Clinical Pharmacology Overview From the Antiviral Perspective

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Antiviral Drug Products Team

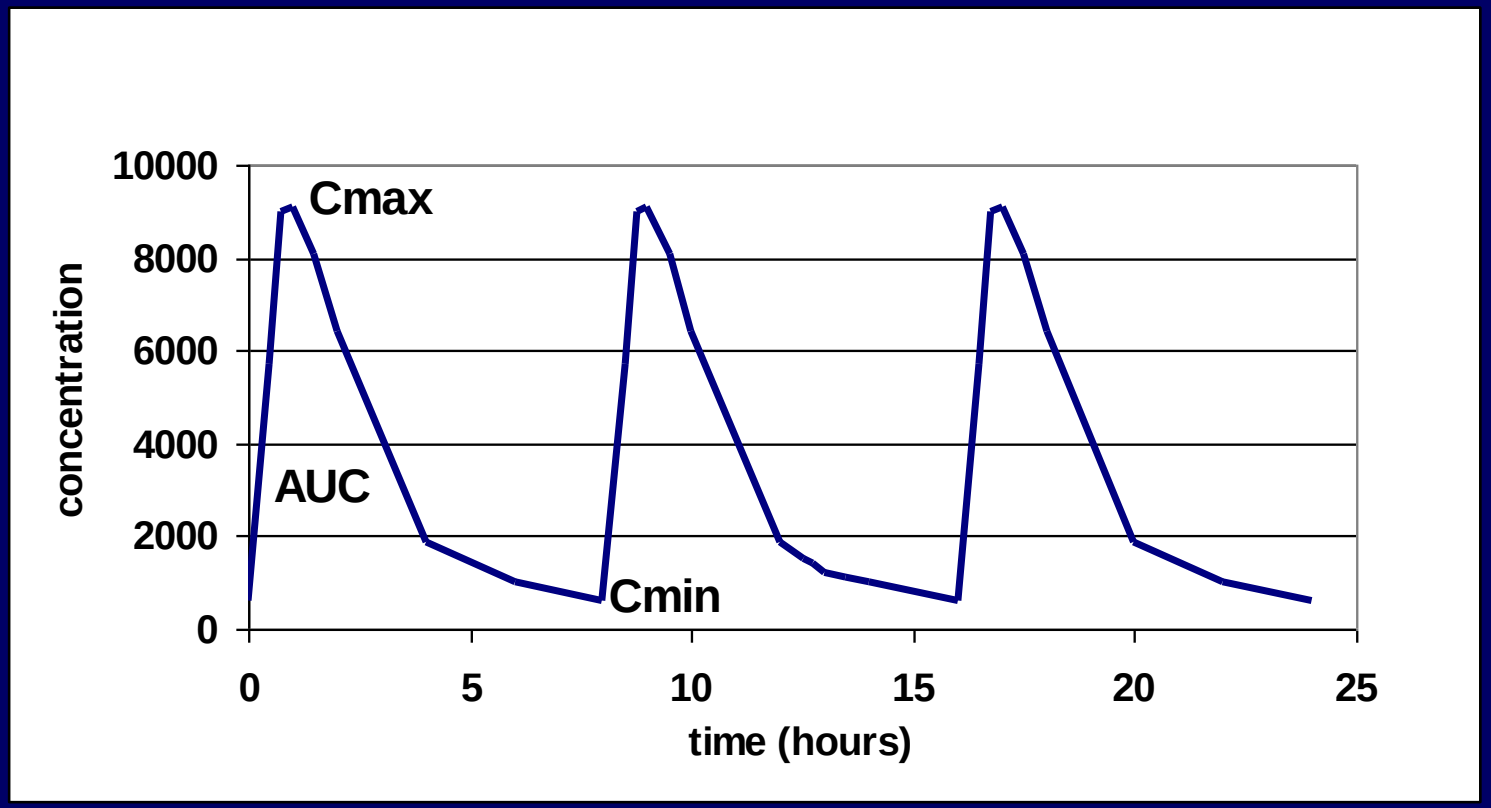
Outline

- Terminology
- Bioequivalence
- Scenarios with antiretroviral drugs
  - New formulations
  - Alternative dosing regimens
  - Drug interactions
  - Dosing pediatric patients
- PK/PD Considerations
- Standard of Evidence

