Clinical Pharmacology 2: Clinical Pharmacology Considerations During Phase 2 and Phase 3 of Drug Development

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Objectives

- Describe information needed to interpret clinical significance of factors that alter drug exposure
- Discuss the need to evaluate specific populations
- Discuss Phase 2 and Phase 3 drug development decisions that are affected by drug interaction information
- Understand the impact of complete and incomplete clinical pharmacology programs on information available to health care providers

Outline

- The goals of a clinical pharmacology program throughout drug development
- The value of exposure-response information
  - specific situations when the information is valuable
- Barriers to informative exposure-response evaluation
- Case studies (drug interactions)
- Conclusions- relevance and impact

The Ultimate Goal

RIGHT DRUG

RIGH PATIE

GOAL

RIGHT

RIGHT TIME

Phases 2 & 3 of Drug Development

Phase 2 studies

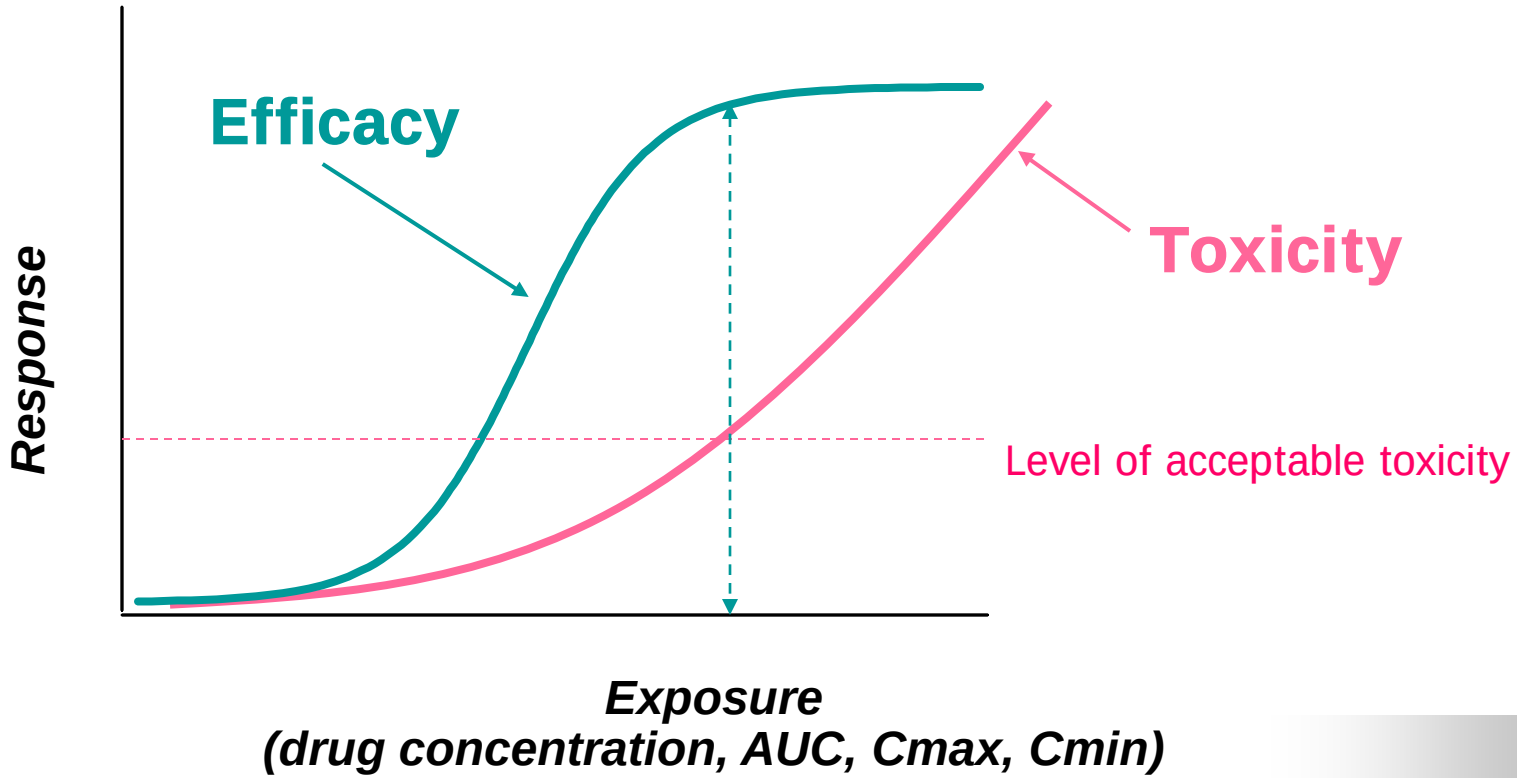
- provide preliminary data on the effectiveness of the drug
- allow selection of appropriate dose range for evaluation in Phase 3

