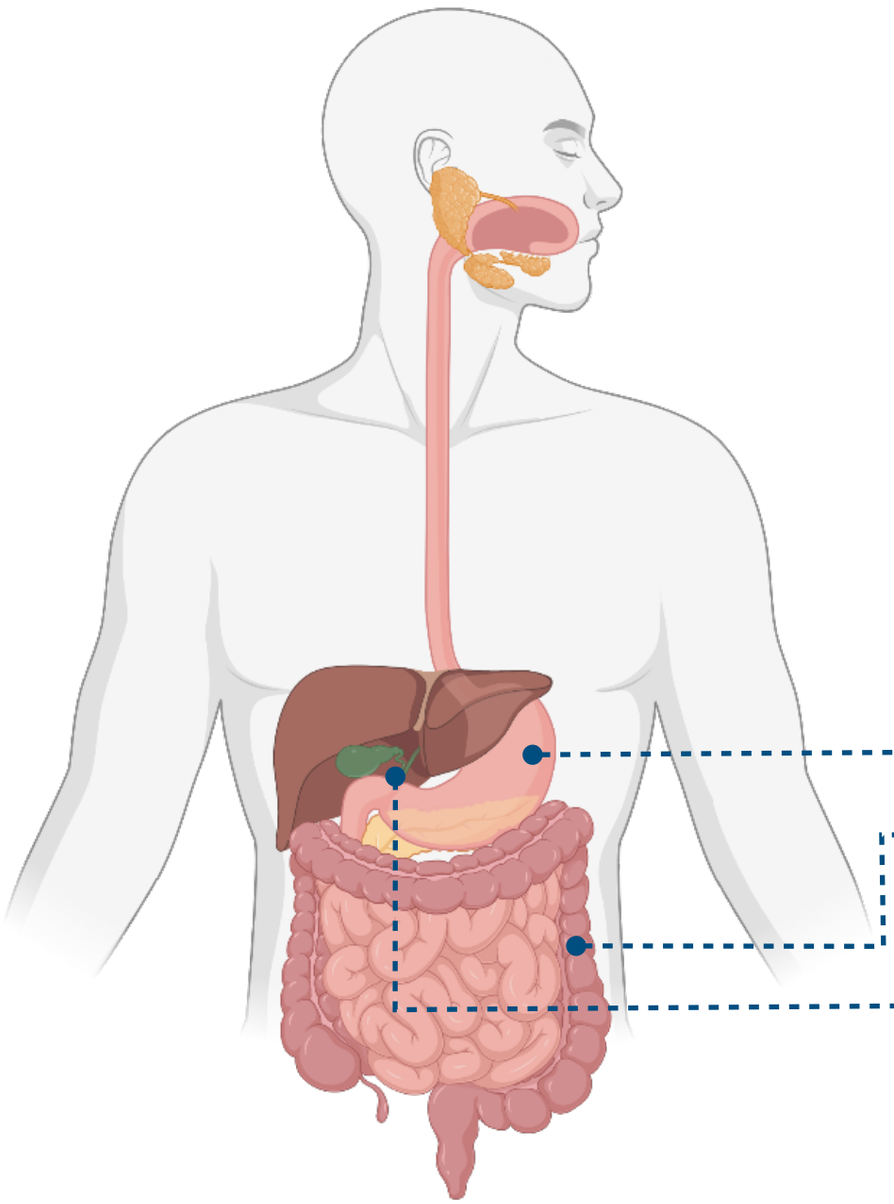
Assumptions:

*(f_a*f_g) = is consistent across species*

Hepatic extraction is negligible

Devery III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Flowers II, R. A.; Stephenson, C. R. J. *Chem. Sci.* **2015**, *6*, 537.

Oral Bioavailability



F%

Oral Bioavailability

Fraction of drug (%) that makes it in to systemic circulation

$$F\% = f_{absorbed} * f_g * (1 - E_h)$$

- *F_a = fraction absorbed*
- *F_g = fraction escaping gut metabolism*
- *E_h = hepatic extraction ratio (first pass metabolism)*

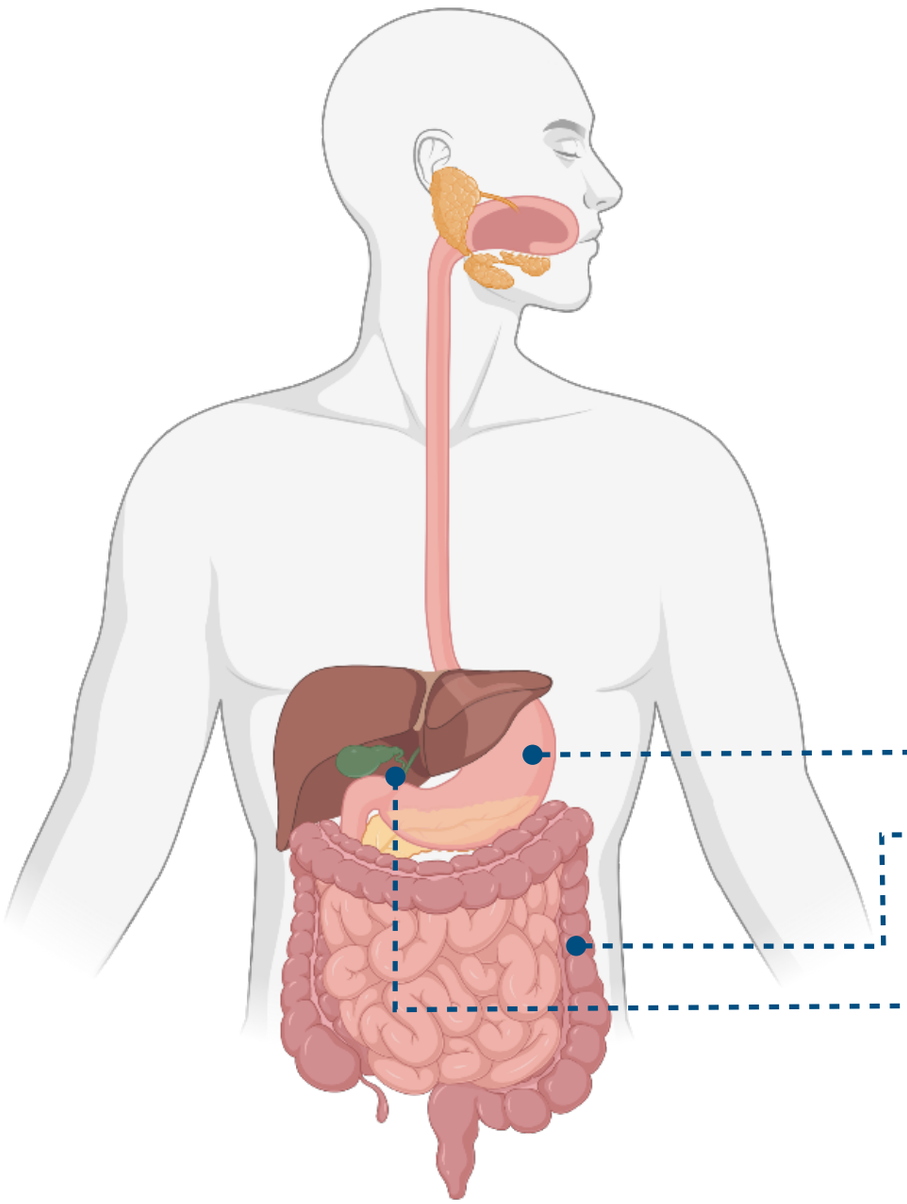
$$E_h = \frac{Cl}{Q_h}$$

Cl = clearance

Q_h = hepatic blood flow

Smith et. al. *J. Med. Chem.* **2019**, 62*,* 2245.*;* Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

Oral Bioavailability



F%

Oral Bioavailability

Allometric Projection:

*(f_a*f_g) = is consistent across species*

Clearance prediction is accurate

$$F\% = f_{absorbed} * f_g * (1 - E_h)$$

F_a = fraction absorbed

F_g = fraction escaping gut metabolism

E_h = hepatic extraction ratio (first pass metabolism)

$$E_h = \frac{Cl}{Q_h}$$

Cl = clearance

Q_h = hepatic blood flow

Smith et. al. *J. Med. Chem.* **2019**, 62*,* 2245.*;* Hosea, N. L. et. al. *J. Clin. Pharmacol.* **2009**, *49*, 513

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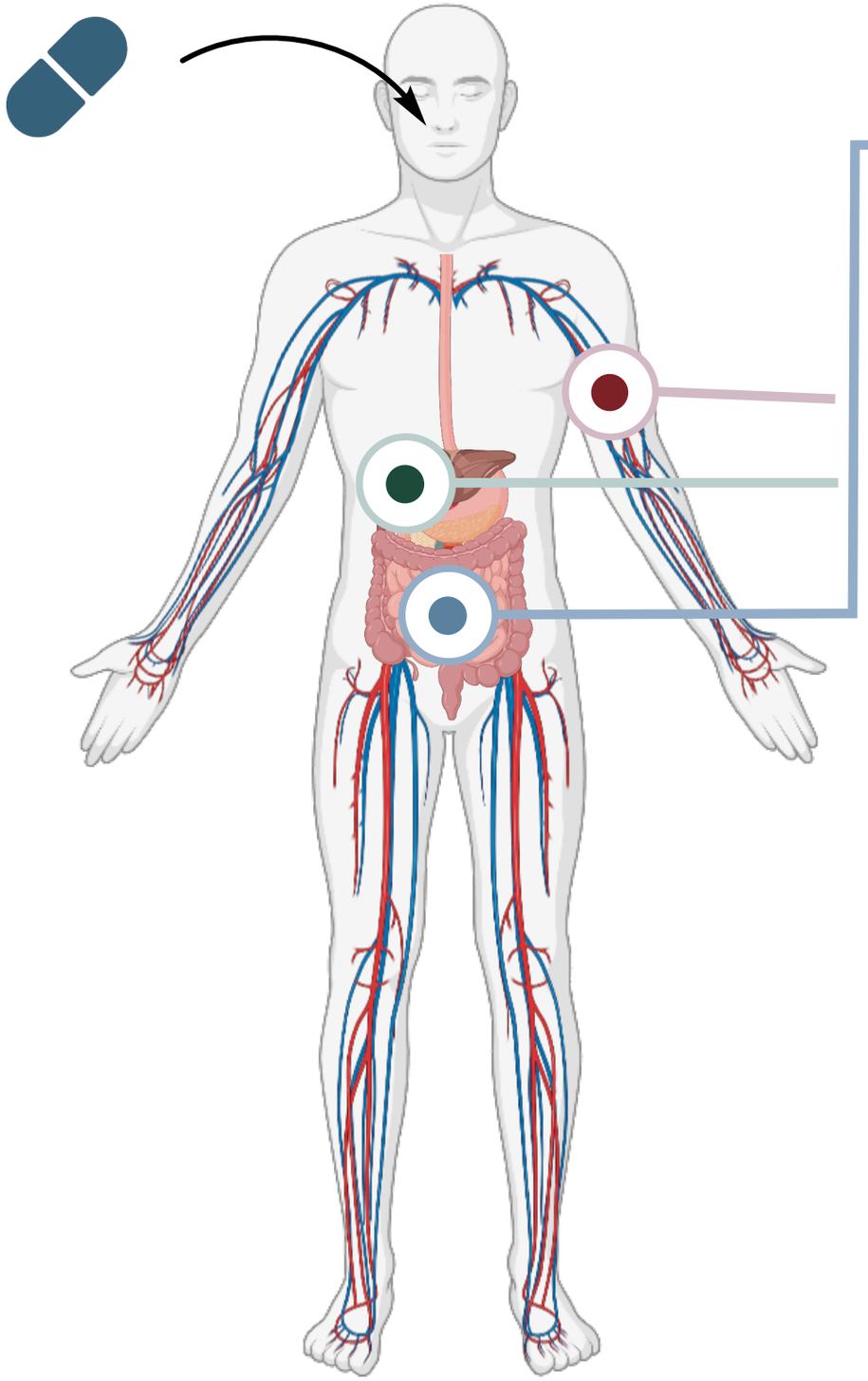