Terminology

- **Pharmacokinetics (PK):** time course of drug concentrations in the plasma (sometimes in other fluids and tissues) resulting from a particular dosing regimen.
- **Pharmacodynamics (PD):** relationship between drug concentrations in plasma (or other fluids and tissues) and a resulting pharmacological effect.

Terminology



Terminology

- IC_{50}: Concentration of a drug required to inhibit viral replication by 50%.
- EC_{50}: concentration where patients demonstrate 50% maximal reduction in HIV RNA.

Outline

- Terminology
- Bioequivalence
- Scenarios with antiretroviral drugs
  - New formulations
  - Alternative dosing regimens
  - Drug interactions
  - Dosing pediatric patients
- PK/PD Considerations
- Standard of Evidence

Bioequivalence

- Relative Bioavailability
- Comparison between a test and reference drug product
  - commercial formulation vs. clinical trial material
  - generic drug vs. reference listed drug
  - drug product changed after approval vs. drug product before change

Bioequivalence

- 21 CFR 320.1 (e)
- the lack of a difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

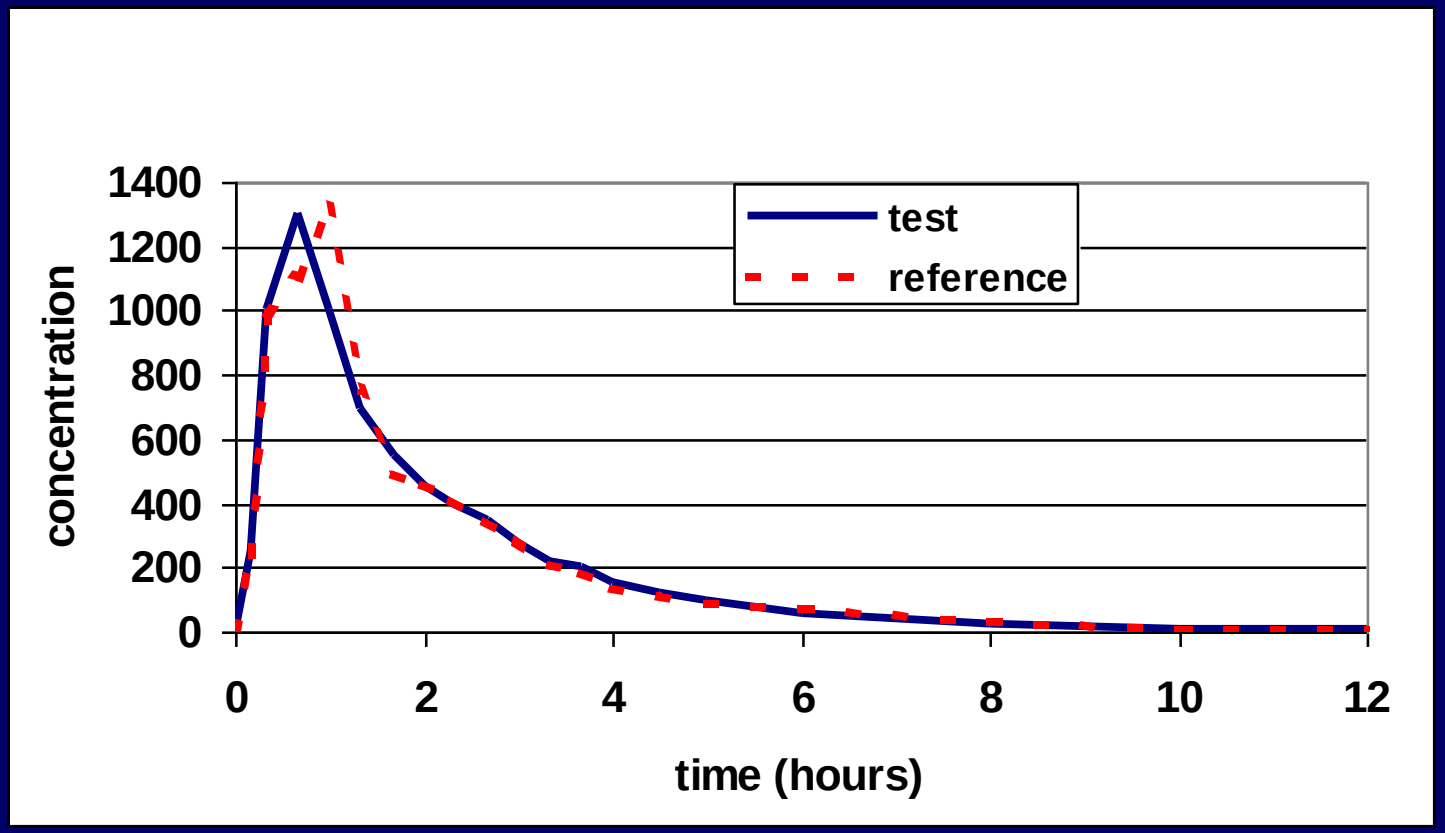
Determining Bioequivalence

- Formulations:
  - Reference
  - Test
- Study design (typical):
  - healthy volunteers
  - single dose, two-way crossover
  - administer drug under fasted conditions

Determining Bioequivalence

- Compare Test vs. Reference
  - Ratios for AUC and Cmax
