Applications of PBPK Modeling in Preclinical Drug Development

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Goals

- Present examples of multiple ways that PBPK modeling can be used to address key issues for preclinical projects
- Describe how PBPK models can be used to generate hypotheses and prioritize additional experiments
- Provide a method for developing physiologically based oral absorption models and discuss the factors that might impact oral absorption for BCS Class 1, 2, 3 and 4 compounds
- Illustrate how PBPK/PD modeling can be used to assess the likelihood that a compound will be efficacious in the clinic and to characterize the therapeutic window
PBPK models have many applications in preclinical drug development because of the need to integrate data.
Outline

- PBPK models for generating hypotheses
- Oral absorption modeling
- PBPK modeling for candidate selection
- Predicting exposure window using PBPK/PD
PBPK modeling is an evolving process

- **New paradigm**: See if you can predict in preclinical species. If you cannot, perform appropriate experiments to fill the knowledge gap.

- Mechanistic knowledge and availability of key data determine the confidence you can have in model predictions.

Compare model to data to gain knowledge of mechanisms missing from model

Simulation

PBPK animal

model refinements

Confirmation

Simulation

PBPK human

Confirmation
Fundamental value of modeling

- Models allow you to integrate multiple sources of data and information with a mechanistic description based on your fundamental understanding of the system.

  - *If the model prediction is correct, it is useful.*
    - Instead of making predictions based on rat data, you can take it a step further. After testing your understanding of the system with rat, you can extend that knowledge to make predictions in man.

  - *If the model prediction is incorrect, it is also useful.*
    - The disconnect between the model and data suggests your understanding of the system is flawed.
    - The model can be used to rule out hypotheses that are inconsistent with the data and determine additional experimentation that is most likely to be informative.
Example: Lack of IVIVC from nonlinear CL

**Problem:** Modeling indicated lack of good IVIVC

**Experiments:**
- Rat and dog bile-duct cannulated studies to better understand clearance mechanisms: No significant biliary secretion
- Using lower concentration of drug (0.1 µM instead of 1 µM) for clearance measurement in vitro to prevent saturation of metabolic enzymes in hepatocyte or microsome to obtain accurate intrinsic clearance
Outcome: IVIVC achieved for the compound within 2-fold uncertainty using newly obtained microsome clearance. Proceeded with PBPK simulation in human.
Example: Impact of enterohepatic circulation (EHC) on PK

Courtesy of Dr. Werner Rubas
For this compound, CL is overpredicted and t1/2 is underpredicted by the in vitro model parameters.

Hypothesis: Enterohepatic circulation of parent

Estimation of fraction $EHC = (CL_{obs} - CL_{pred})/CL_{obs} = 0.25$

W. Rubas
Inclusion of predicted EHC (25%) improves simulation

Experiment using bile duct cannulated rats: Fraction EHC was determined to be 0.33.

W. Rubas
PK profiles are well simulated when enterohepatic circulation is included (33%)

- **IV 0.5 mg/kg**
- **PO 2 mg/kg**

Predicted AUC and t1/2 are within 10 % of observed

Cmin prediction is improved

W. Rubas
Outline

- PBPK models for generating hypotheses
- Oral absorption modeling
  - Validating the model
  - Using the model
- Compound prioritization based on early preclinical data
- Predicting exposure window using PBPK/PD
Recently, several powerful PBPK approaches have been developed to predict oral absorption.

*Example: ACAT model in GastroPlus*

The model can also include degradation of compound passing through the GI tract, the impact of transporters, and differences in permeability with region.

Species differences in regional pH, compartment volume, etc. are included in the model.

Other examples:
ADAM (advanced dissolution, absorption & metabolism) model (Jamei et al., in press), GI tract described as tube with spatially varying properties (Willman et al., 2003)
How can M&S increase efficacy and speed in drug discovery?

Data (in vitro/in vivo) → Validation model (few compounds) → Sensitivity analysis

Critical parameters
Which one to focus on first?
- Metabolic stability?
- Protein binding?
- Solubility?