Phase 3 studies

- provide pivotal information about effectiveness and safety
- allow evaluation of the overall benefit-risk relationship of the drug

Exposure-response relationship

- **Determine relationships for safety and efficacy in phase 2 and phase 3**



The value of exposure-response information

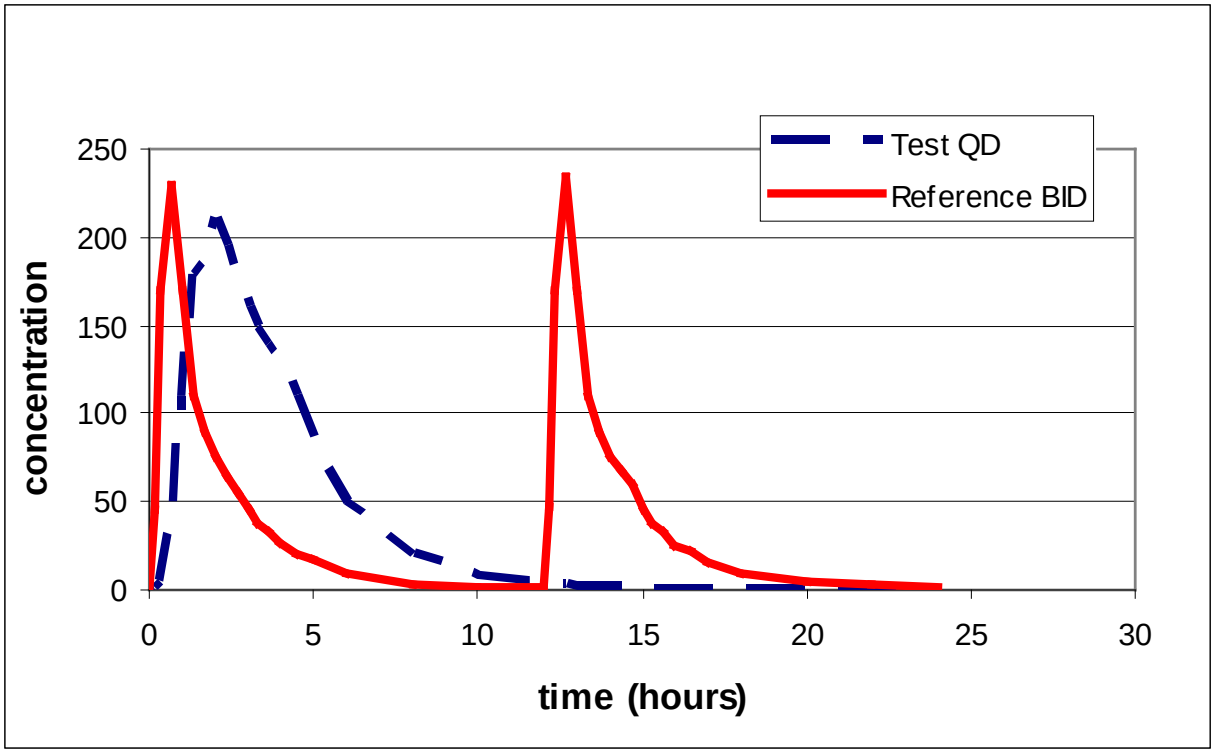
Add to weight of evidence supporting efficacy and safety

- **Allow better understanding of clinical trial data**
- **Explain results based on concentration data and knowledge of exposure-response relationship**
  - **Resolve safety concerns**
  - **Understand or support evidence of subgroup differences**