  - Determine 90% confidence interval for ratios
  - Criteria for log-transformed data:
    - 90% CI: 0.8 to 1.25 (80% to 125%)

Bioequivalence



Bioequivalence: Assumptions

- Plasma concentration data- surrogate for active site
- Rate and extent of absorption are similar- no significant difference in exposure to drug
- Can extrapolate safety and efficacy data from reference product to test product

Bioequivalence

- Flexibility of BE criteria
  - No flexibility for approval of generic drugs
  - Innovator drugs- There is some room for flexibility. Safety and efficacy data or exposure-response data may make it possible to determine that differences are not meaningful.

Bioequivalence- Flexibility Example

- Ritonavir SGC vs. Liquid

Parameter	Point Estimate	90% Confidence Interval
AUC	1.351	1.036 – 1.762
Cmax	1.350	1.028 – 1.773

Bioequivalence- Flexibility Example

- Ritonavir SGC vs. Liquid
- Assessment
  - Outliers
  - Low reference formulation bioavailability
    - Review of previous studies
  - Supporting safety data from NDA: 700 mg bid

Outline

- Terminology
- Bioequivalence
- Scenarios with antiretroviral drugs
  - New formulations
  - Alternative dosing regimens
  - Drug interactions
  - Dosing pediatric patients
- PK/PD Considerations
- Standard of Evidence

Scenarios with Antiretroviral Drugs

- New formulations
- Alternative dosing regimens
- Drug interactions
- Dosing pediatric patients

