U.S. Food and Drug Administration

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

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Food and Drug Administration

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

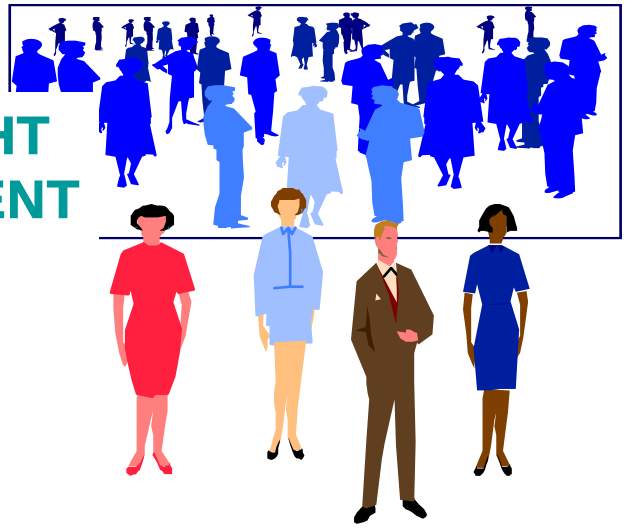
Outline

- 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

RIGHT PATIENT



GOAL

RIGHT DOSE

RIGHT TIME

Phases 2 & 3 of Drug Development

Phase 2 studies

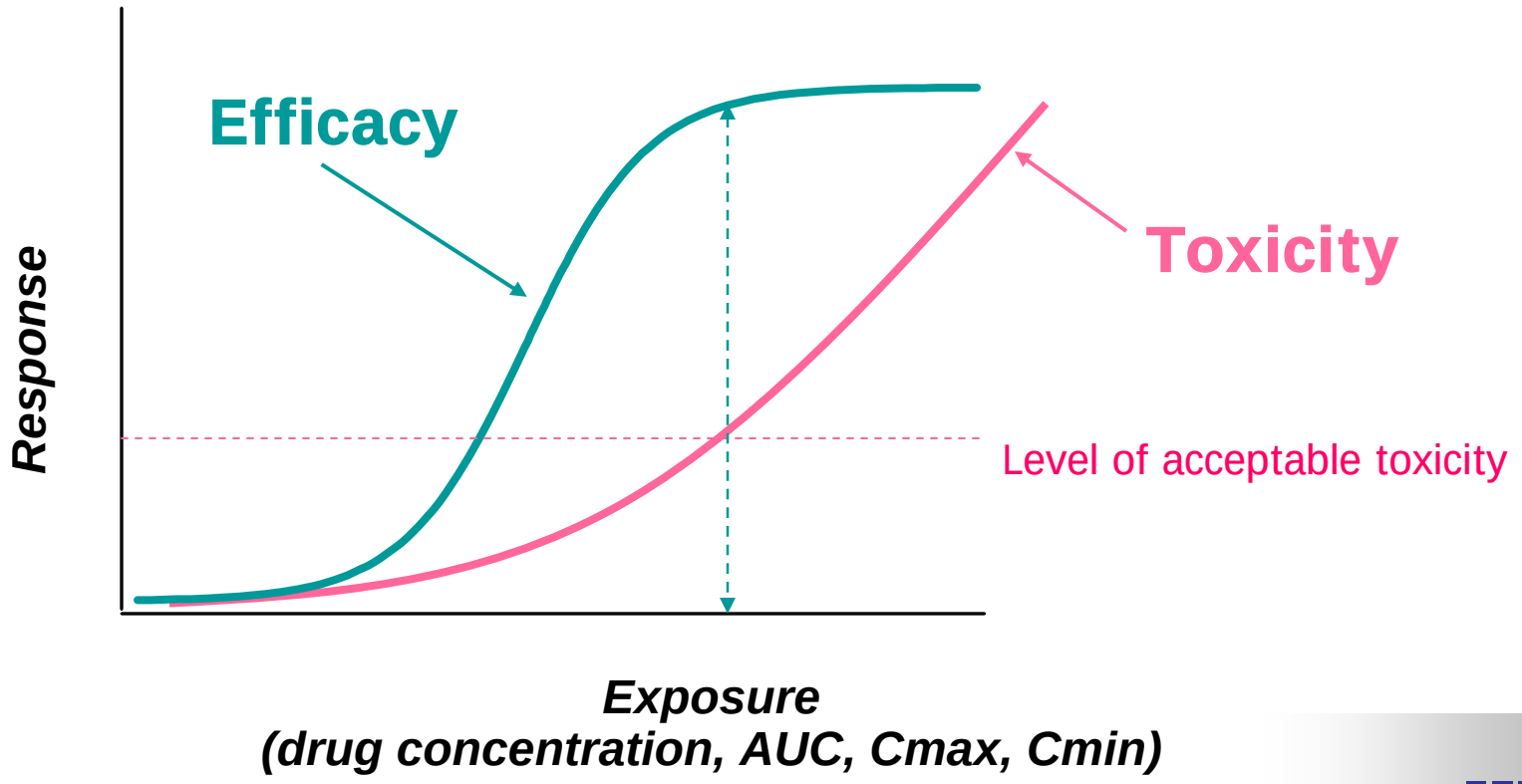
- provide preliminary data on the effectiveness of the drug
- allow selection of appropriate dose range for evaluation in Phase 3