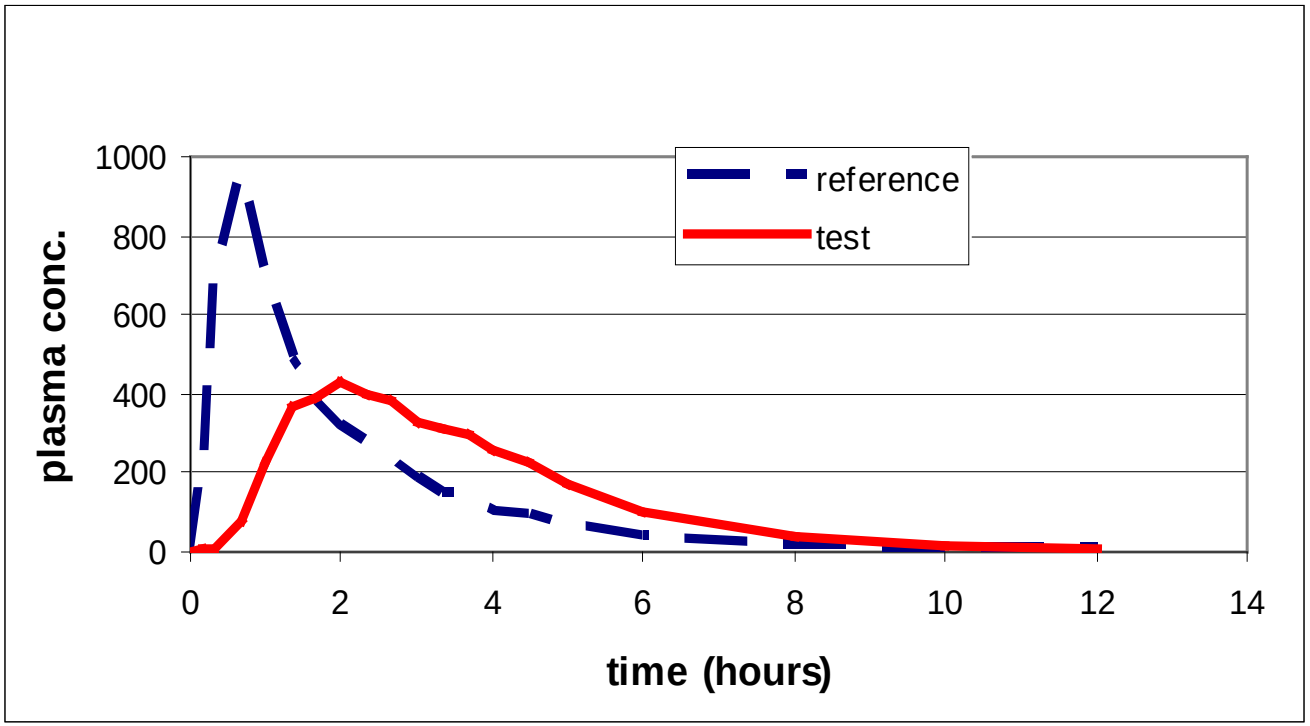
New drug administration scenarios

- New dosing regimen (e.g., BID to QD)
- New dosage form or formulation
- New route of administration