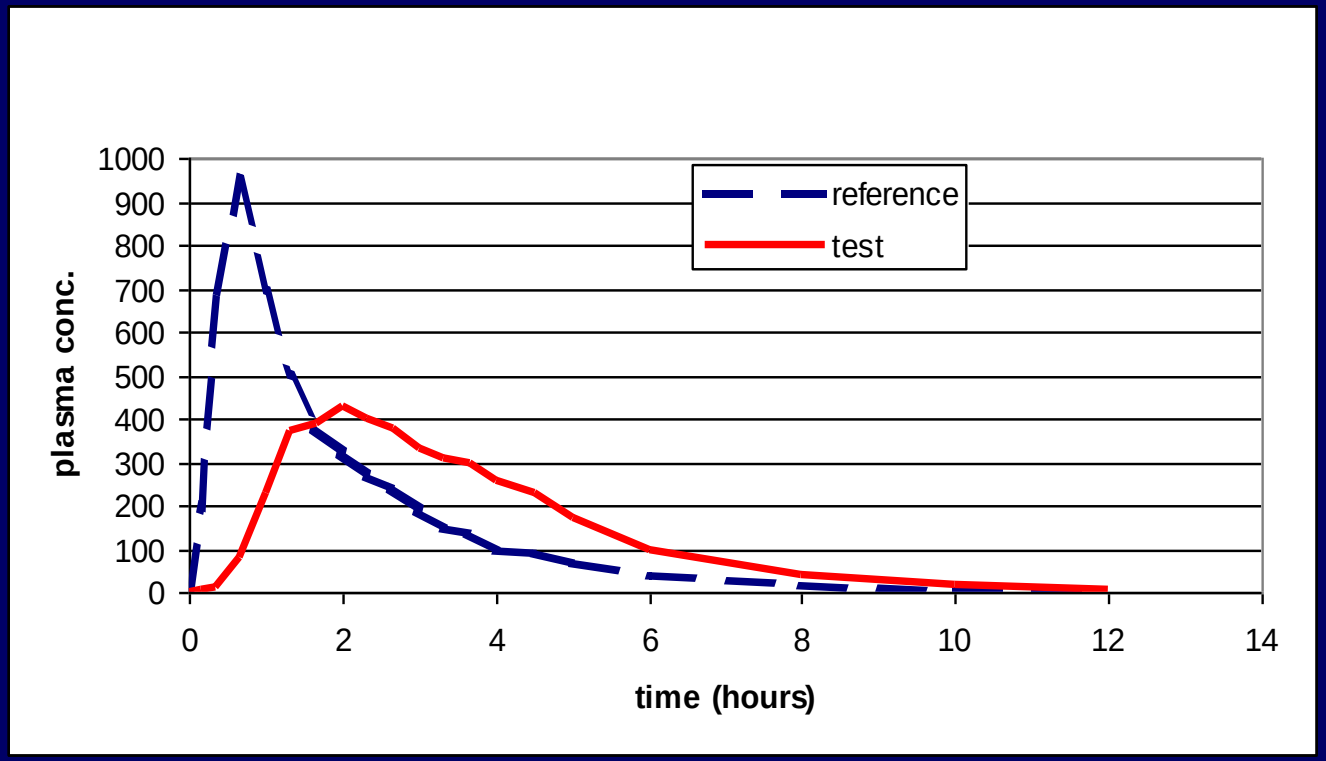
- Apply principles of bioequivalence, to demonstrate “comparable pharmacokinetic profiles”.

New Formulations

- Apply typical BE criteria
- In many cases, we do not expect the formulations to be bioequivalent.
- Examples:
  - Modified release formulations and prodrugs
  - Formulations with increased bioavailability

New Formulations

- Modified release formulations or prodrugs



New Formulations

21 CFR 320.23 (b)

… Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.

New Formulations

- No approved modified release or prodrug antiretroviral drug products
- Another situation: new formulation with increased bioavailability

New Formulations

Formulations with increased bioavailability

- Example: Fortovase vs. Invirase
- Fortovase 1200 mg tid vs. Invirase 600 mg tid: approximately a 9-fold increase in AUC.
- Concentrations higher at all times with Fortovase
- Safety question
- Need to demonstrate improved efficacy

Change in Dosing Regimen

- Attempting to simplify dosing regimens (TID to BID, BID to QD)
- Attempt to demonstrate comparable plasma drug exposure to the approved regimen
- Not likely that all exposure measures will be similar between regimens

Change in Dosing Regimen

Example- Nelfinavir

- Nelfinavir:
  - Original regimen: 750 mg TID
  - New regimen: 1250 mg BID
- Sponsor conducted clinical trial
- PK data submitted with clinical trial data