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

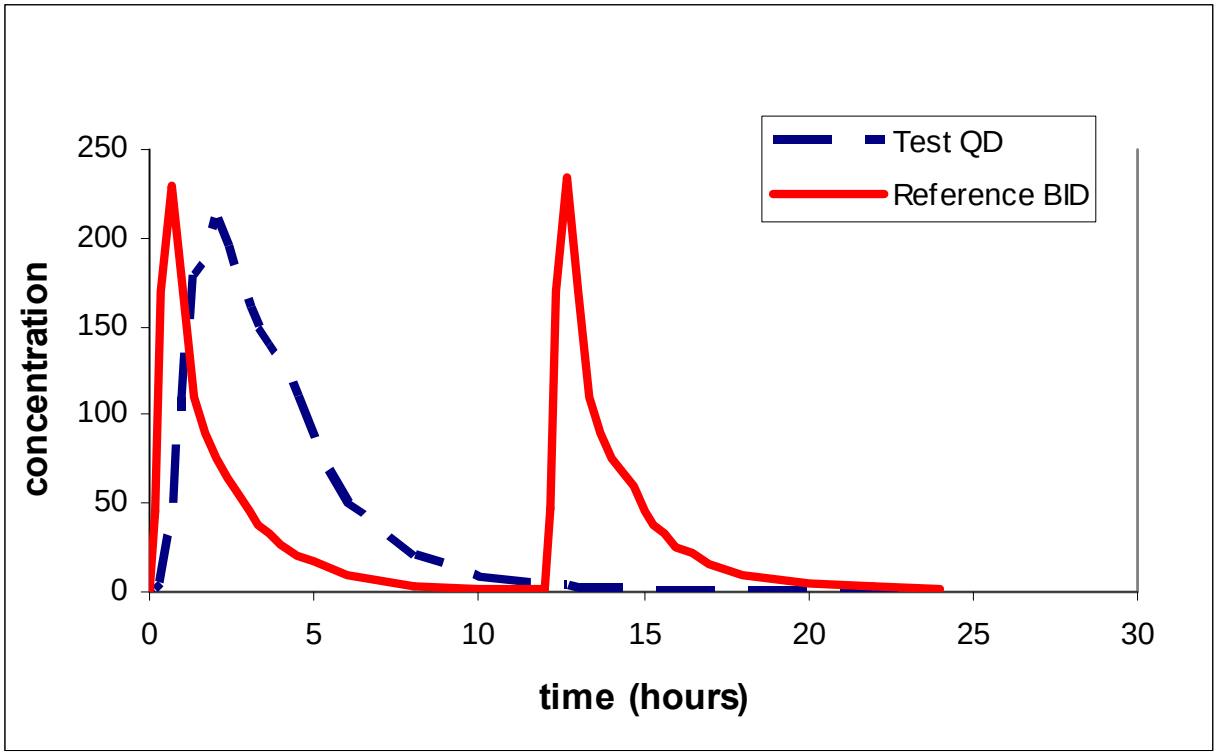
Add to weight of evidence supporting efficacy and safety