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Cl_T

$$\frac{Q_H * f_{u,blood} * Cl_{int,u,in\ vivo}}{Cl_{int,u,in\ vivo} * (Q_H + f_{u,blood})}$$

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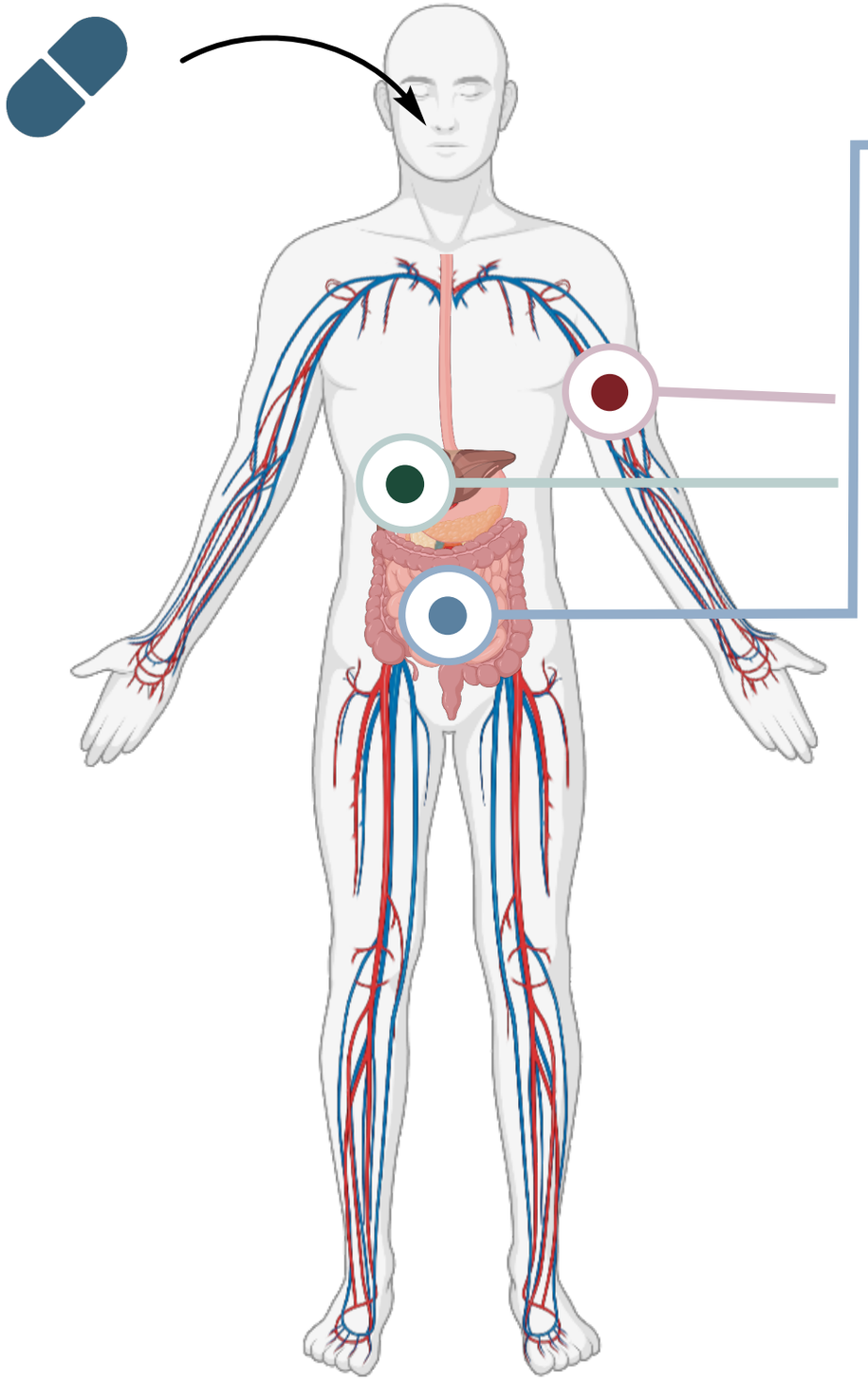


F%

$$f_a * f_g * \left(1 - \frac{Cl_h}{Q_h}\right)$$

C_{eff}

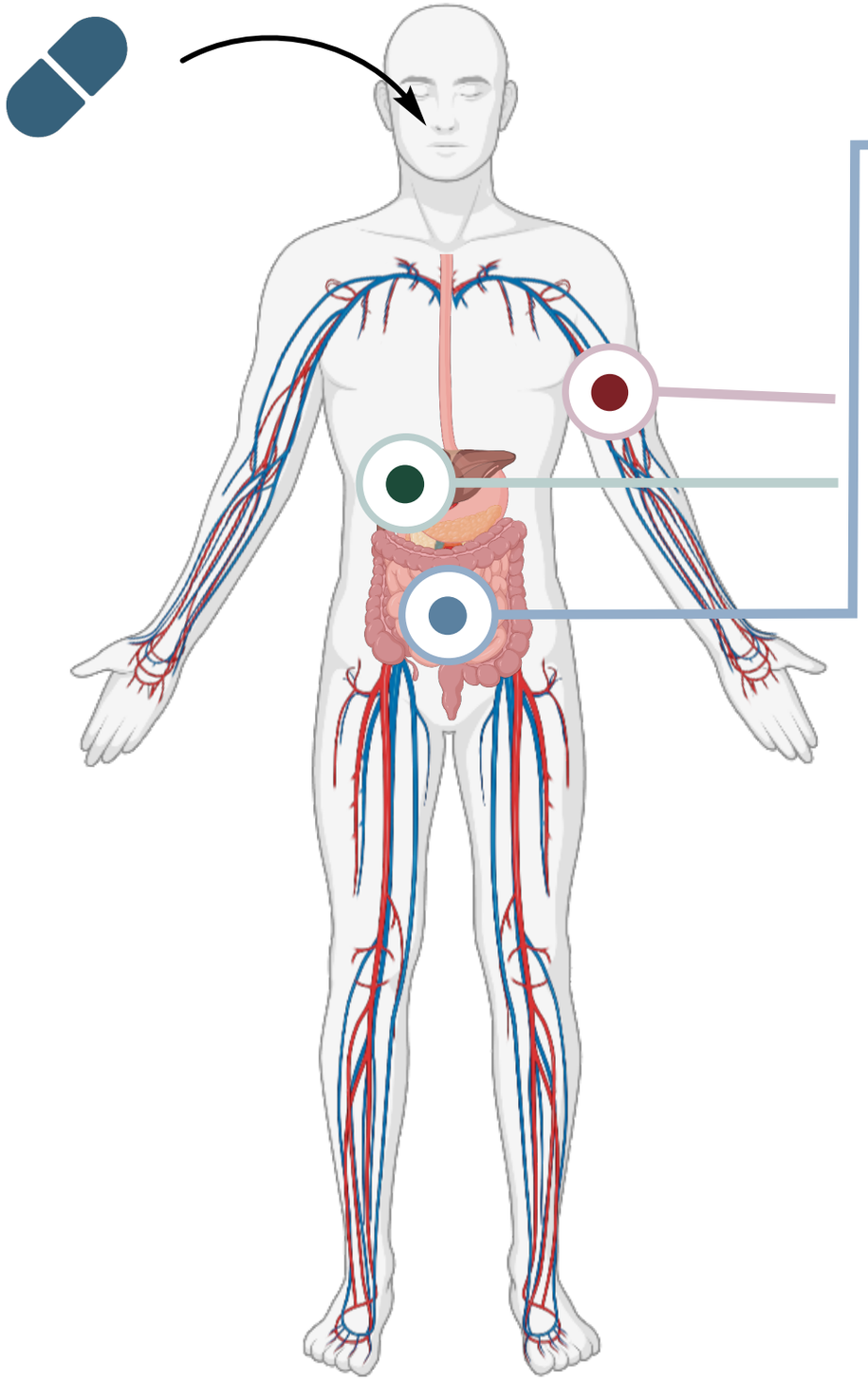
$$IC_{50,human} * \left(\frac{C_{eff,u,animal}}{IC_{50,animal}}\right) * \left(\frac{1}{f_{u,human}}\right)$$

Cl_T

$$\frac{Q_H * f_{u,blood} * Cl_{int,u,in\ vivo}}{Cl_{int,u,in\ vivo} * (Q_H + f_{u,blood})}$$

$$Dose = \frac{C_{eff,avg,ss} * Cl_h}{F\%}$$

How much drug do you actually need?