Change in Dosing Regimen

Example- Nelfinavir

PK change for 1250 mg BID vs. 750 mg TID

AUC ↑ 20%

Cmax ↑ 35%

Cmin, a.m. ↑ 57%

Cmin, p.m. ↓ 28%

Concern: safety and efficacy

Change in Dosing Regimen

Example- Nelfinavir

- Clinical Trial Data
- Study 542: 1250 BID vs. 750 TID, with stavudine and lamivudine
- Results at 48 weeks
  - 1250 BID (n=323): 61% of patients had <400 copies/mL
  - 750 TID (n=192): 58% of patients had <400 copies/mL
  - Safety: similar for both regimens

Change in Dosing Regimen

- Example: Protease inhibitor with short plasma half-life
  - Change from TID to BID
  - Expect:

    Similar or higher AUC over 24 hrs.

    Higher Cmax (safety question)

    Lower Cmin (efficacy question)

Change in Dosing Regimen

Example of efficacy data

- Indinavir 800 mg q8hr vs. 1200 mg q12hr
- 24 weeks:

  The 1200 mg q12hr regimen was less efficacious than the 800 mg q8hr regimen.

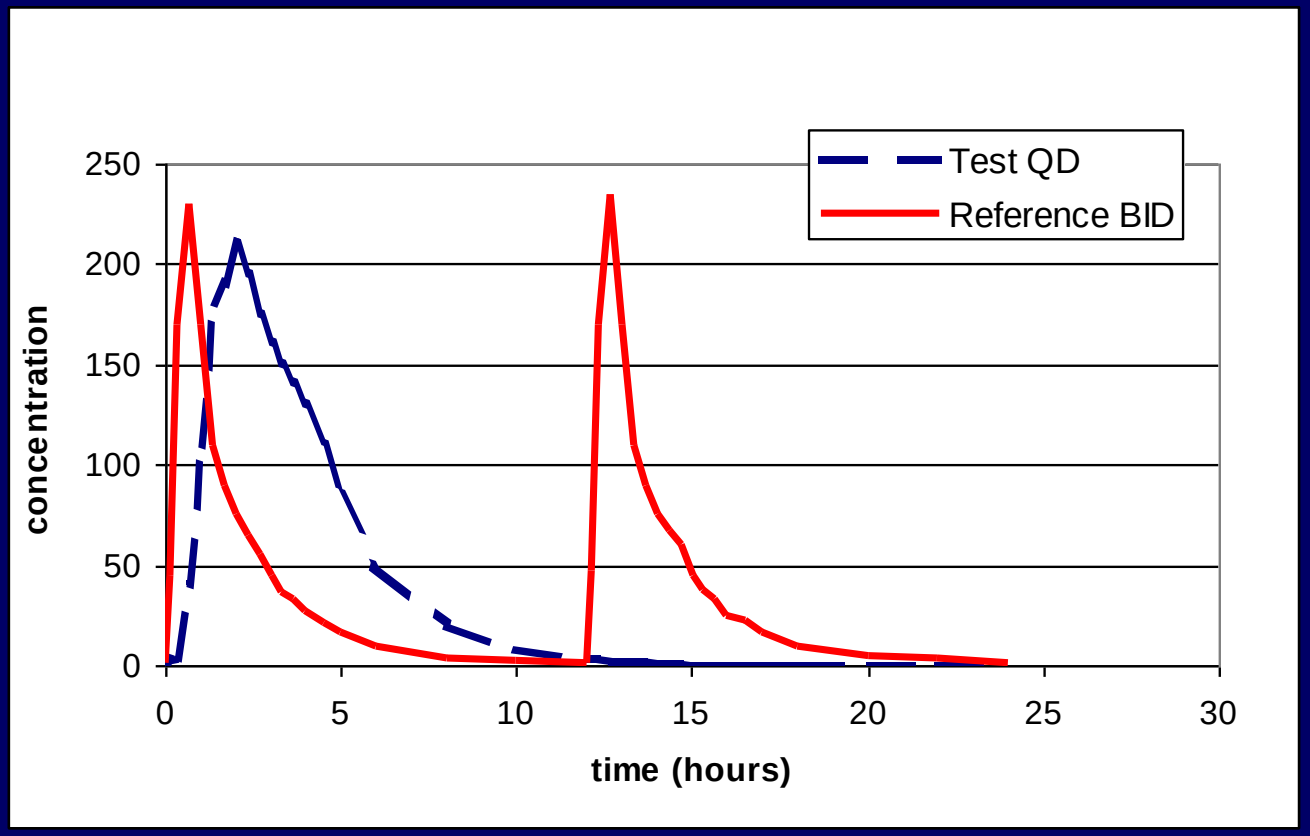
Change in Dosing Regimen

- Not likely that all exposure measures will be similar between regimens.
- In some cases, may change formulation and dosing regimen.

Change in Dosing Regimen

- Formulation change may allow a change in dosing regimen, with little change in AUC, Cmax or Cmin.
- In addition to comparing AUC, Cmax and Cmin, need to consider shape of the concentration vs. time curve.

Change in Dosing Regimen



Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products

To use pharmacokinetic data for approval, when BE or “comparable concentrations” have not been demonstrated:

- Need to understand the relationship between blood concentrations and response, including the time course of the response.

Drug Interactions