- 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

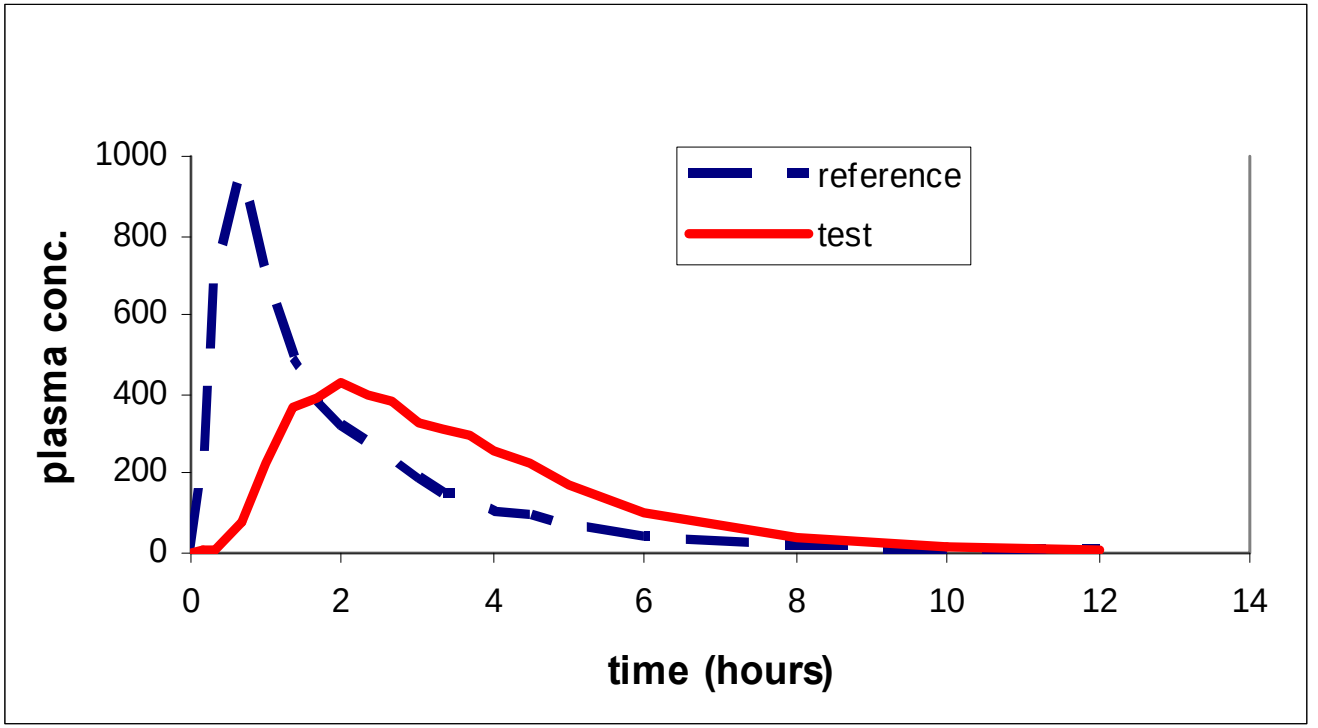
New drug administration scenarios

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

New Dosing Regimen



New Formulations