New Dosing Regimen



New Formulations

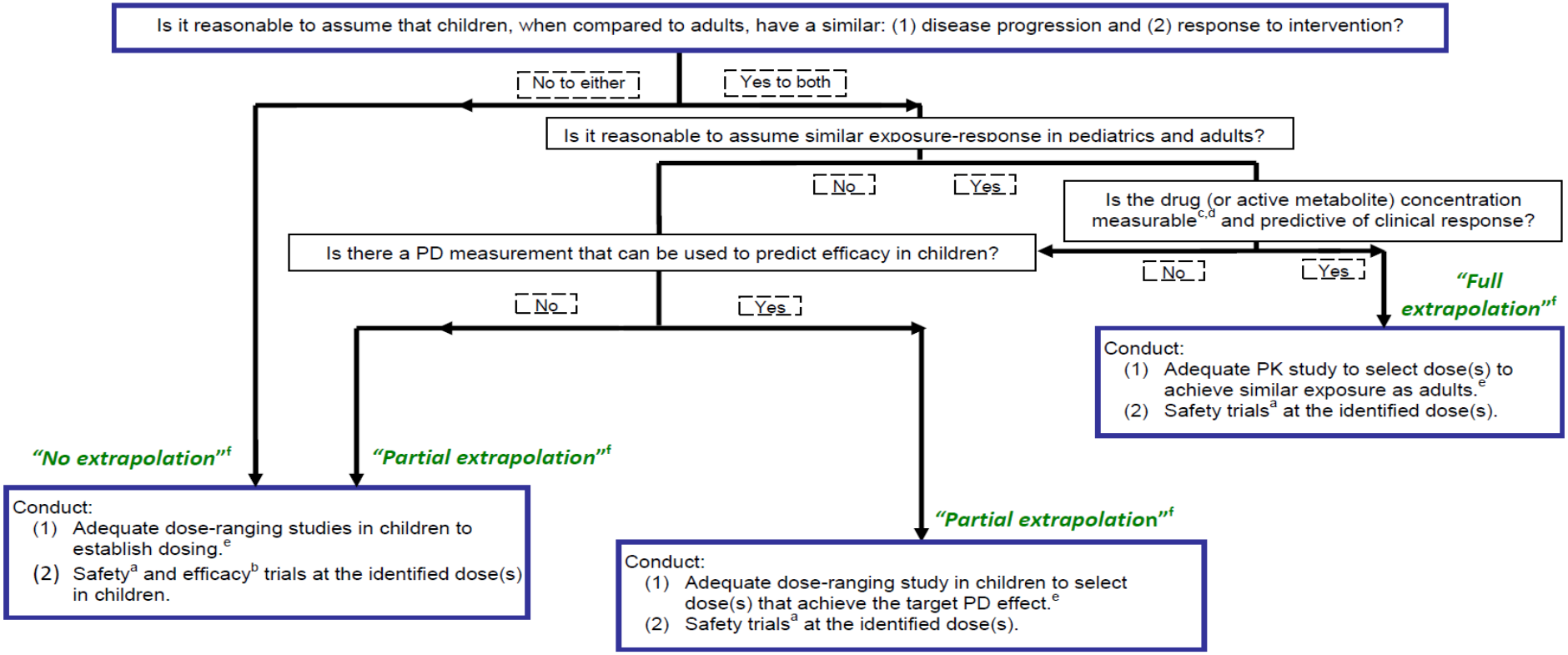


New Populations or Specific Populations

EXAMPLES-

- **Age groups**
  - **Elderly**
  - **Pediatric (decision tree)**
- **Renal or Hepatic Impairment**
  - **consider phase 1 results**
  - **can collect exposure data in Phases 2 and 3**
- **Women**

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

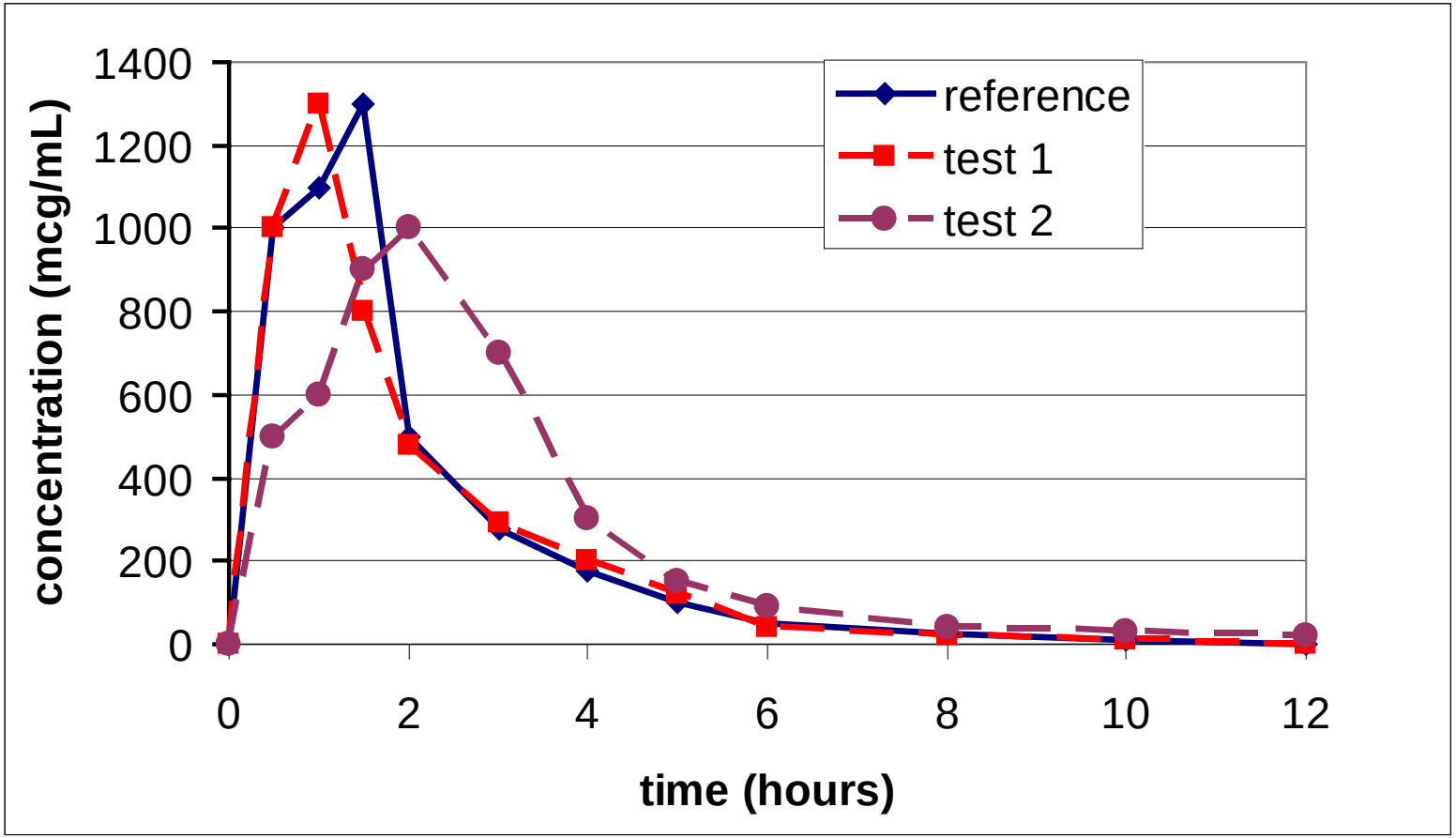
a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