- Coadministration of two or more drugs results in a change in exposure and the potential need for a dose adjustment

- PK enhancer: intentional use of subtherapeutic dose one drug to increase concentrations of another drug

Drug Interactions

- Antiretroviral drugs in combination with other drugs: conventional dose modification situation
- Example: Indinavir and rifabutin

Drug Interactions- Typical

- IDV 800 mg q8hr + RIF 150 mg qd vs. IDV 800 mg q8hr
  - IDV AUC ↓ 32%
  - IDV Cmax ↓ 20%
  - IDV Cmin ↓ 40%
- Recommendation:
  - Increase IDV dose to 1000 mg q8hr when administered with RIF.

Drug Interactions

- RIF 150 mg qd + IDV 800 mg q8hr vs. RIF 300 mg qd
  - RIF AUC ↑ 54%
  - RIF Cmax ↑ 29%
  - 25-desacetyl-RIF AUC ↑ 300%
  - 25-desacetyl-RIF Cmax ↑ 143%
- Recommendation:
  - Reduce RIF dose to one-half the standard dose when administered with IDV.

Drug Interactions

- Medical decision: coadminister two antiretroviral drugs. However, there may be a PK interaction between these drugs.
- Should the dose of either drug be altered?

Drug Interactions

- Indinavir and efavirenz
- Indinavir 800 mg q8hr plus efavirenz:
  - **No significant change in efavirenz PK**
  - **Indinavir AUC ↓ 31%**
  - **Indinavir Cmax ↓ 16%**

Drug Interactions

- Increase indinavir dose to 1000 mg q8hr:
  - **AUC similar to typical 800 mg q8hr**
  - **Cmax higher (50%)**
  - **Cmin similar**
- Clinical trial included indinavir 1000 mg q8hr with efavirenz 600 mg qd (n=429)

Drug Interactions

PK Enhancers

- PI in combination with potent metabolic inhibitor (e.g., low dose ritonavir)
- Intent: increase concentrations of PI, not antiviral efficacy of 2nd drug
- Alter dosing regimen for PI
- Exposure measures may be quite different from approved regimens