Not critical → Stop experiment → Front load

Screening funnel → Multiple series → Clinical lead
PBPK modeling for oral absorption

PBPK modeling approaches for predicting human oral absorption can be used to simulate

- absorption as a function of time
- the amount absorbed from various regions of the GI tract
- plasma concentrations as a function of time

Approach:

- Develop a model in a preclinical species and check it against whatever data is available (e.g., po SDPK data)
- Determine how to improve the model based on mismatches between model and data; perform critical experiments to elucidate key mechanisms
- Develop the human model based on what was learned in the preclinical species
Applications of oral absorption modeling

- Predicting bioavailability
- Evaluate potential absorption and bioavailability for large number of compounds with very limited data
- Determine the sensitivity of bioavailability and PK to various input parameters
- Maximum absorbable dose
- Predicting whether a food effect is expected
- Determining an appropriate formulation strategy
An absorption model can be developed using permeability and solubility data

**Physicochemical properties**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early in development (LO)</th>
<th>Late in development (CLS, EIGLP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cLogP / Log D @ reference pH</td>
<td>In silico</td>
<td>Measured Log D-pH profile</td>
</tr>
<tr>
<td>pKa’s</td>
<td>In silico</td>
<td>Measured</td>
</tr>
<tr>
<td>Permeability (human Peff)</td>
<td>In silico</td>
<td>Cell-based permeability assay (e.g., MDCK, Caco-2) or PAMPA</td>
</tr>
<tr>
<td></td>
<td>Optional: cell-based permeability assay (e.g., MDCK, Caco-2) or PAMPA</td>
<td></td>
</tr>
<tr>
<td>Solubility @ reference pH</td>
<td>Aqueous; HT Fessif/Fassif for low solubility compounds (e.g., &lt; 20 ug/ml aqu. sol.)</td>
<td>pH-solubility profile, including Fessif/Fassif</td>
</tr>
<tr>
<td>Solubility factor</td>
<td>In silico</td>
<td>Based on solubility data for range of pH’s</td>
</tr>
</tbody>
</table>
Outline

- PBPK models for generating hypotheses
- Oral absorption modeling
  - Validating the model
  - Using the model
- PBPK modeling for candidate selection
- Predicting exposure window using PBPK/PD
To check your absorption model

Simulation results can be compared to:

1. Bioavailability for a single experiment
2. Bioavailability as a function of dose
3. Fraction absorbed into the portal vein
4. Plasma time-course concentrations (requires a PK study)

Before using absorption modeling to make decisions, it is good practice to check the model results against PK data at multiple doses and in one or more species if possible.
Using absorption modeling to predict bioavailability

\[ F = F_{\text{abs}} \times F_{\text{h}} \times F_{\text{g}} \times \ldots \]

- \( F_{\text{abs}} \) is the fraction that is absorbed into enterocytes
- \( F_{\text{h}} \) is the fraction that makes it through the liver
- \( F_{\text{g}} \) is the fraction that makes it through the enterocytes without being metabolized

- There could be additional sources of loss (e.g., metabolism by microflora in the gut, instability in the stomach, etc.).
- Absorption modeling provides a prediction of fraction absorbed, but to predict in vivo bioavailability, first-pass processes must also be incorporated.
Definition of Bioavailability (F)

- Bioavailability (F) is the fraction (or percent) of administered dose that reaches systemic circulation intact.
- Bioavailability is typically calculated by comparing AUC from iv PK data to AUC from po PK data.
- Often bioavailability is < 1 because loss can occur from factors like:
  - incomplete absorption (e.g., from low permeability or solubility)
  - first pass extraction by the gut and liver
  - chemical degradation in the lumen
- Sometimes estimated F is > 1 than because of factors such as:
  - saturable metabolism
  - enterohepatic circulation
  - incomplete administration of iv dose

\[
F = \frac{AUC_{po}}{D_{po}} / \frac{AUC_{iv}}{D_{iv}}
\]
Comparing $F_{abs}$ to Bioavailability

- One mechanism that often has a large impact on bioavailability is first-pass hepatic extraction.
- At a minimum, the effect of first-pass extraction ($E_h$) should be combined with $F_{abs}$ for estimating bioavailability. (Assume $F_g=1$ if no phenotype data are available.)

$$F = F_h \times F_{abs}$$

$F_h = \text{fraction that makes it past the liver, } 1 - E_h$

$F_{abs} = \text{fraction absorbed}$

- When can $F_{abs}$ be compared directly to bioavailability?
  - For compounds that are cleared by mechanisms other than hepatic metabolism or biliary excretion
  - For low-clearance compounds (CL < 0.1 x QL)
Methods for calculating $F_h$

- $F_h$ can be calculated as: $F_h = 1 - E_h = 1 - \text{CL} / \text{QL}$
- $E_h$ can be calculated from hepatocyte or microsome in vitro data
- $E_h$ can also be estimated using CL from an iv SDPK study (CL / QL)
  - Caution: Is the mechanism of CL hepatic metabolism?
- Which method to use? Do scaled hepatocyte or microsome data:
  - predict IV CL? Either method can be used.
  - underpredict IV CL? Metabolism is probably not the only mechanism of CL, and so scaled hepatocyte or microsome data should be used.
  - overpredict IV CL? Most CL is probably from metabolism, and the IV CL can be used as the more accurate CL estimate.