F%

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C_{eff}

$$IC_{50,human} * \left(\frac{C_{eff,u,animal}}{IC_{50,animal}}\right) * \left(\frac{1}{f_{u,human}}\right)$$

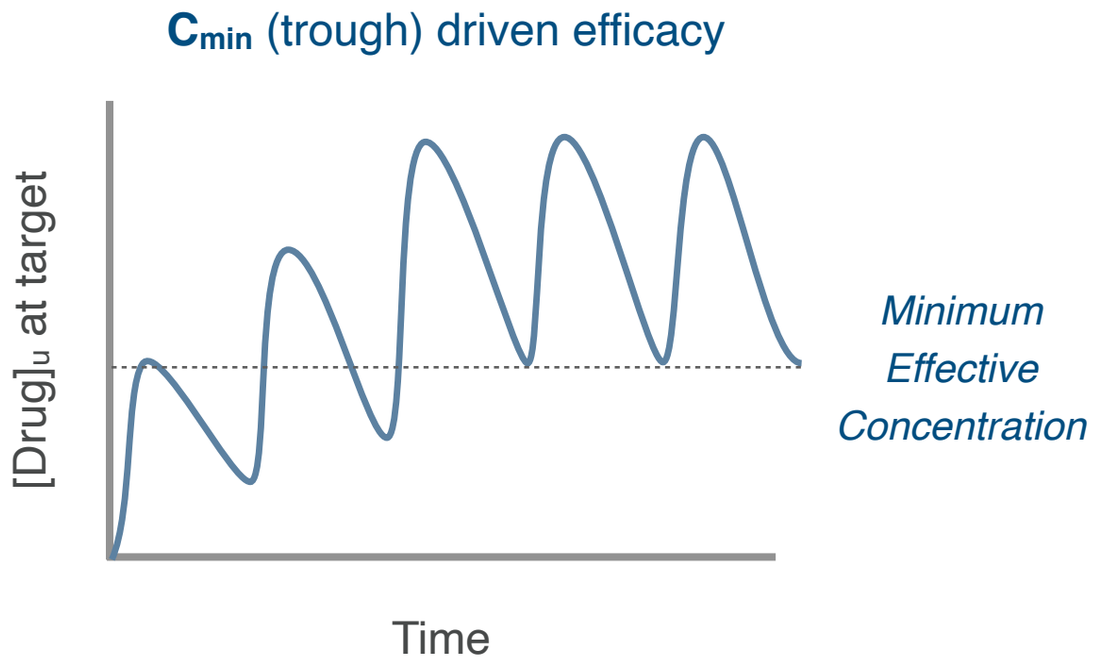
Cl_T

$$\frac{Q_H * f_{u,blood} * Cl_{int,u,in\ vivo}}{Cl_{int,u,in\ vivo} * (Q_H + f_{u,blood})}$$

$$Dose = \frac{C_{eff,avg,ss} * Cl_h * \tau}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63*, 6423.

How much drug do you actually need? – C_{min} and C_{max}



$t_{1/2}$

Must account

*for **half life***

$$t_{\frac{1}{2}} = \ln(2) * \left(\frac{V_{ss}}{Cl}\right)$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273

Volume of Distribution

V_{ss}

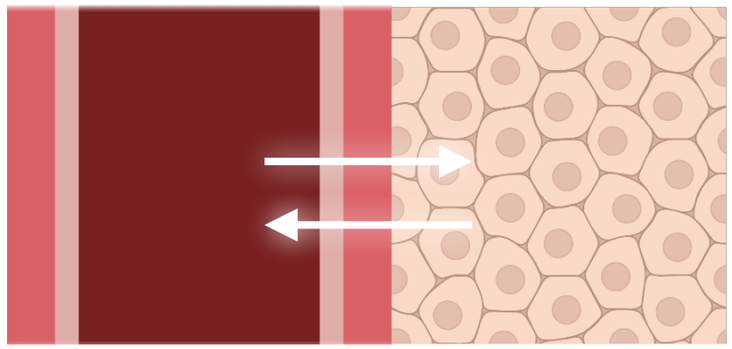
Volume of distribution

drug distribution between blood and tissues

Large V_{ss} = highly distributed in tissues

Low V_{ss} = centrally located in the blood

Must also consider unbound fraction in tissues ($f_{u,t}$)

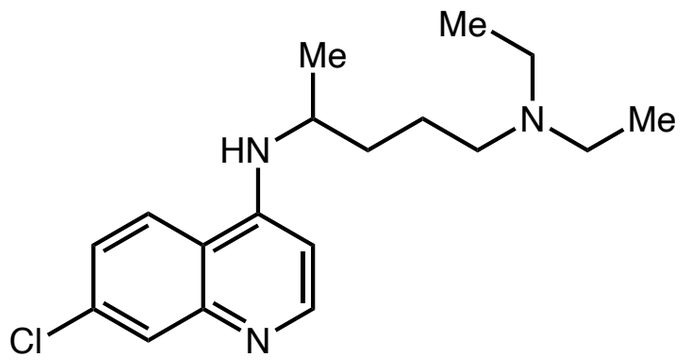


Basic compounds

High volume of distribution:

Partition in to acidic phospholipids in tissues

Low fraction unbound in tissues



chloroquine

V_{ss} = 200 L/kg

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

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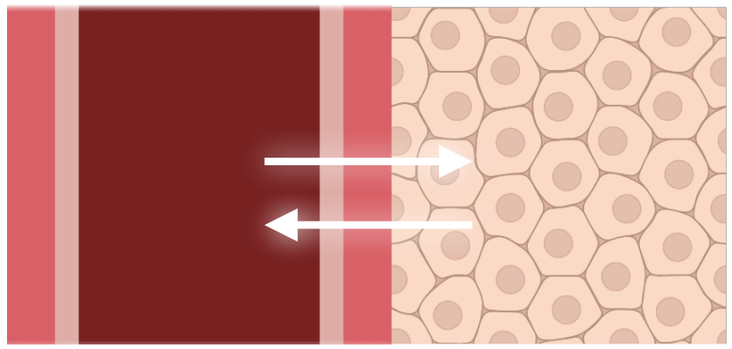
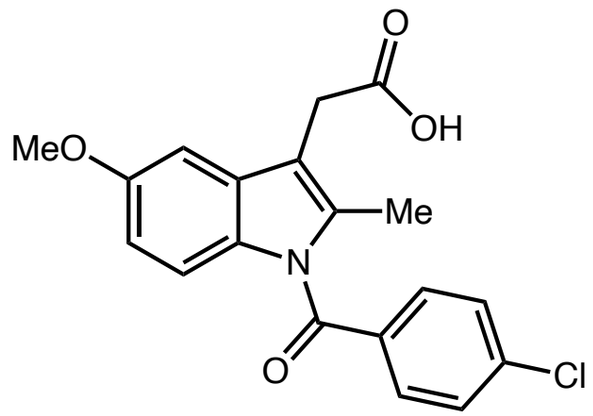


Acidic compounds

Low volume of distribution:

Bind strongly to albumin in plasma

Low fraction unbound in plasma



indometacin

V_{ss} = ~2 L/kg

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution

V_{ss}

Volume of distribution

drug distribution between blood and tissues

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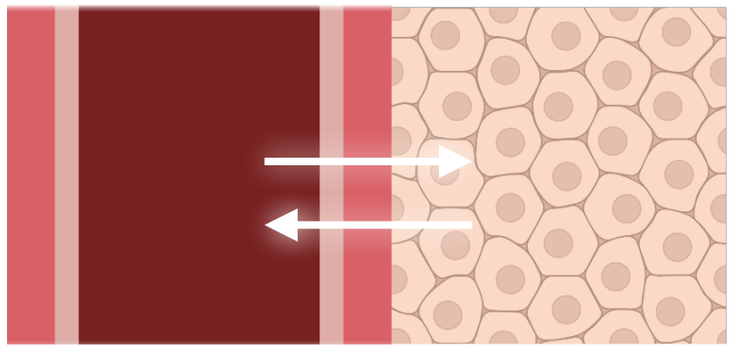
Low V_{ss} = centrally located in the blood

Must also consider unbound fraction in tissues ($f_{u,t}$)



Multispecies Allometric Scaling

$$\log(V_{ss}) = ab * \log(BW)$$

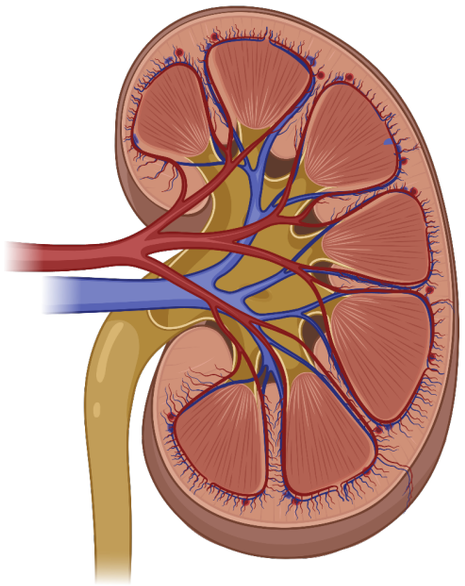
Single Species Allometric Scaling

$$V_{ss,human} = f_{u,p,human} * \left(\frac{V_{ss,animal}}{f_{u,p,animal}}\right)^{1.0}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Clearance, volume of distribution and half life