Bioequivalence (BE) Studies

- **(Pivotal BE) Formulation change after phase 3 studies are complete**
- **Alter formulation of active control (blinding)**

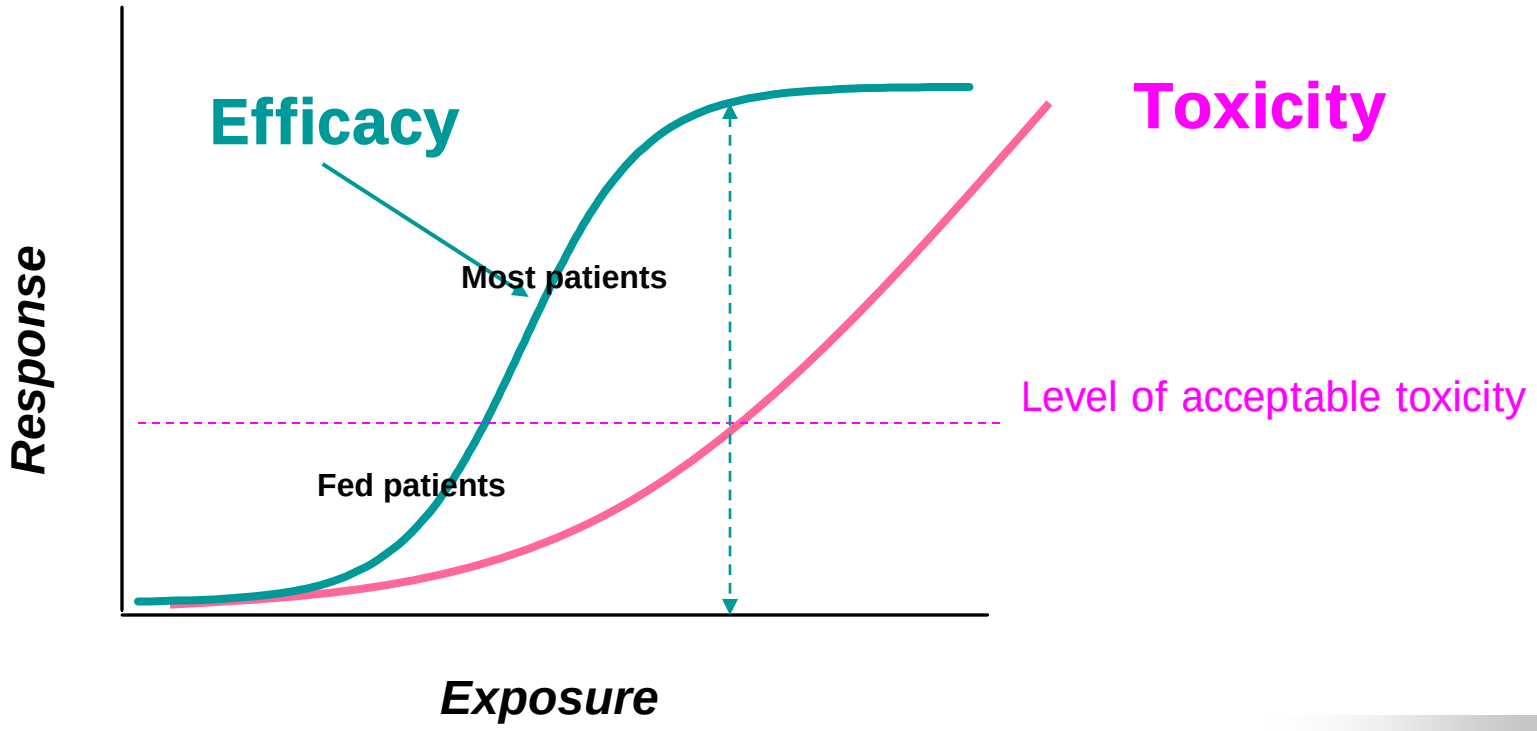
- **For valid phase 3 results**
  - **need to determine whether the formulation change alters exposure**
  - **if exposure changes, are the changes clinically relevant?**