$\text{CL} = \text{CLplasma} / \text{BPR}$ where BPR = blood to plasma ratio

In some cases (e.g., high extraction compounds that do not partition into red blood cells) it is critical to have BPR data for interpretation of PO PK data!
## Checking model prediction of bioavailability

Selected drug properties and F from rat SDPK data with Fabs from GastroPlus and Fh from an appropriate method.

<table>
<thead>
<tr>
<th></th>
<th>Solubility, µg/ml (^a)</th>
<th>Caco2 (P_{\text{eff}}), cm/sx10(^{-6})</th>
<th>ER</th>
<th>F</th>
<th>(F_{\text{abs}})</th>
<th>(F_{\text{h}})</th>
<th>(F_{\text{abs}} \times F_{\text{h}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>145 (Aq)</td>
<td>13.2</td>
<td>1.2</td>
<td>0.26</td>
<td>0.96</td>
<td>0.23</td>
<td>0.22</td>
</tr>
<tr>
<td>Compound 2</td>
<td>21.2 (Aq)</td>
<td>16.3</td>
<td>1.1</td>
<td>0.34</td>
<td>0.55</td>
<td>0.34</td>
<td>0.19</td>
</tr>
<tr>
<td>Compound 3</td>
<td>2 (Aq)</td>
<td>15.3</td>
<td>0.77</td>
<td>0.46</td>
<td>0.079</td>
<td>0.31</td>
<td>0.024</td>
</tr>
<tr>
<td>Compound 3</td>
<td>38.7 (Fa)</td>
<td>15.3</td>
<td>0.77</td>
<td>0.46</td>
<td>0.78</td>
<td>0.31</td>
<td>0.24</td>
</tr>
<tr>
<td>Compound 4</td>
<td>6.1 (Aq)</td>
<td>1.52</td>
<td>8.4</td>
<td>0.38</td>
<td>0.077</td>
<td>0.37</td>
<td>0.029</td>
</tr>
<tr>
<td>Compound 4</td>
<td>32.9 (Fa)</td>
<td>1.52</td>
<td>8.4</td>
<td>0.38</td>
<td>0.35</td>
<td>0.37</td>
<td>0.13</td>
</tr>
<tr>
<td>Compound 4</td>
<td>32.9 (Fa)</td>
<td>13.2 (w/ elac.(^b))</td>
<td>0.87</td>
<td>0.38</td>
<td>0.62</td>
<td>0.37</td>
<td>0.23</td>
</tr>
</tbody>
</table>

\(^a\) Aq = aqueous solubility at pH=6.5. Fa = FaSSIF solubility at pH=6.5.  
\(^b\) Elacridar is a P-gp inhibitor.
Checking bioavailability prediction for a range of doses

Multiple mechanisms affect exposure as a function of dose. However, in terms of $F_{\text{abs}}$, one would generally expect the following:

- BCS Class 2 and 4 may exhibit dose-proportional or less-than-dose-proportional increases in AUC and Cmax as the dose increases.
  - If the model predicts that dose-limited absorption occurs (i.e., simulated $F_{\text{abs}}$ decreases with increasing dose), there should be a less-than-dose-proportional increases in AUC and Cmax as the dose increases in po SDPK studies.
- BCS Class 1 and 3 may exhibit dose-proportional or greater-than-dose-proportional increases in AUC and Cmax as the dose increases in po SDPK studies.
Checking fraction absorbed into the portal vein *

- The Fabs into the portal vein will not reflect the effects of first-pass hepatic metabolism (although other first-pass processes, such as metabolism by enterocytes, might still have an impact).
- Therefore, Fabs into the portal vein can be used more easily to check the model prediction of Fabs.