Drug

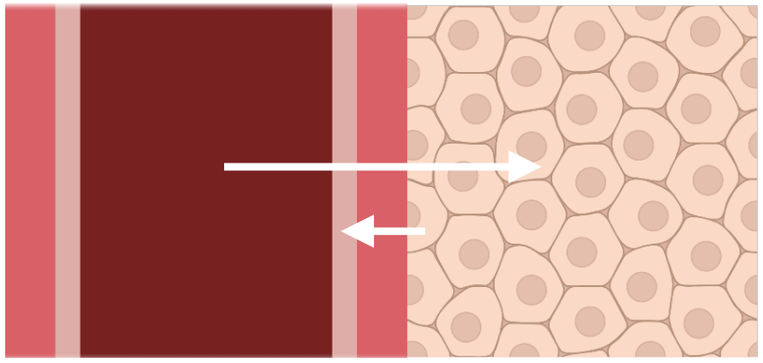


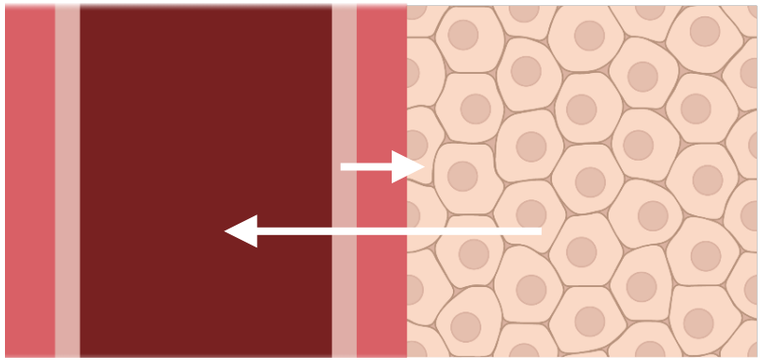
Renal Clearance

only clears ***unbound***

drug in plasma

$$t_{\frac{1}{2}} = \ln(2) * \left(\frac{V_{ss}}{Cl}\right)$$



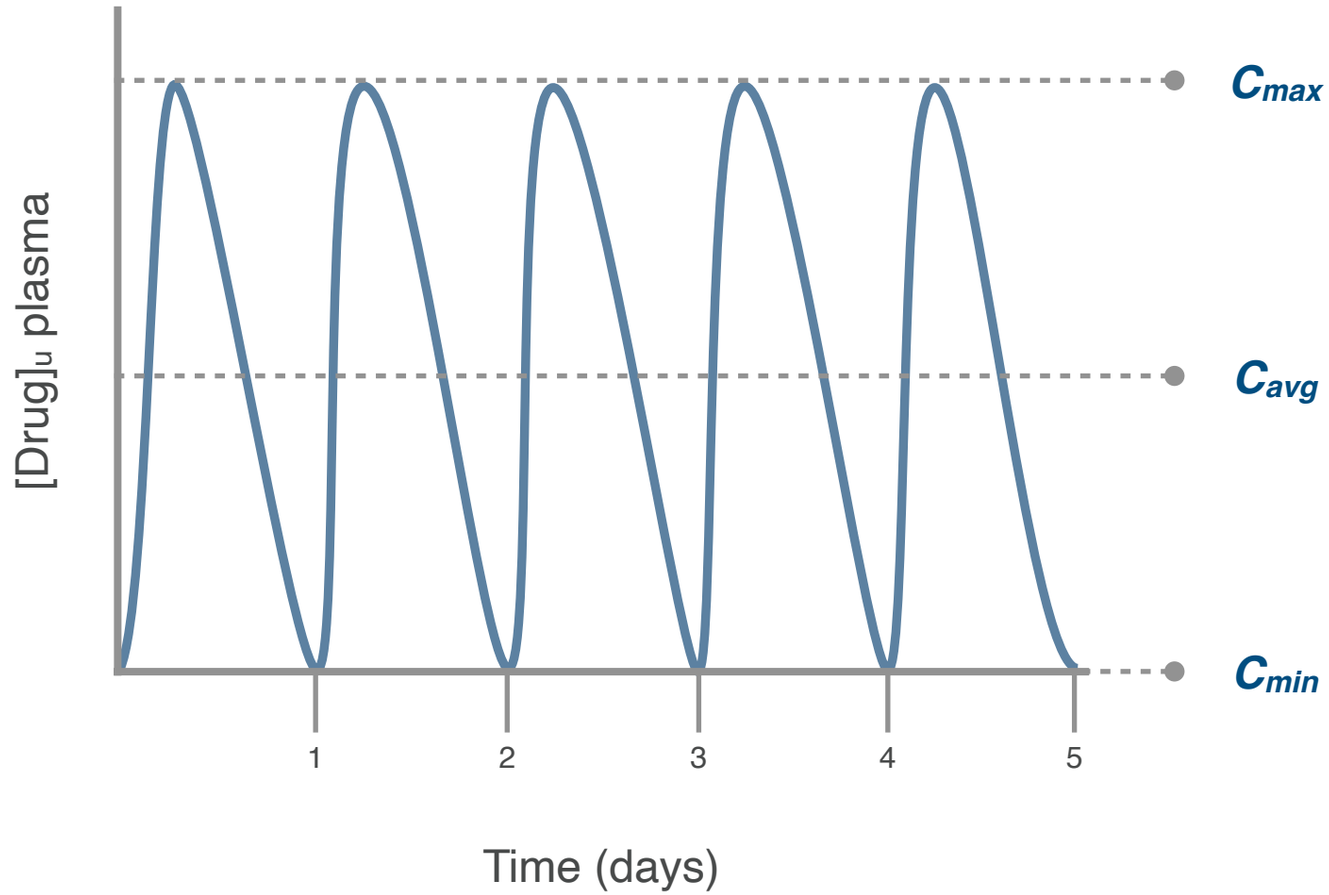


V_{ss} ***$t_{1/2}$***

V_{ss} ***$t_{1/2}$***

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life

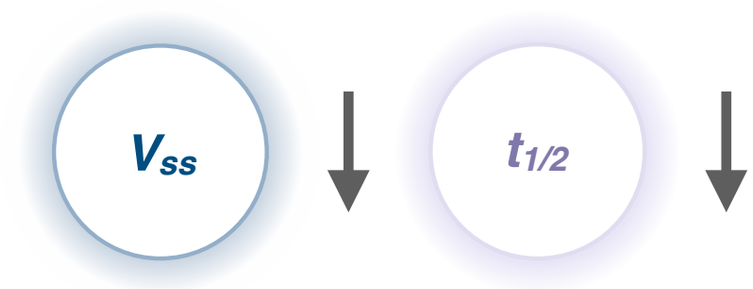


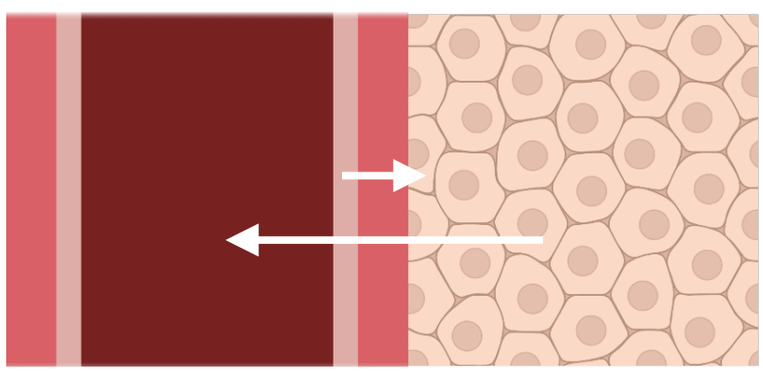
Low volume of distribution

Very high C_{max} / Very low C_{min}

All drug is localized in plasma

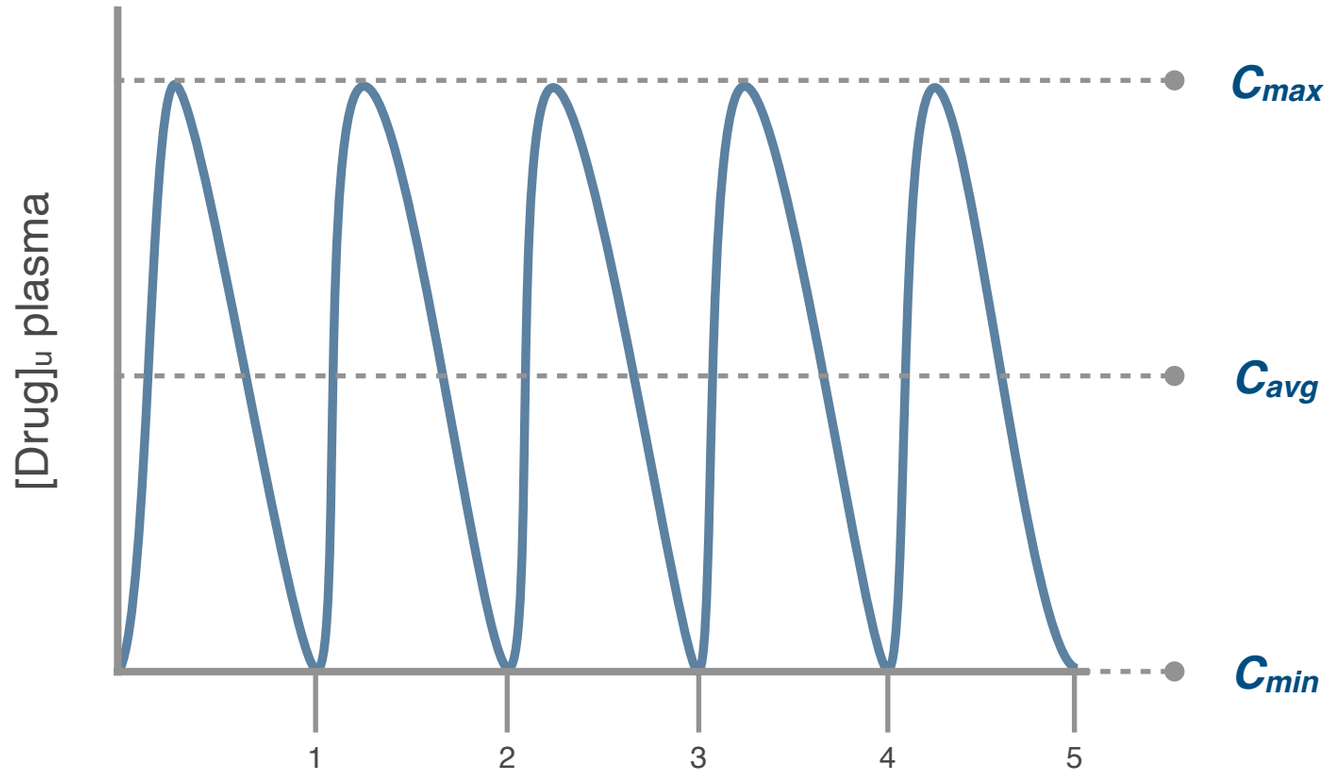
Half life controlled by clearance





Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life



Low volume of distribution

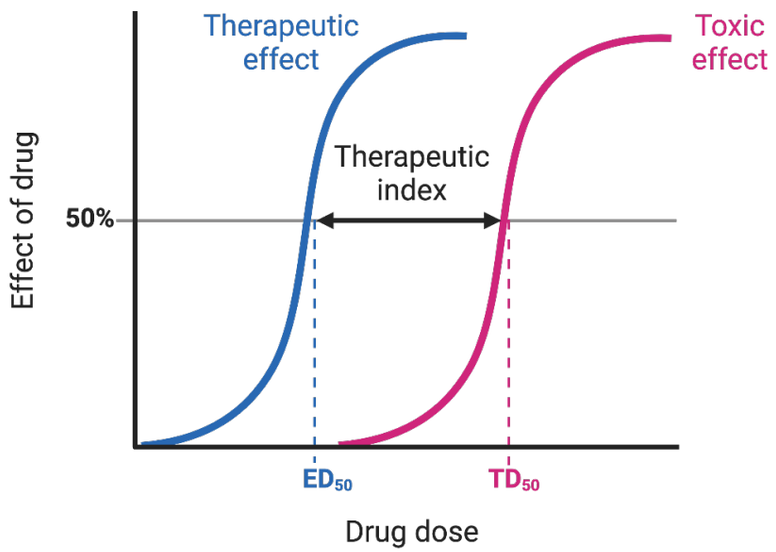
Very high C_{max} / Very low C_{min}

All drug is localized in plasma

Half life controlled by clearance

High swings in concentration undesirable

High max concentration risk for idiosyncratic toxicity



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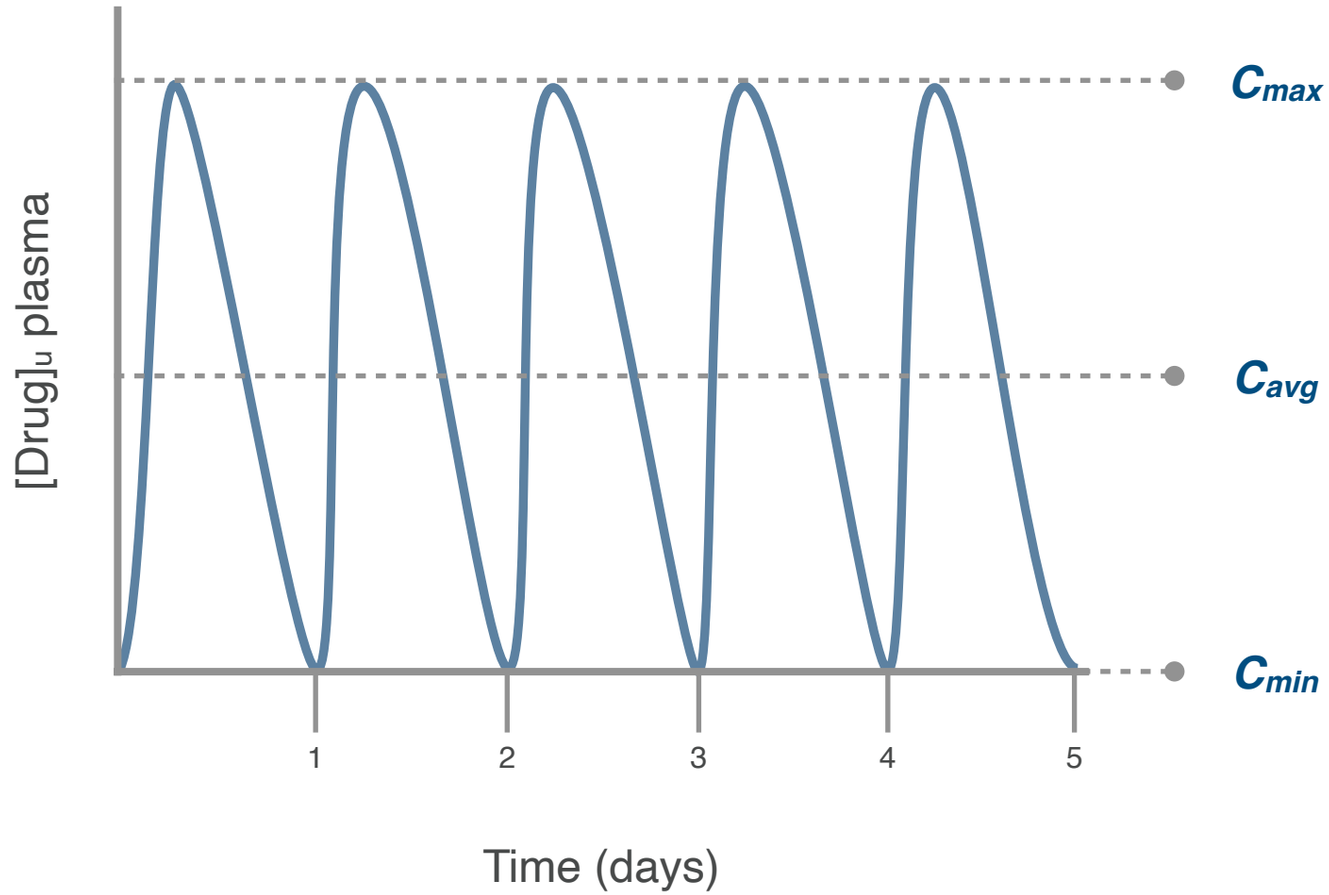
Volume of Distribution and half life