Bioequivalence



Impact of food effect

- **Administration of drugs with food may….**
  - **Alter drug concentrations (increase or decrease)**
  - **Alter efficacy and safety**
- **A possible scenario…..**



Impact of food effect
Possible sequence of events…

- First food effect study: no effect of food
- Phase 2 studies allow administration with or without food; evaluate a range of doses
- Formulation change prior to Phase 3
  - New formulation is not bioequivalent to old formulation, but it is possible to select a dose for Phase 3
- New formulation is administered without food restrictions in Phase 3

Impact of food effect
Possible sequence of events…

- **Food effect study conducted in parallel with Phase 3 trials**
  - **Food decreases AUC and Cmax by 30%**
- **The results of the Phase 3 study (conducted with no food restrictions) are positive: the drug is safe and effective**
  - **Can we conclude that the food effect is not clinically significant?**

Impact of food effect
Possible sequence of events…

- ….. Can we conclude that the food effect is not clinically significant?

- To answer the question, consider-
  - How often was drug given with food/without food
  - Exposure-response relationship

Barriers to informative exposure-response evaluation

Barriers to informative exposure-response evaluation

- Exposure data are not collected in late phase 2 or phase 3
- Study design flaws
- Study conduct flaws

Two case studies

Case 1- Maraviroc

- **HIV CCR5 inhibitor**
- **Indication: treatment of HIV infection in patients infected with CCR5-tropic HIV-1 virus**

Maraviroc
Phase 2b/3 Dose Selection

- **Phase 2a conclusion (Viral dynamic modeling; exposure-response evaluation)**
  - **Evaluate maraviroc 300 mg qd and 300 mg bid in Phase 2b/3**
- **Drug interaction data**
  - **Maraviroc is a CYP3A substrate**
  - **Other drugs in antiretroviral regimen may increase or decrease maraviroc concentrations**
  - **Maraviroc does not affect concentrations of other drugs**

Maraviroc
Phase 2b/3 Dose Selection

Drug interaction results

- **Effect of other drugs on maraviroc**
  - **CYP3A inhibitors- ↑maraviroc concentrations 3-11 x**
  - **CYP3A inducer (efavirenz)- ↓maraviroc concentrations by 50%**
  - **CYP3A inducer (nevirapine)- little effect on maraviroc concentrations**
  - **CYP3A inhibitor and inducer- ↑maraviroc concentrations**

Maraviroc Phase 2b/3 Doses

Doses were selected based on exposure-response information and drug interaction study results

Concomitant medications	Maraviroc Phase 2/3 dose (q.d or b.i.d.)
CYP3A inhibitor (with or without CYP3A inducer), including Protease inhibitor (except tipranavir/rtv)	150 mg
CYP3A inducers (efavirenz)	600 mg
Other concomitant medications	300 mg