* Useful for compounds with high hepatic extraction!
Calculation: Amount Absorbed

The amount absorbed as a function of time can be calculated from the concentrations in the portal and peripheral vein.

\[
\frac{d\,A_{abs}}{dt} = Q_{pv} \times (C_{pv} - C_{p}) \times BPR
\]

- **A_{abs}** = amount absorbed
- **t** = time
- **Q_{pv}** = portal vein blood flow rate (~85% of liver blood flow)
- **C_{pv}** = plasma concentration in portal vein
- **C_{p}** = plasma concentration in peripheral vein
- **BPR** = blood-to-plasma ratio
Checking the model against plasma time-course concentrations

Rat, 2 mg/kg

Rat, 20 mg/kg

Monkey, 2 mg/kg

Monkey, 20 mg/kg
Approach: Reduce confounding factors by using a compartment model for systemic PK.

- For rat PO PK, first use a compartment model to simulate iv PK to remove one source of uncertainty and check the absorption prediction.
  
  - Assumption: linear kinetics
  - First-pass Eh will need to be calculated and included
  - After checking absorption model, redo calculation to check the PO PK profile using the PBPK model.

![Graph showing iv PK profile](image1.png)  
**0.5 mg/kg iv PK**

![Graph showing po PK profile](image2.png)  
**Change to po exposure, parameterize oral absorption model**

![Graph showing po PK profile](image3.png)  
**2 mg/kg po PK**

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Roche Pharmaceuticals
Next, switch to the PBPK model for systemic PK to verify that the model is still predictive.

- After checking the absorption model, redo the calculation to check the PO PK profile using the PBPK model.

![Graph showing PBPK model for systemic PK](image)

- Change to po exposure, parameterize oral absorption model.

![Graphs showing 0.5 mg/kg iv PK and 2 mg/kg po PK](images)
What do you do if the model does not match the data?

Several avenues of exploration

- **User error**
  - Double check input, paying close attention to units
  - Are solubility, permeability, and compound properties entered correctly?

- **Inappropriate input for BCS Class 2, 3 or 4**
  - BCS Class 2, 4: need appropriate solubility data
  - BCS Class 3, 4: carefully consider best way to estimate $P_{eff}$

- **Important mechanism impacting absorption or PK not yet identified (e.g., metabolism by gut, nonlinear metabolism)**
  - Need to design appropriate experiments
Absorption models for BCS Class 1 compounds tend to be reliable, but issues can still arise.

Example: Dissolution data was necessary to simulate absorption of diltiazem (BCS Class I)

- The initial model overpredicted Cmax and underpredicted tmax. Dissolution data was required to simulate absorption.
- Input: Dissolution data, solubility = 3000 µg/ml @pH = 6.4, PAMPA Peff = $1.9 \times 10^{-6}$ cm/s, hepatic extraction = 54%
For human simulation, dissolution data and first-pass extraction by the gut had to be incorporated.

One way to determine the impact of first pass extraction by the gut is to do a grapefruit juice (GFJ) study because it inhibits CYP3A4 in the gut (Yang et al. 2007). $F_g < 1$ for many CYP3A4 substrates, e.g., midazolam ($F_g = 0.57$), felodipine ($F_g = 0.58$), and saquinavir ($F_g = 0.67$).

* Most PBPK software packages include CYP expression in the gut and can predict $F_g$ if reaction phenotyping data is available.
Considerations for dissolution data

- Dissolution data might improve your prediction, depending on how the study is designed and whether dissolution is rate limiting.

- Considerations for study design:
  - Sink conditions
  - Physiologically relevant media (FeSSIF, FaSSIF, FeSGF, FaSGF)
  - Two-stage design (e.g., pH 1 and then pH 6)

Key plot for diagnosing whether dissolution might be rate-limiting

![Plot showing dissolution and absorption over time with BCS Class II compound and Piroxicam examples.](image)
BCS Class 2
Low solubility, high permeability

- For BCS Class 2 solubility is a very sensitive model parameter, and appropriate (i.e., physiologically relevant) solubility data is critical.
- FeSSIF and FaSSIF solubility data have been shown to dramatically improve the predictive accuracy of the absorption model for low-solubility compounds.
- If the dosing solution contains solubility enhancers, solubility data with solubility enhancers might also be appropriate.
- Different batches of drug can have very different solubilities. A mismatch between Fabs in a po SDPK study and the model prediction of Fabs could be because the compound administered to the animals and the compound used to determine the solubility were from different batches.
- Efflux transporters might be an issue.
Verify that sufficient data are available to set solubility