Low volume of distribution

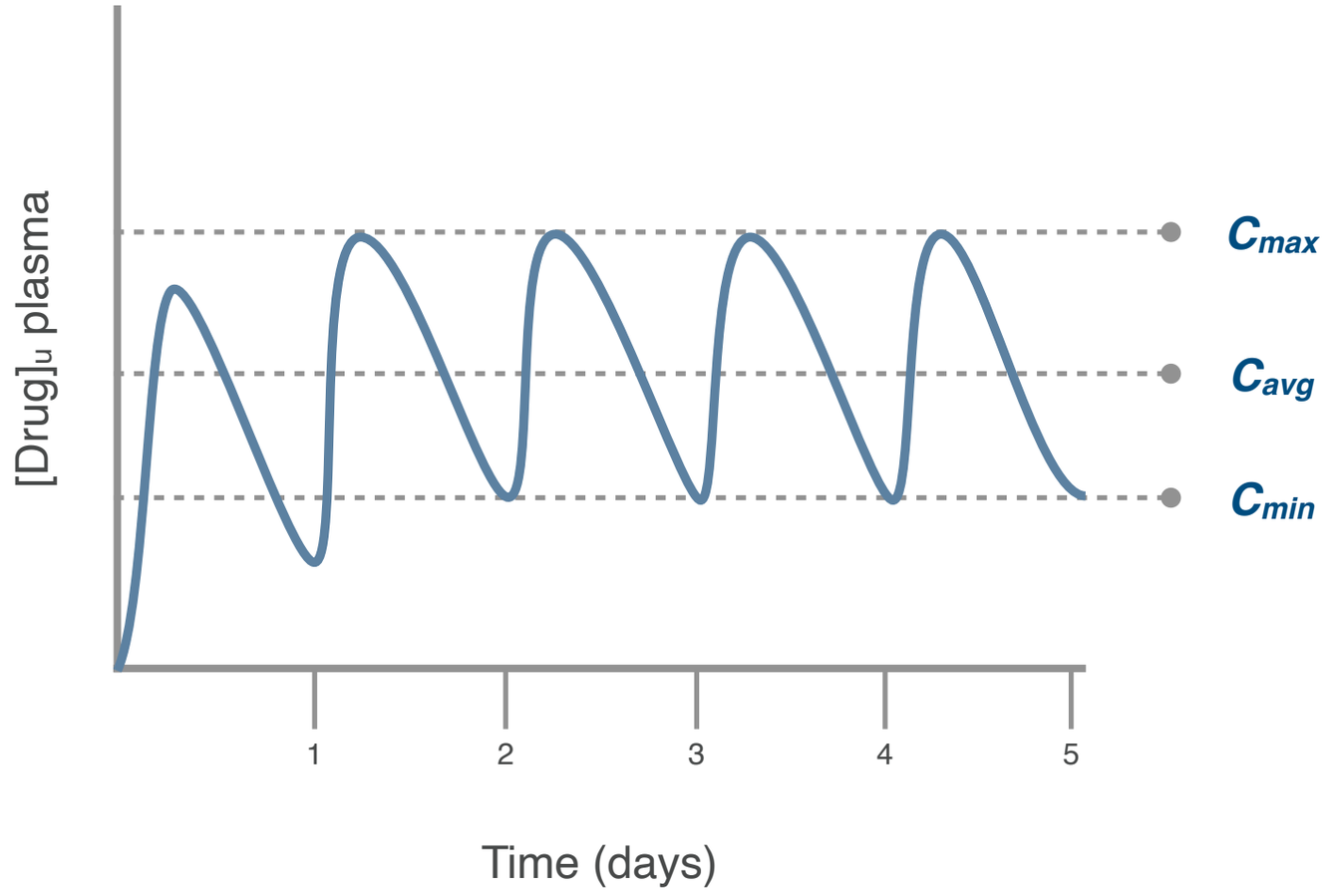
Very high C_{max} / Very low C_{min}

All drug is localized in plasma

Half life controlled by clearance

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life



Medium volume of distribution

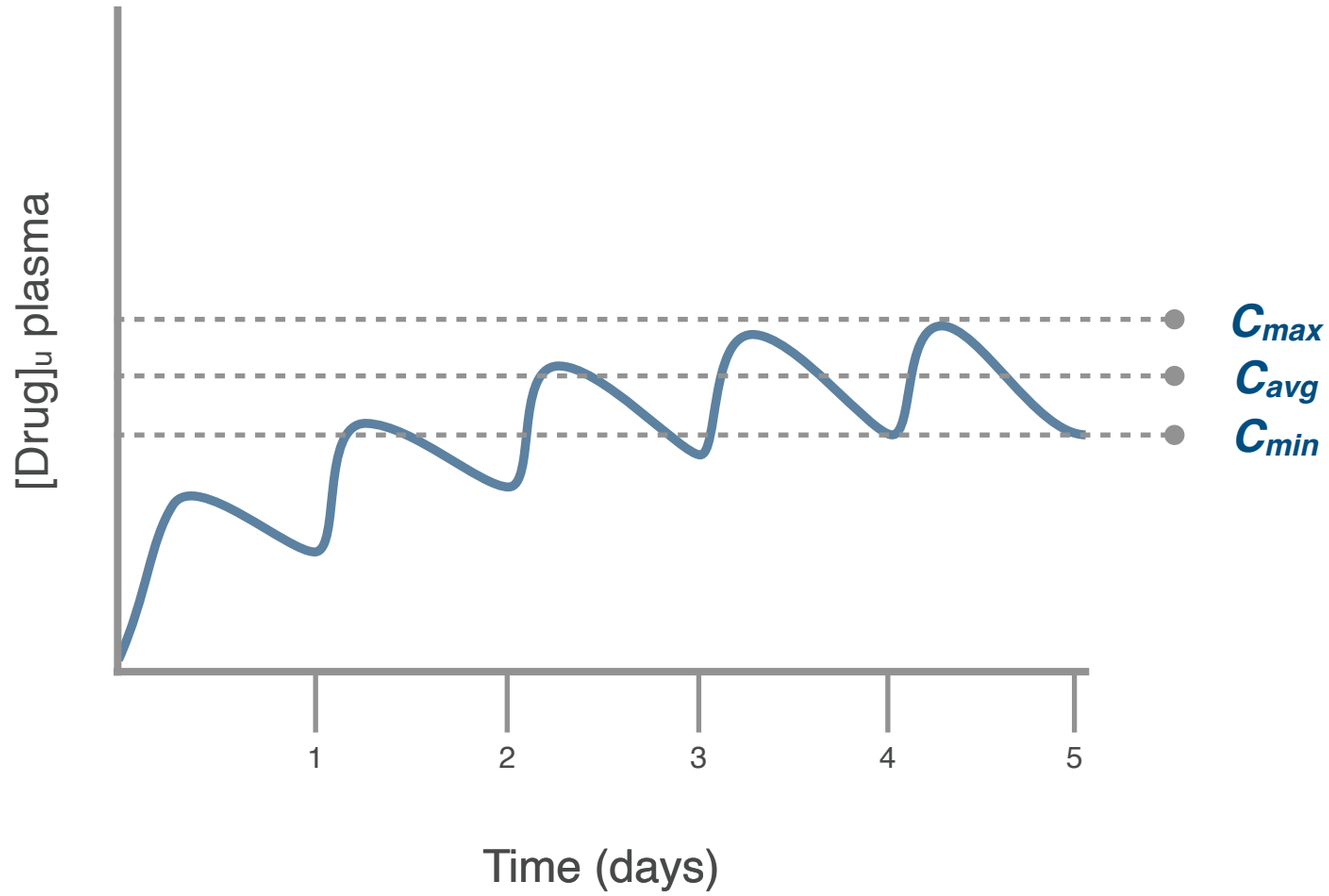
Moderate C_{max} / moderate C_{min}

drug is partially distributed

Half life controlled by clearance and V_{ss}

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life

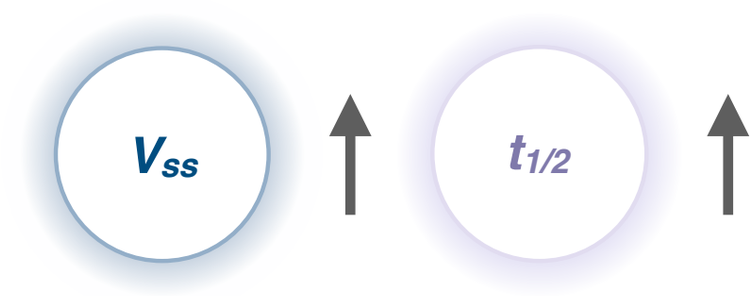