Case 2 - Etravirine

- **Non-nucleoside reverse transcriptase inhibitor for treatment of HIV (part of combination therapy)**
- **Two identical phase 3 studies**
  - **Etravirine 200 mg b.i.d. + optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.**
  - **Vs. optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.**

Drug interaction: etravirine and darunavir/ritonavir

- **Phase 1 drug interaction study results**
  - **coadministration of darunavir/ritonavir <u>decreases</u> etravirine plasma concentrations by 30 to 50%**

- **No efficacy concern- the etravirine efficacy data were collected in the presence of darunavir/ritonavir**

Potential safety concern

- **Etravirine may be administered without darunavir/ritonavir.**
- **Etravirine may be administered with drugs that increase its concentrations.**
- **Thus, etravirine plasma concentrations may be higher than observed in Phase 3 studies.**
  - **How much higher?**
  - **Are the higher concentrations safe?**
  - **What is the risk/benefit for specific populations?**

Etravirine + lopinavir/ritonavir (How much higher?)

- ↑mean etravirine AUC by 17%
- (↑mean etravirine AUC by ~85% compared to etravirine + darunavir/ritonavir)
- No effect on lopinavir concentrations

Etravirine + Lopinavir/Ritonavir
Are higher concentrations safe?

	Observation from Phase 3 data	Multiply each AUC by 1.85 to account for administration of lopinavir/rtv rather than darunavir/rtv
AUC12 (ng*hr/mL) range	**145 to 69,997**	**268 to 129,495**
% subjects with AUC > 70,000	0	0.51%
% subjects with AUC 50,000 to 70,000	0.34%	0.51%
% subjects with AUC 30,000 to 50,000	0.69%	4.47%
% subjects with AUC 10,000 to 30,000	**16.67%**	**48.97%**

Etravirine + Lopinavir/Ritonavir Risk/benefit

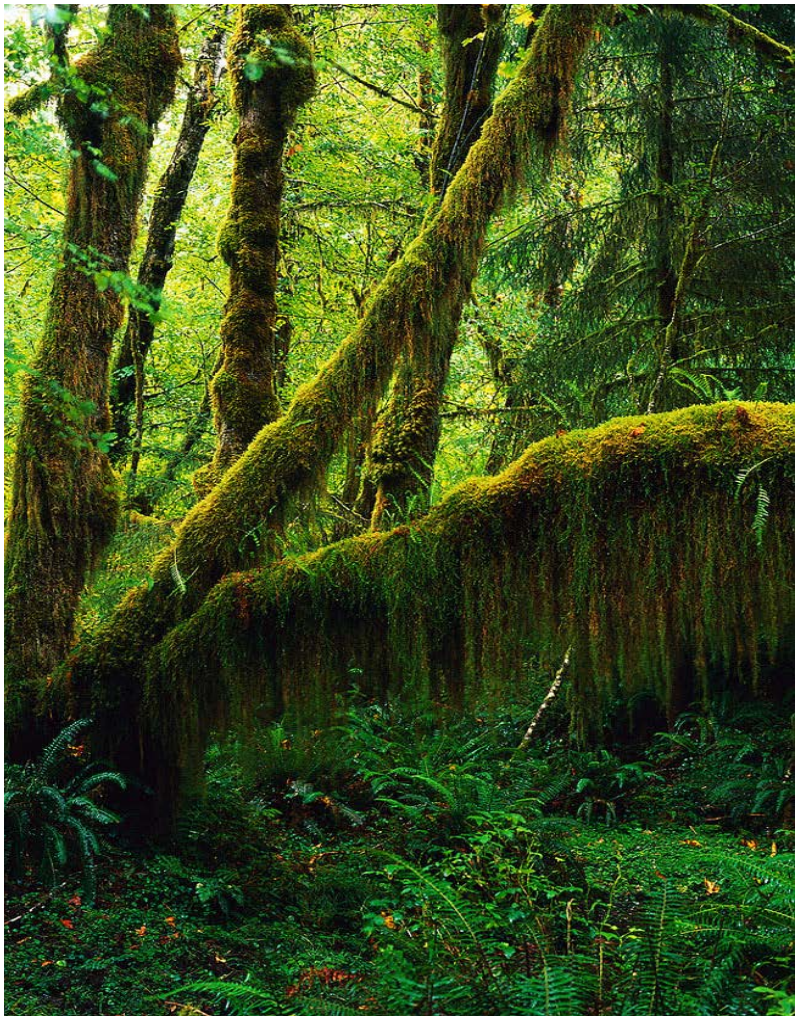
Considerations

- **etravirine concentration data from Phase 3**
- **anticipated etravirine concentrations when etravirine is given with LPV/RTV**