If a compound has a physiologically relevant pKa, carefully consider if solubility data have been generated for a sufficient range of pH values.
Early stage prediction of bioavailability in rats for BCS Class 2 compounds

Used to verify understanding of factors impacting series %F

Compounds:
- CLogP, pKa from ADMET Predictor;
- Dose form: IR suspension;
- Solubility: phosphate (if >20 ug/mL) and FaSSIF
- Particle density 1.2 g/mL
- Particle size 25 µm
- Peff from Caco2 AB

Physiology: Rat (fasted), Opt LogD Model
Simulation: 24h
First-pass extraction: In vivo IV clearance

12 within 2-fold
2 over-predicted
2 under-predicted
BCS Class 3
Low permeability, high solubility

- For BCS Class 3, the effect of transporters may have a large, and not easily predicted, impact on PK.
  - At low doses, the impact of transporters will be largest.
  - At high doses, transporters could saturate.
  - Solution: include saturable transport into the model.

- For estimating Peff for Pgp substrates, Caco2 (A>B) data with elacridar is likely more predictive. But for lower solubility or permeability compounds, Caco2 (A>B) data without elacridar could be more predictive. Looking at the Fabs calculation using both Peff values could provide a reasonable range of values.

- In the intestines (duodenum, proximal jejunum scrapings), CYP3A4 was the most abundant P450 (80% of intestinal P450), followed by CYP2C9 (15%) (Paine et al. 2006). Gut metabolism may be most important for low permeability CYP3A4 substrates (Yang et al. 2007).
The gut expresses many efflux and uptake transporters. Expression levels can vary depending on location in GI tract.

Figure from:
Early stage prediction of bioavailability in rats for BCS Class 3 compounds

Used to verify understanding of factors impacting series %F

Data: In silico cLogP, pKa; Caco2 Peff with no inhibitor, THESA solubility, Eh calculated using Mx data

5 over-predicted
8 within 2-fold

Courtesy of S. Larrabee
BCS Class 4
Low solubility, low permeability

- For BCS Class 4, the issues that occur with BCS Class 2 and 3 might both occur.
- For BCS Class 4, it might be important to do more checking than for the other BCS classes, and to be more careful with interpretation of results, particularly if transporters are involved.
- Absorption modeling can still be useful, but results should be carefully interpreted. The key is to interpret more qualitatively than quantitatively unless you have validated the model appropriately.
Outline

- PBPK models for generating hypotheses
- Oral absorption modeling
  - Validating the model
  - Using the model
- PBPK modeling for candidate selection
- Predicting exposure window using PBPK/PD
Examples from the literature

- Peters (2008): Assess any “lineshape” mismatch between simulated and observed oral profiles to gain mechanistic insights into processes impacting absorption and PK
  - for example, drug-induced delays in gastric emptying and regional variation in gut absorption.

- Jones et al. (2006): GastroPlus human oral absorption models were established for six compounds. Food effects were predicted for a range of doses and compared to the results from human food effect studies.
  - In general, the models were able to predict whether a food effect would be major (i.e., for two compounds) or minor (i.e., for four compounds).
Example: Is a CR formulation feasible?

- CR formulation development is expensive, but can be necessary for a compound with a short t1/2 in humans.
- Extensive PK experimentation is typically performed to determine whether a CR formulation is feasible (i.e., whether the compound can be absorbed in the colon) before resources are spent on the effort.
  - Surgically modified animals with cannulas for administering compound to various parts of the GI tract
  - Cross-over IV and PO PK studies for deconvolution to determine the amount absorbed as a function of time
  - Enterion™ capsule, Pharmaceutical Profiles
- Modeling can help to focus and reduce the experimentation.
**Site-of-absorption study**
Example: Furosemide (BCS Class 4)

Based on the po PK profiles alone, it is not clear where absorption occurs.

Simulations performed with GastroPlus demo database.
Deconvolution of po PK data (an empirical approach) can also be useful for understanding absorption.

- If iv and po PK data are available, numerical deconvolution can be used to estimate the fraction of drug absorbed as a function of time.
  - The results are sometimes noisy and difficult to interpret.
  - Better results are obtained with a cross-over design so that iv and po data are available in the same animal.
- This analysis will not necessarily result in clear information on where drug is absorbed (i.e., results may be difficult to interpret).
- For compounds that are well absorbed in the small intestines, the po data will have no information on the rate of absorption from the colon.
Example: Ketoprofen (BCS Class 1)

Simulation for humans administered a 50 mg dose of ketoprofen:

Most ketoprofen absorption occurs in the duodenum and jejunum. The po PK data contains no information on rate of absorption from the large intestines.