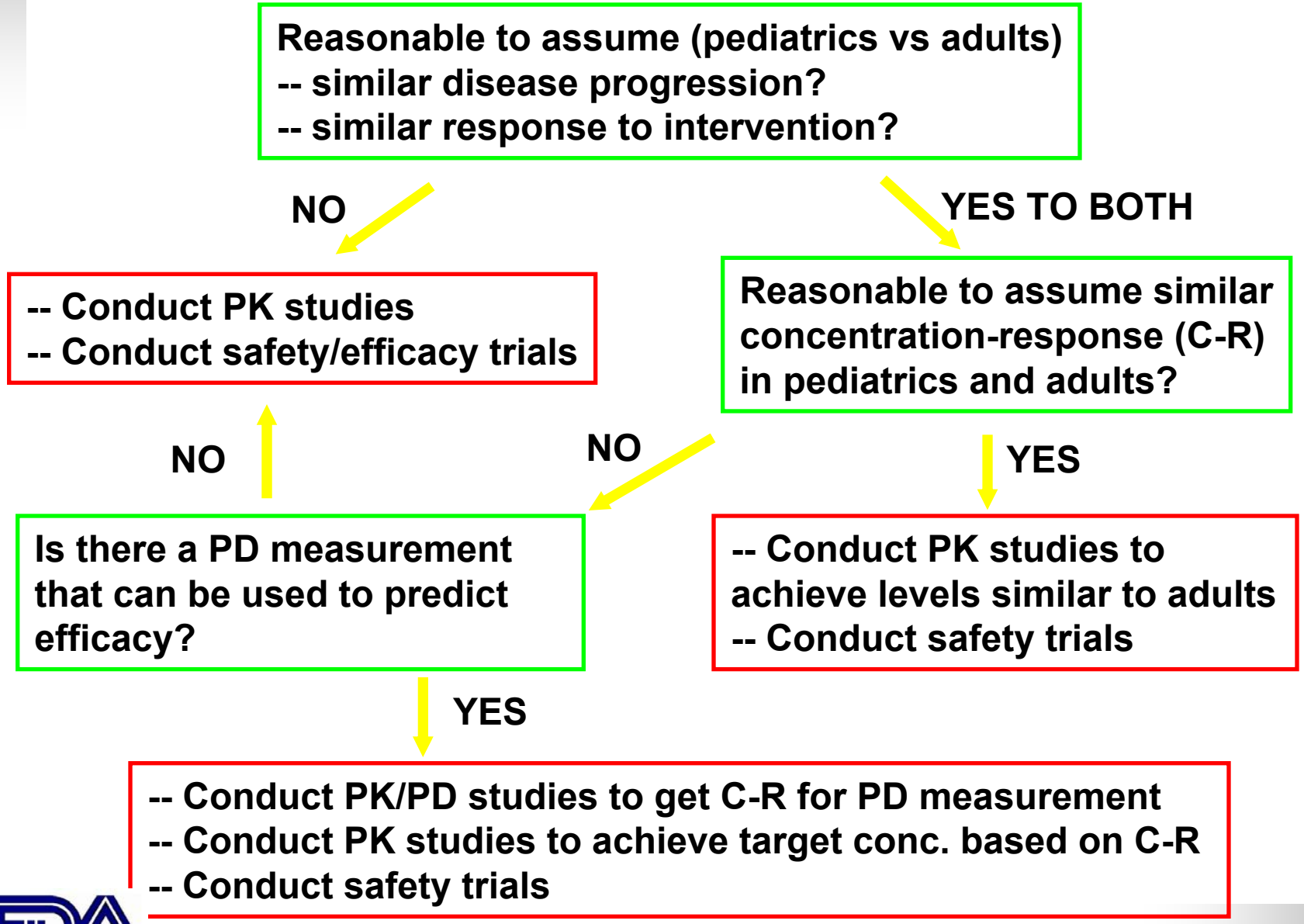
New Populations or Specific Populations

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

- May not be possible to adjust the dose to achieve similar AUC, Cmax and Cmin as in previous population