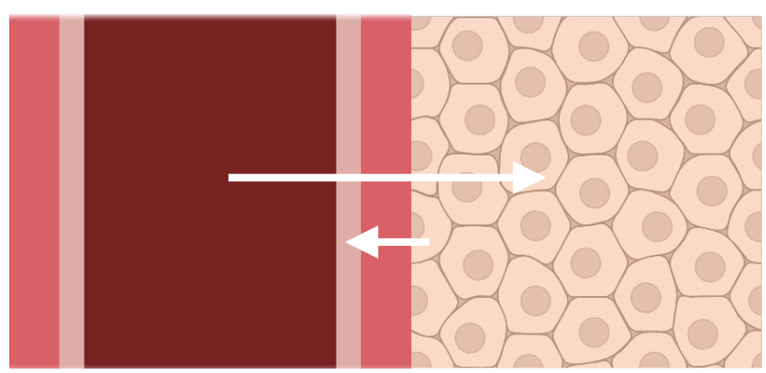
High volume of distribution

Low C_{max} / High C_{min}

drug is highly distributed

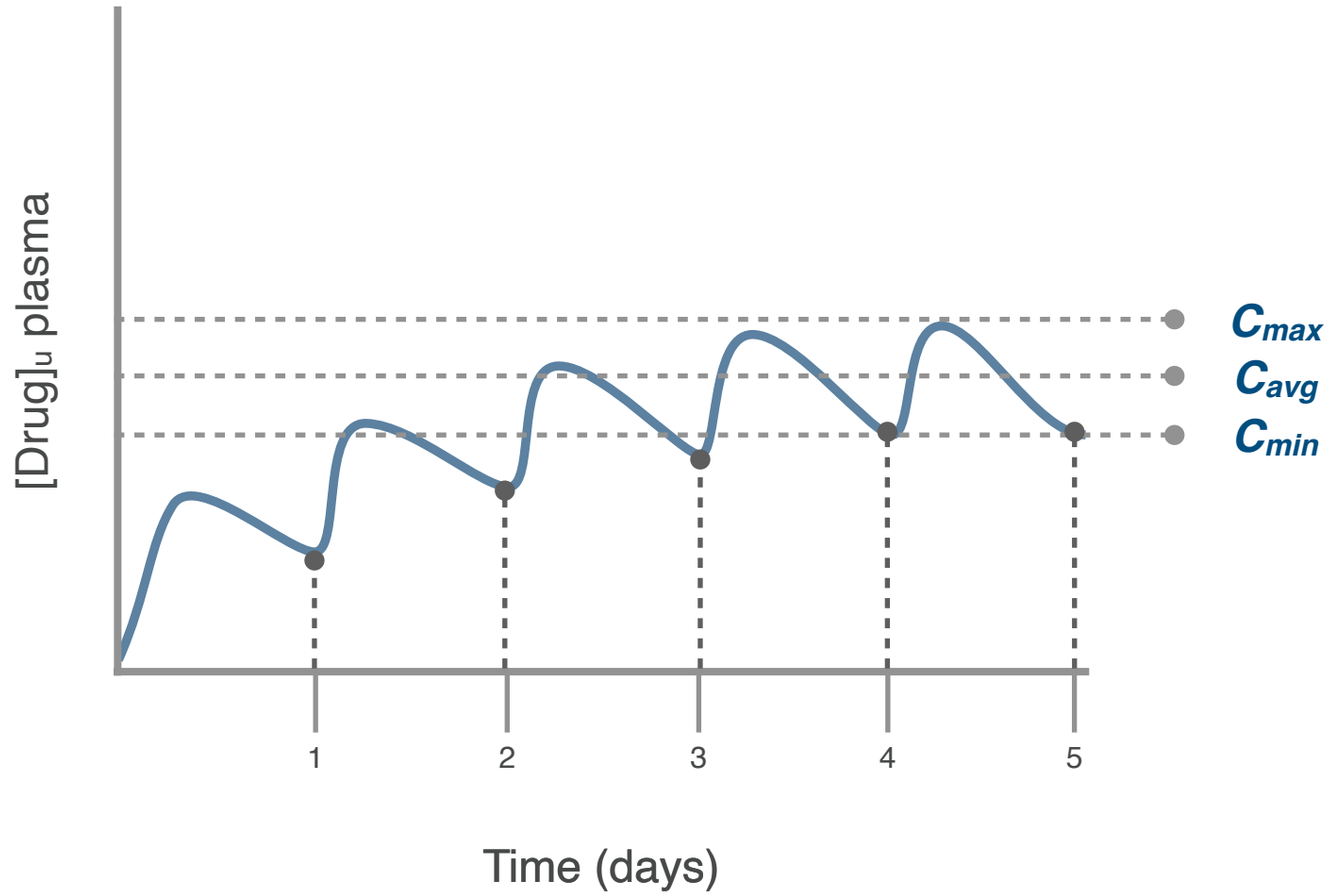
Half life controlled by clearance and V_{ss}





Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life

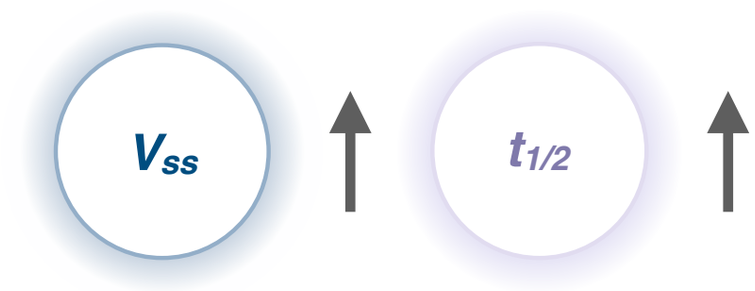


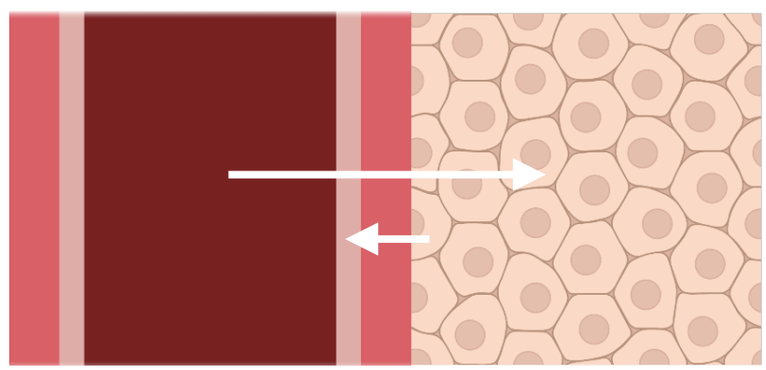
High volume of distribution

Low C_{max} / High C_{min}

drug is highly distributed

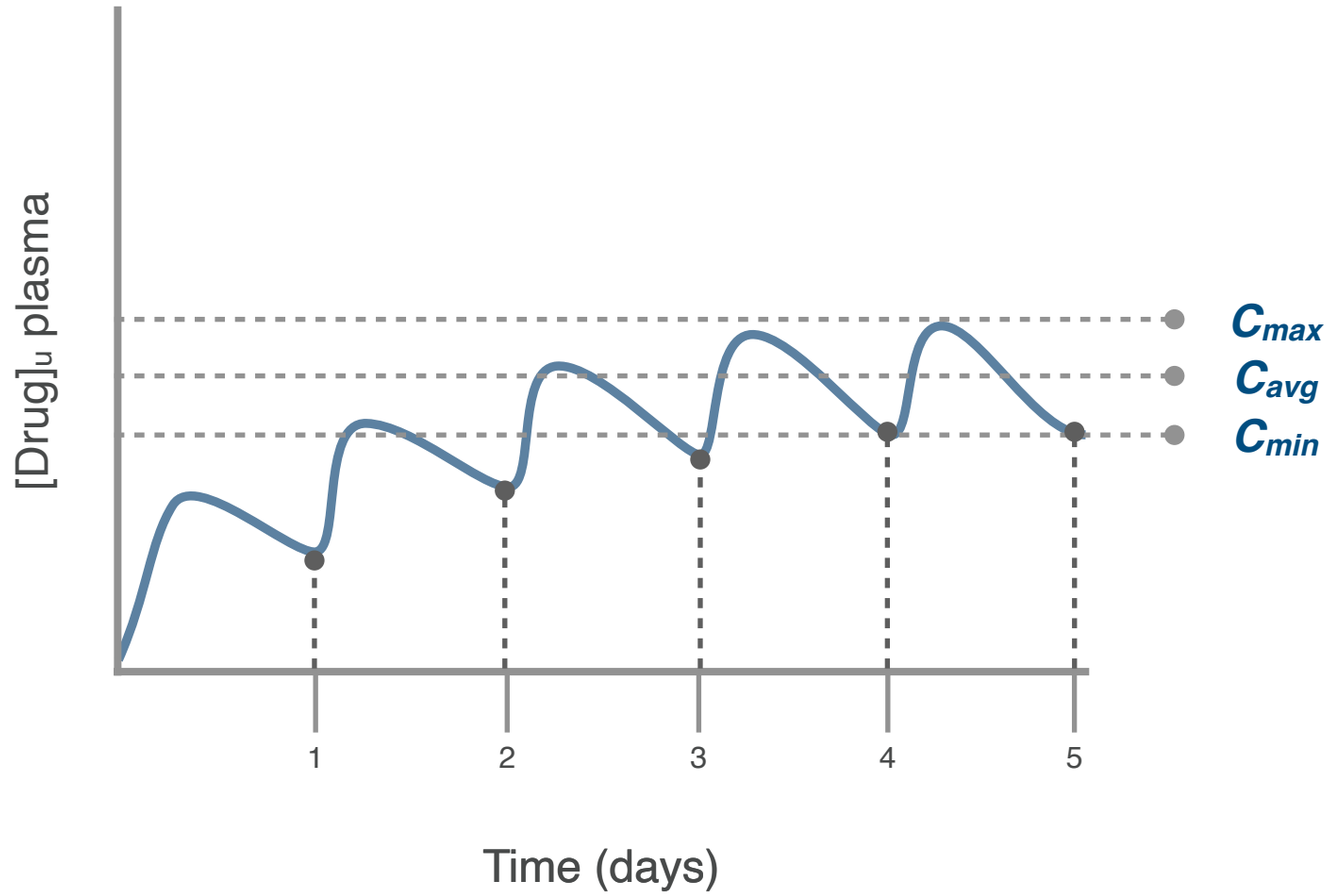
Half life controlled by clearance and V_{ss}





Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life



High volume of distribution

Low C_{max} / High C_{min}

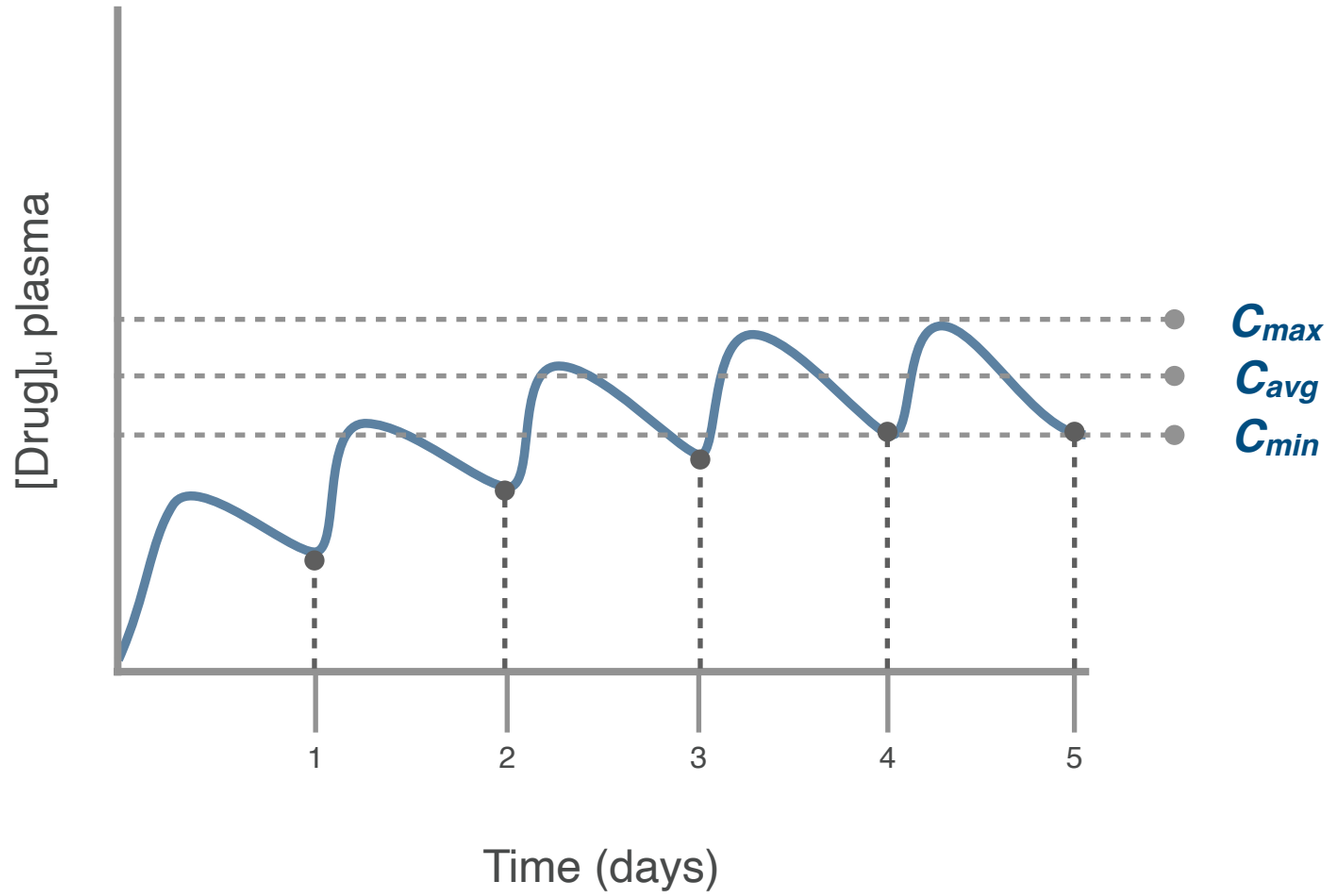
drug is highly distributed

Half life controlled by clearance and V_{ss}

Small Dose Required to achieve high C_{min}

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Volume of Distribution and half life



High volume of distribution

Low C_{max} / High C_{min}

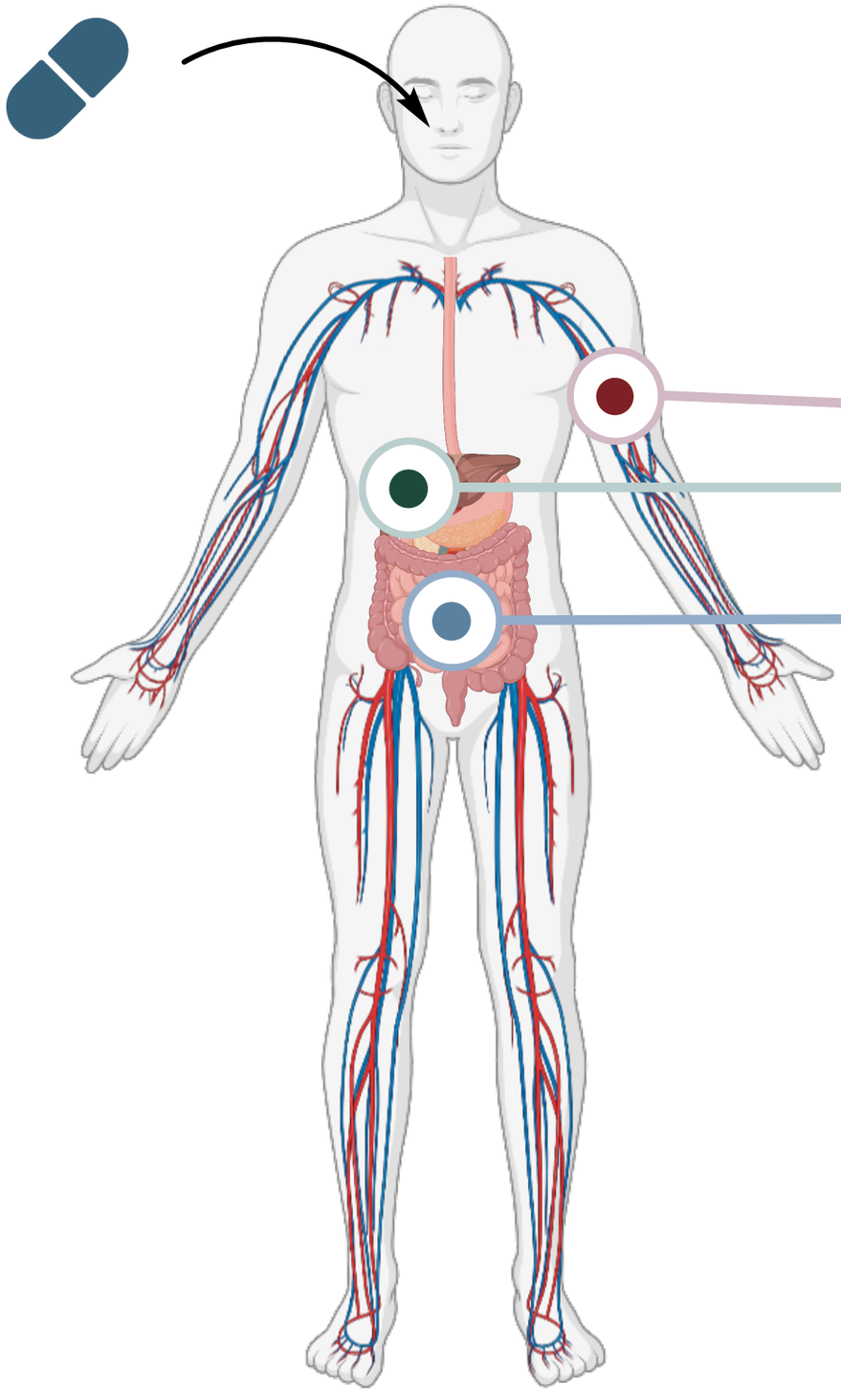
drug is highly distributed

Half life controlled by clearance and V_{ss}

$$Dose\ for\ C_{min} = \frac{C_{min} V_{ss} (k_a - k_{el})}{F * k_a} \left(\frac{1}{1 - e^{-k_{el}\tau}} - \frac{1}{1 - e^{-k_a \tau}} \right)^{-1}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

How much drug do you actually need?



$F\%$

Oral bioavailability:

Inversely proportional to dose

C_{eff}

Efficacious concentration of drug:

Directly proportional to dose

Cl_T

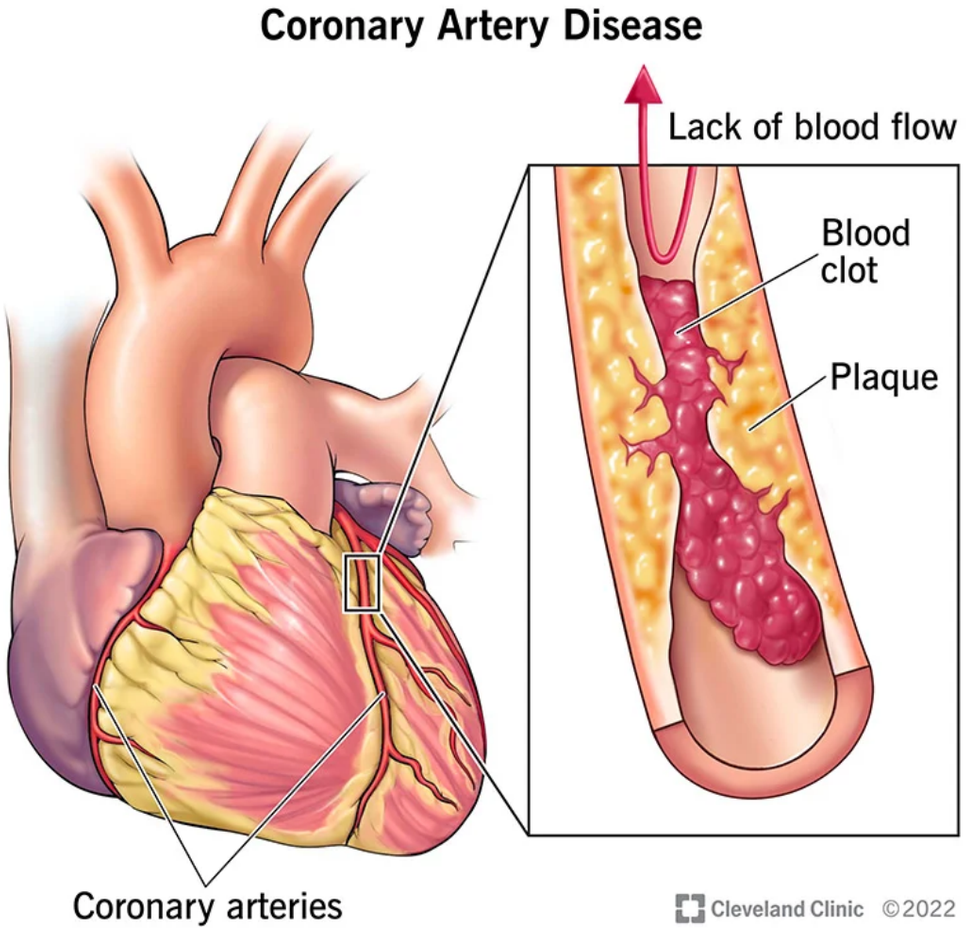
Total clearance:

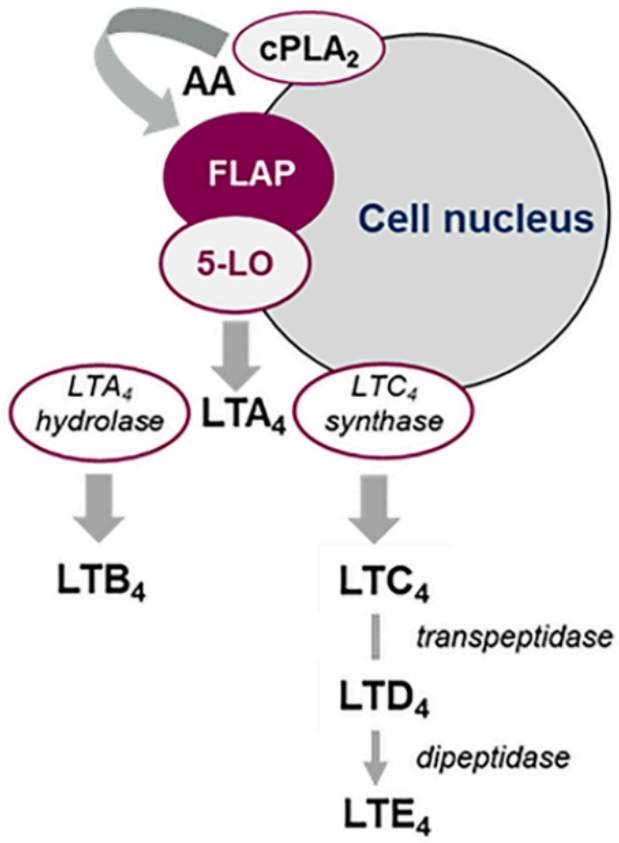
Directly proportional to dose

$$Dose \propto \frac{C_{eff} * Cl_T}{F\%}$$

Maurer et. al. *J. Med. Chem.* **2020**, *63,* 6423.*;* Smith, D. A. *J. Med. Chem.* **2018**, *61*, 4273; Smith, D. A. *J. Med. Chem.* **2015**, *58*, 5691

Case Study: AZD5718





Associated with chronic inflammation

Treatments: Lifestyle changes and blood thinners

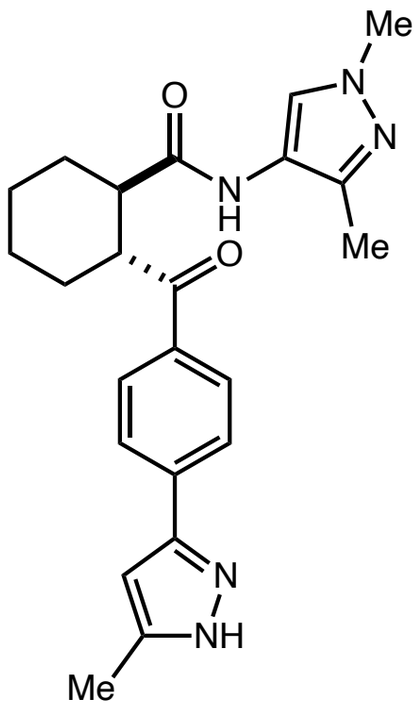
Therapeutic Hypothesis

Reduction of inflammatory leukotrienes

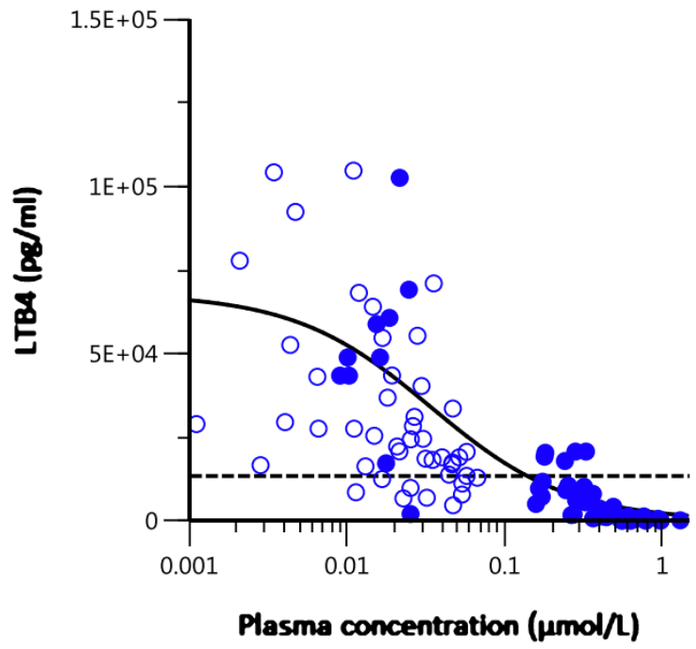
Via FLAP inhibition will reduce disease severity

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Case Study: AZD5718



FLAP IC_{50}	→	*7.4 nm*
$Cl_{int,human,hep}$	→	*4.0 ul/min/10^6 cells*
Mutagenic in Ames test?	→	*Negative*
Early predicted Human dose	→	***1900 mg***



Followup Goals:

Lower *predicted human* ***dose***

Improve ***safety margins***

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Case Study: AZD5718

C_{min}

3x coverage of IC_{50} at trough

Over 24 hour period

F%

Assume f_a, and f_g = 1

only E_h considered

Cl_{hep}

IVIVC scaling from

human hepatocytes

V_{ss}

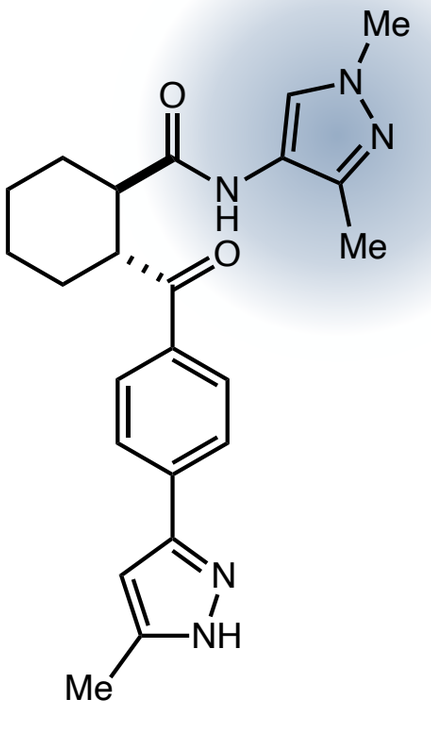
Single species

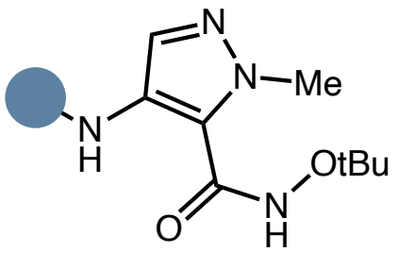
Scaling

$$\frac{C_{ss,min}[\mu mol/L] \cdot V_{ss,hum,pred}[L/kg] \cdot (1 - e^{-k_e \cdot \tau[h]}) \cdot (k_a - k_e) \cdot MW[g/mol] \cdot BW_{hum}[kg]}{k_a \cdot (e^{-k_e \cdot \tau[h]} - e^{-k_a \cdot \tau[h]}) \cdot F \cdot 1000}$$

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Case Study: AZD5718



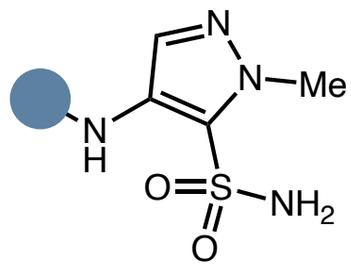


10

Predicted Human Dose

55 mg QD

Development halted due to **Cardiovascular Toxicity** in dogs

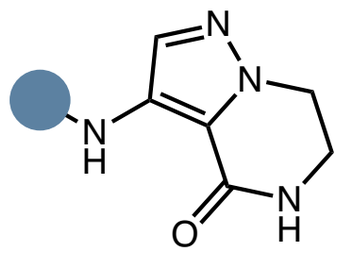


11

Predicted Human Dose

80 mg QD

Development halted for **off target toxicity** observed in dogs



12

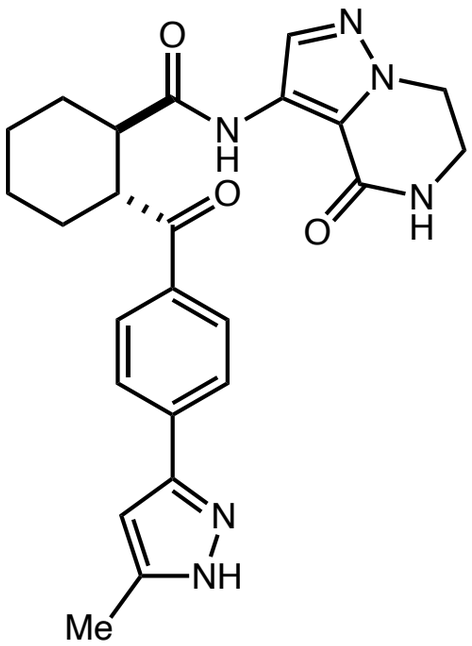
Predicted Human Dose

44 mg QD

No adverse effects Observed up to 110 x predicted human C_{max}

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Case Study: AZD5718



AZD5718

Phase II Clinical Trial:

Dose dependent inhibition

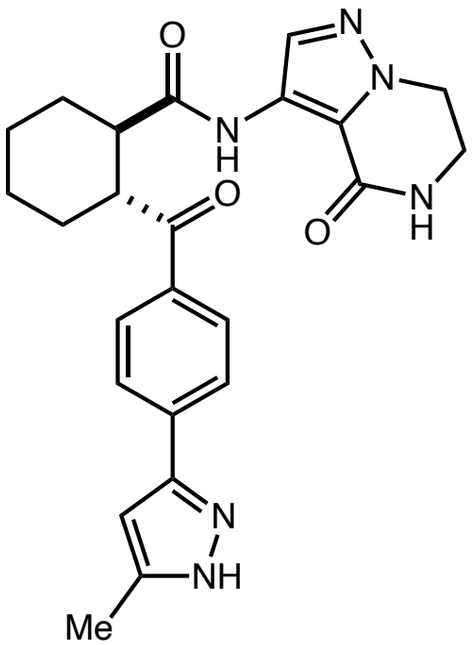
Of leukotrienes

No improvement in coronary

microvascular function observed

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Case Study: AZD5718



AZD5718

Good Failure

clearly demonstrate

pharmacological engagement

therapeutic hypothesis has

been tested with confidence

Petteson, D. et. al. *J. Med. Chem.* **2019**, *62*, 4312.*;* Ericsson, H. *Clin. Transl. Sci.* **2018**, *11*, 330

Questions?