- Simulations can provide useful information about whether deconvolution of po PK data will yield useful information.

Simulation performed with GastroPlus demo database.
Example: Should a CR formulation be developed for a compound with a short t1/2?

For this compound, Caco2 Peff data had been measured and exhibited 10-fold variability.

Simulations indicate that the intracolonic route in humans may result in 31-46% of the PO AUC. ➜ Sensitivity analysis shows that Peff is critical for making the prediction.
Model refinement with new data suggests that CR development would be very challenging.

- Peff was a sensitive model parameter.
- Additional experimentation revealed that the compound had permeability in the low end of the range.
  - Refined simulations indicated that the IC route in humans would likely result in 31% of the PO AUC or less.
- In a recent PharmaProfiles poster by Connor et al. (2008), CR development is classified as very challenging for compounds with a relative bioavailability of < 30% upon administration to the colon.
- Based on this assessment, CR development would likely be very challenging.
Outline

- PBPK models for generating hypotheses
- Oral absorption modeling
- PBPK modeling for a parent compound and metabolite
- PBPK modeling for candidate selection
- Predicting exposure window using PBPK/PD
PBPK For Candidate Selection

**Aim**: to use physiologically based simulation tools to combine the available PK and PD data and assist in selection of the optimal clinical candidate

**Steps taken**:  
- **Verification**: compare simulated and observed PK in rat  
- **Predict PK**: estimate human PK  
- **Predict PD**: effective concentrations in human  
- **Estimation**: clinical doses and exposures

**Outcome**:  
- Balanced comparison of PK/PD incorporating variability and uncertainty to be weighed with other factors (early tox, synthetic tractability, formulation ease etc...)

N. Parrott
Available data for 5 compounds

- Physicochemical
- In vitro hepatocytes rat & man
- Protein binding rat & man
- In vivo PK i.v. and p.o. in rat
- Effect versus concentration in rat

N. Parrott
Simulated \textbf{Cmax} in human for a dose of 25mg including variability in both CL and V based upon in vitro and in vivo data

Mean with 95% limits shown

N. Parrott
Effective concentration in human estimated from rat PD data rat and in vitro data in both species (Fu% rat & human, Ki rat & human)

Variability is based on the observed variability in the rat

N. Parrott
Multiple Discovery Data

- Integrates multiple PK and PD data
- Aids rational and balanced decision
- Focuses on expected human PK/PD

Prediction in Human

Simulation

CL Rat (ml/min/kg)

Concentration

Conc. for 90% effect in human (ng/mL)

Daily dose [mg]

N. Parrott
Outline

- PBPK models for generating hypotheses
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**Hypothetical example**

Predicting therapeutic window for drug with safety issue and nonlinear PK

- A BCS Class II compound has dose-limited absorption.
- Efficacy for the compound is related to percent inhibition, which can be described using a simple Emax model with EC50 = 40 ng/ml.
- The compound has an off-target effect, and the PD for this effect also can be described using a simple Emax model with EC50 = 2000 ng/ml.
- A simple modeling approach can be used to understand whether efficacy can be achieved while avoiding the PD that is a safety concern.
Even at low doses, dose-limited absorption is expected to occur.

![Graph showing time (h) vs. Cp (ug/ml) for different doses of 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. The graph indicates that Fabs varies from 31% to 62% across different doses.](image)
Dose-limited absorption might make it difficult to achieve efficacious Cp

- For efficacy, a minimum of 50% inhibition is required.

![Graph showing efficacy over time for different doses](image-url)
At a 100 mg dose, the safety PD would likely be detectable.

- The safety effect cannot be determined as different from the baseline for < 5% response, and so doses up to 60 mg might be acceptable.
Despite a relatively low peak-to-trough ratio, the drug does not have a therapeutic window.
Summary

- PBPK modeling can be useful for multiple applications throughout the preclinical development process.
  - Generating hypotheses and prioritizing experimentation
  - Verifying that processes impacting absorption are understood
  - Selecting the most efficacious compound to move forward
- The key is to use the model appropriately for the amount of validation that was possible.
- PBPK modeling can be used to integrate multiple forms of preclinical data and to make a prediction of human PK/PD for both efficacy and safety end points.
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References

References