Pediatric Study Decision Tree

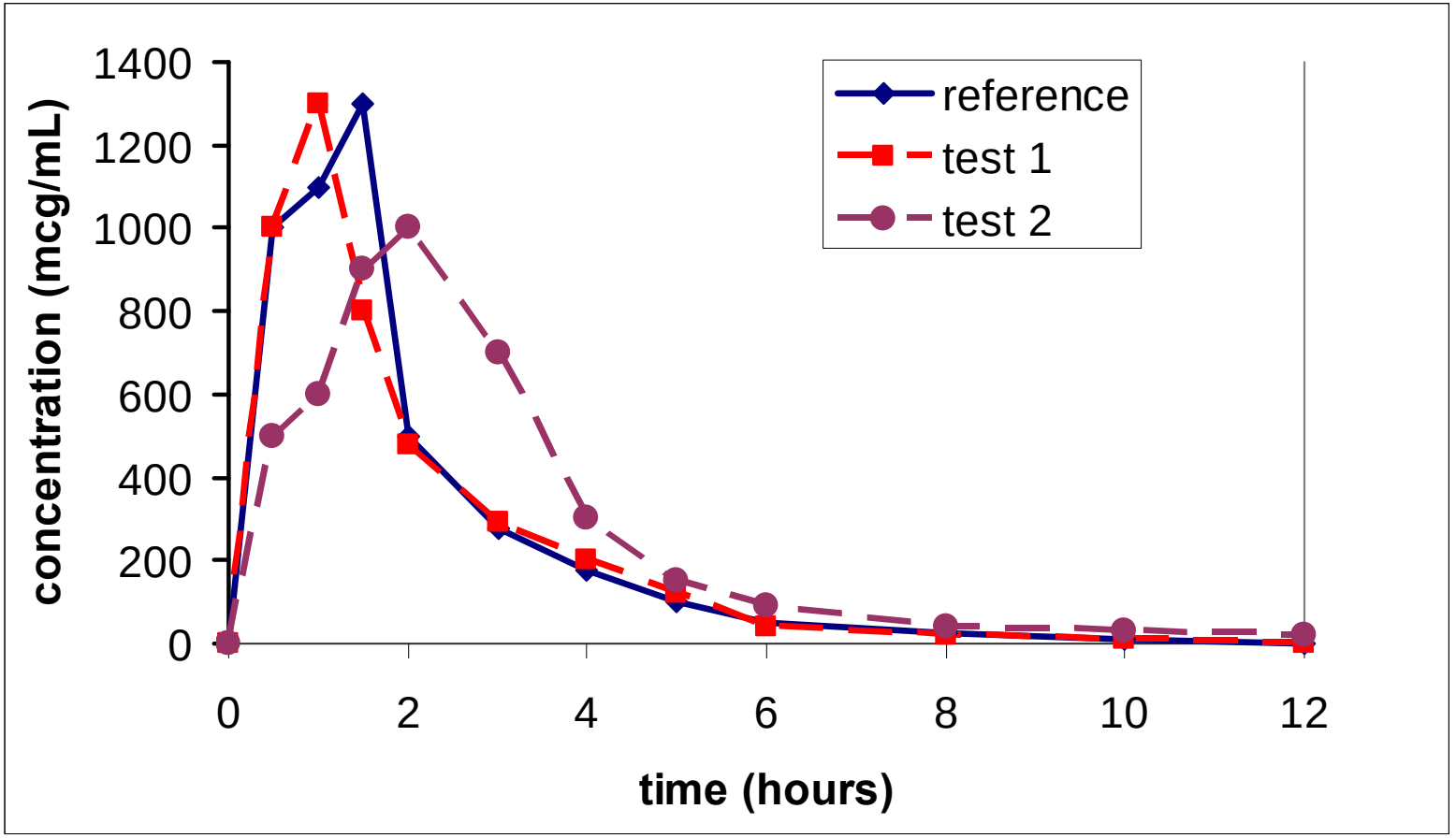


Bioequivalence (BE) Studies

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

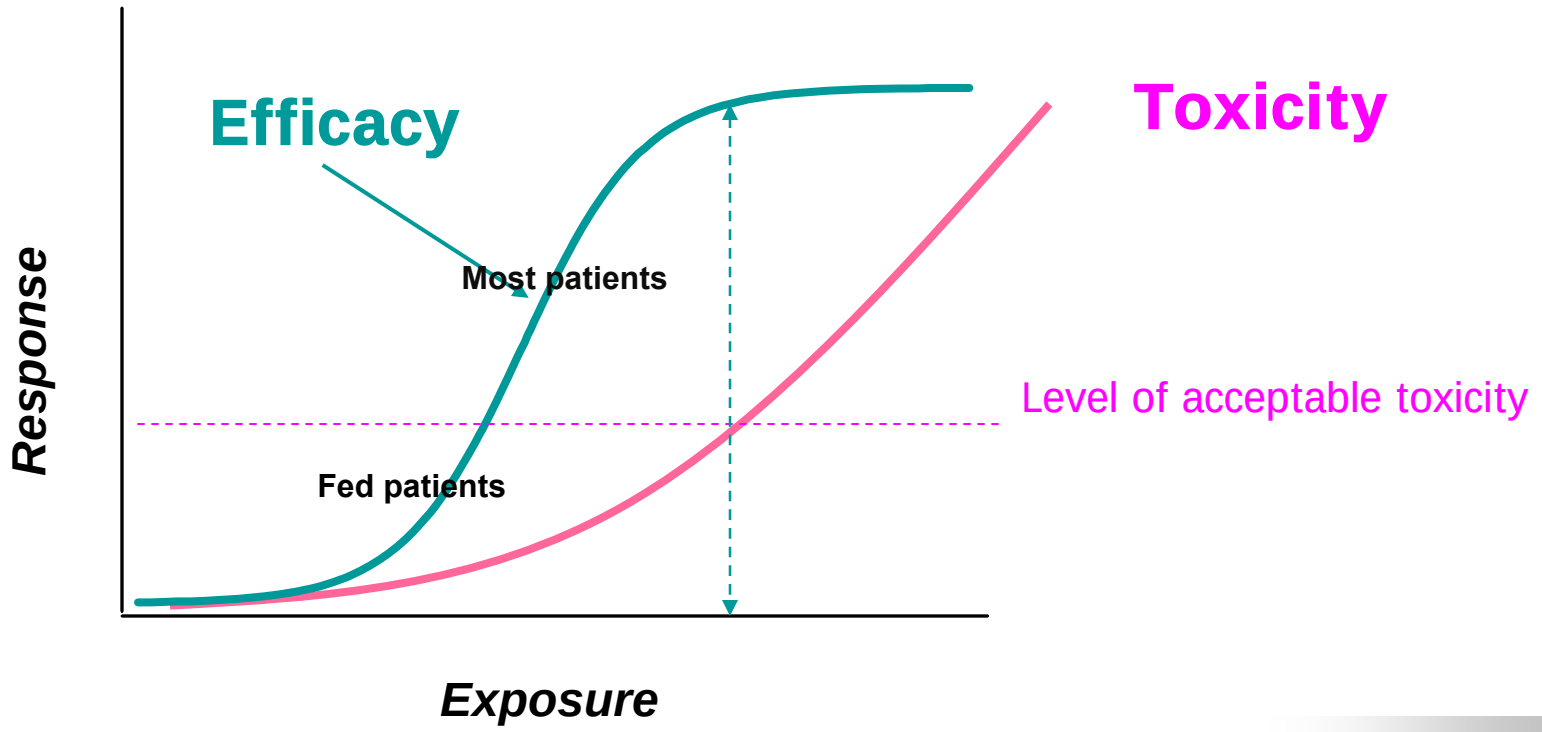
- For valid phase 3 results
  - need to determine whether the formulation change alters exposure
  - if exposure changes, are the changes clinically relevant?

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

Study Design Flaws

- Under-powered for study objectives
- Doses
  - too few
  - doses too close together
- Plasma samples
  - inappropriate timing
  - insufficient number
  - sample for only one drug in multidrug therapy

Flaws in Conduct of Study

- Poor record-keeping
  - dosing times
  - plasma sample times
- Analytical methods
  - bioanalytical method for PK unacceptable
  - unacceptable correction procedures for PD measures

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.

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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?

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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