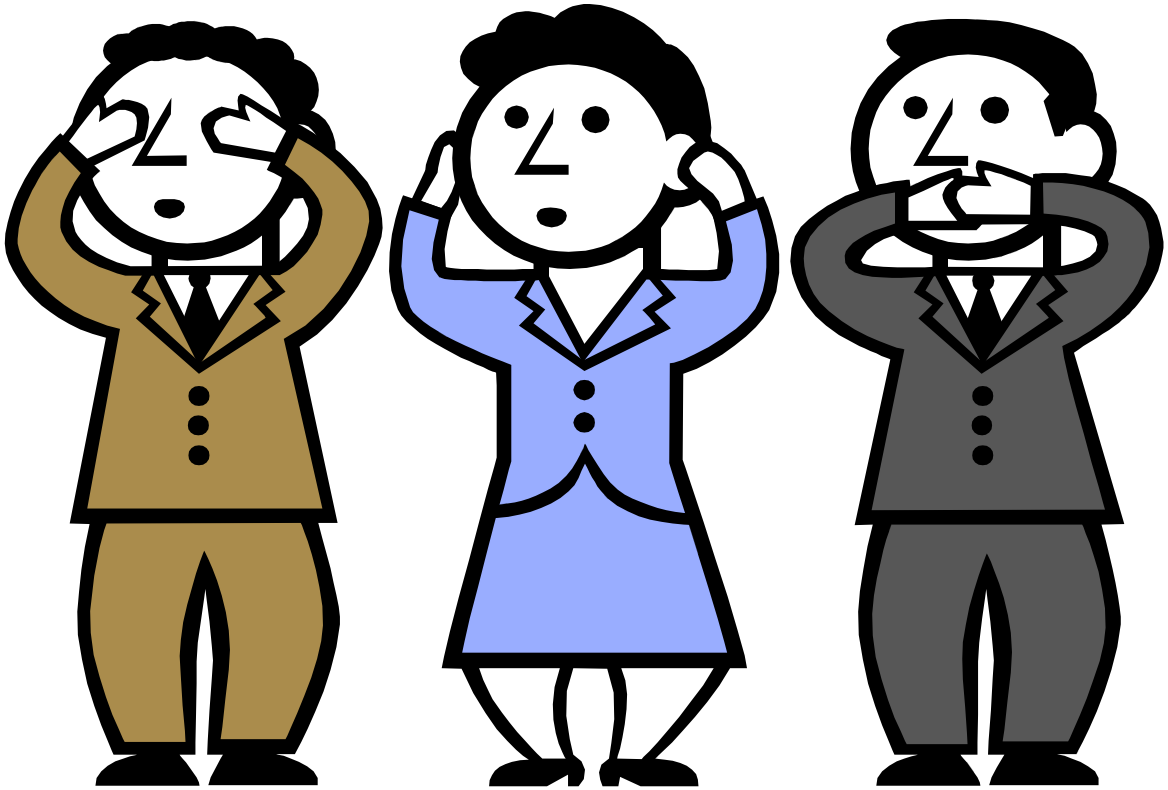
- **the population that would receive lopinavir/ritonavir instead of darunavir/ritonavir**
- **safety risks of etravirine**

Conclusions:
Relevance and impact

If a tree falls in the forest and no one hears it, does it make a sound?



If exposure-response is not evaluated during phase 2 or phase 3, can we optimize therapy for all patient populations?



Answer: NO!!

Other versions of the answer:

- **You don’t know what you don’t know**
- **Ignorance is not bliss**

Conclusions (relevance and impact)

- **Without exposure-response information**
  - **Dose selection may not be optimal**
  - **We cannot interpret significance of exposure changes**

- **Result: Lack of dosing instructions for certain groups**
  - **They are deprived of therapy**
  - **Or, they risk suboptimal safety and efficacy**