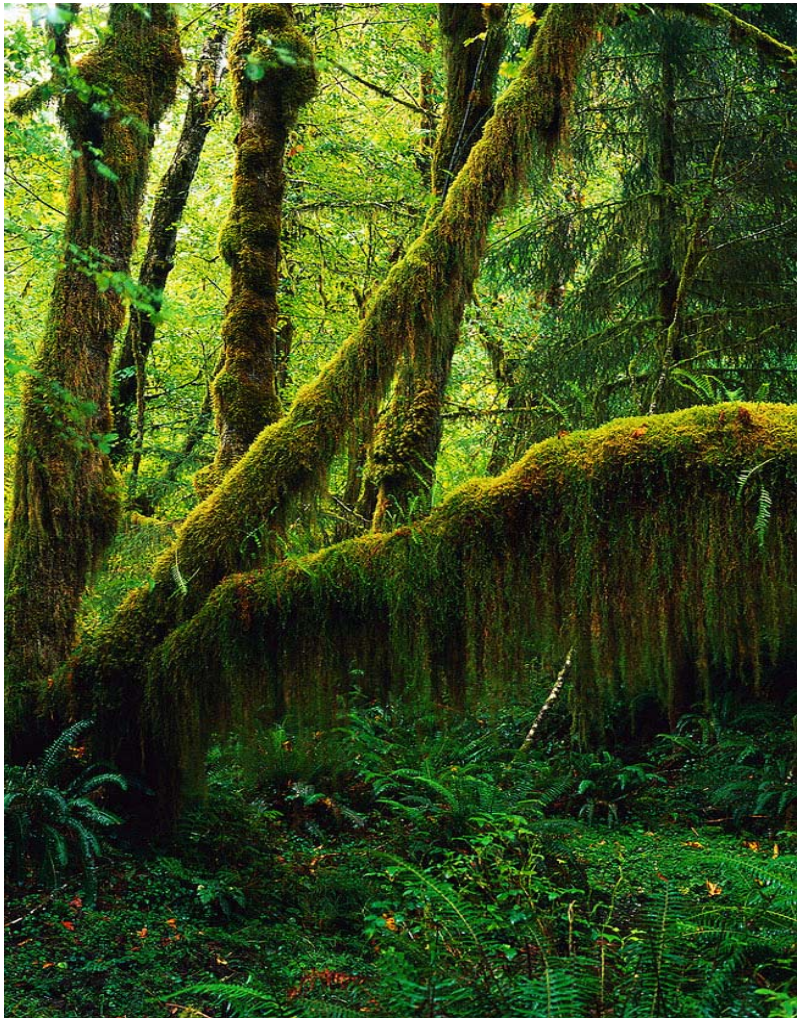
Considerations

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

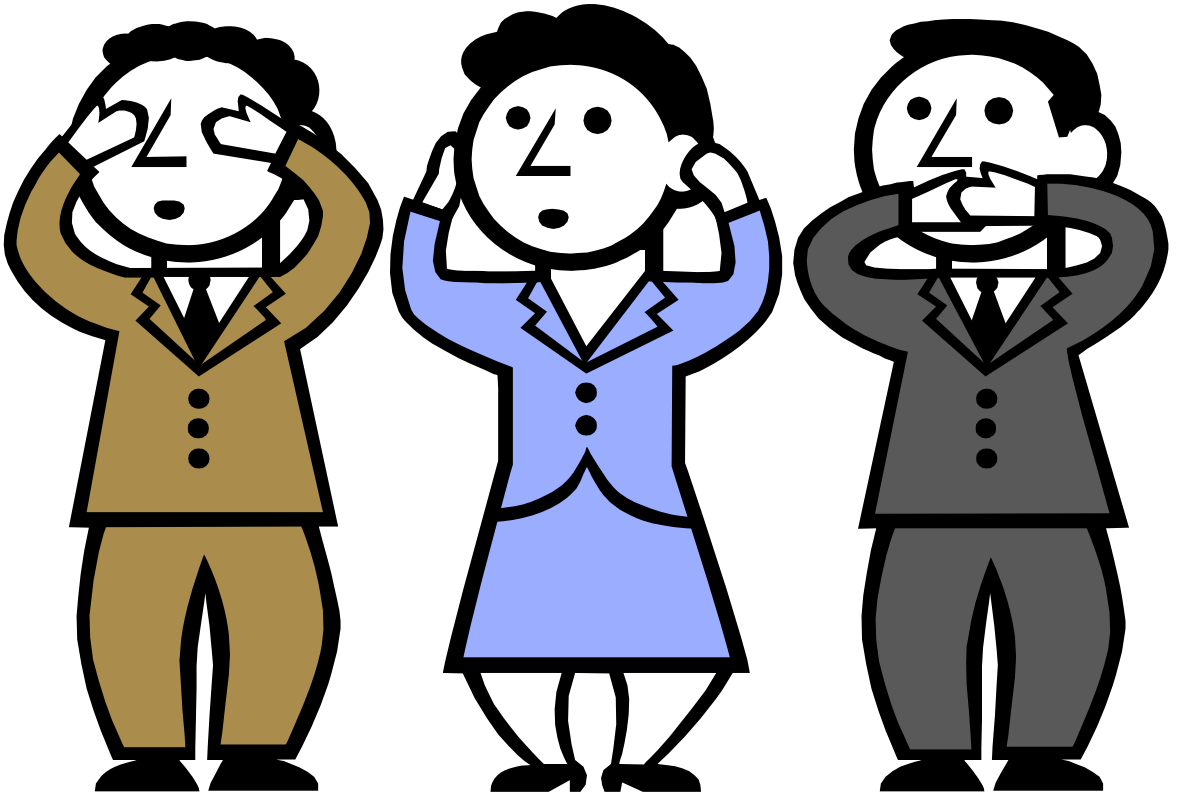
- **<u>the population</u> that would receive lopinavir/ritonavir instead of darunavir/ritonavir**
- **<u>safety risks</u> of etravirine**

Conclusions: Relevance and impact

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



- If an exposure-response relationship exists for a drug, but drug concentrations are not determined 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