Drug Interactions
PK Enhancers

- Example 1:
  - Increase AUC, Cmax, Cmin
- Indinavir/Ritonavir

Drug Interactions
PK Enhancers

- IDV/RTV 800/100 mg BID vs. IDV 800 mg q8hr:
  - **IDV AUC ↑ 170%**
  - **IDV Cmax ↑ 58%**
  - **IDV Cmin ↑ 10-fold**
- IDV/RTV 800/200 mg BID vs. IDV 800 mg q8hr:
  - **IDV AUC ↑ 260%**
  - **IDV Cmax ↑ 79%**
  - **IDV Cmin ↑ 25-fold**

Drug Interactions
PK Enhancers

- Example 2:
  - Cmin higher, other exposure measure(s) lower
- Amprenavir/Ritonavir

Drug Interactions
PK Enhancers

- Simulated amprenavir concentrations
- APV/RTV 450/100 mg BID vs. APV 1200 mg BID:
  - **APV AUC ↔**
  - **APV Cmax ↓ 56%**
  - **APV Cmin ↑ 340%**
- APV/RTV 600/100 mg BID vs. APV 1200 mg BID:
  - **APV AUC ↑ 30%**
  - **APV Cmax ↓ 42%**
  - **APV Cmin ↑ 500%**

Drug Interactions
PK Enhancers

- Simulated amprenavir concentrations (continued)
- APV/RTV 900/200 mg QD vs. APV 1200 mg BID:
  - **APV AUC ↔**
  - **APV Cmax ↓ 34%**
  - **APV Cmin ↑ 200%**
- APV/RTV 1200/200 mg QD vs. APV 1200 mg BID:
  - **APV AUC ↑ 22%**
  - **APV Cmax ↔**
  - **APV Cmin ↑ 300%**

Pediatric Dosing

- There are many factors to consider when evaluating new formulations, alternative dosing regimens and drug interaction results for antiretroviral drugs.
- Considering these factors in the context of dosing pediatric patients adds another layer of complexity.

Pediatric Dosing

- 21 CFR 201.57(f)(9)(iv)
- Allows inclusion of pediatric use information in the label without controlled clinical trials of the use in children.
- Course of disease should be similar in pediatric and adult populations.
- Sponsor must provide other information to support use in children.

Pediatric Dosing

- Additional information- PK data for drug in pediatric population, to allow dose selection
- Evidence of comparable concentrations between children and adults, or exposure-response data, can link efficacy data.
- Some additional safety data may be requested.

Pediatric Dosing

Example: Nelfinavir

- Pediatric dose: 20-30 mg/kg TID
- Compare to Adults: 750 mg TID
- Age 2-7 yr (n=6)
  - **AUC ↔**
  - **Cmax ↑ 30%**
  - **Cmin ↑ 12%**
- Age 7-13 yr (n=8)
  - **AUC ↔**
  - **Cmax ↓ 15%**
  - **Cmin ↑ 16%**
- Greater PK variability in pediatric patients
- No BID PK data available for pediatric patients. Thus, cannot extrapolate from adult BID safety and efficacy data.

Scenarios
Summary of Potential Issues

- New formulations:
  - May not meet BE criteria, particularly for Cmax
- Change in dosing regimen:
  - Target AUC or Cmin, other exposure measures will be different
  - Different shape of concentration vs. time curve
- Drug interactions: typical
  - Target AUC or Cmin; do not have flexibility to match all exposure measures

Scenarios
Summary of Potential Issues

- Drug interactions: PK enhancers
  - Increase all exposure measures (safety question)
  - Increase some exposure measures, decrease others (safety and efficacy questions)
- Pediatric dosing
  - Try to match AUC or Cmin, other exposure measures may be different

Scenarios
Summary of Potential Issues

Overall:

- In most situations, it will not be possible to match AUC, Cmax, and Cmin.
  - Some lower concentrations: efficacy question
  - Some higher concentrations: safety question

Outline

- Terminology
- Bioequivalence
- Scenarios with antiretroviral drugs
  - New formulations
  - Alternative dosing regimens
  - Drug interactions
  - Dosing pediatric patients
- PK/PD Considerations
- Standard of Evidence

Using PK/PD

- Goals:
  - Identify specific exposure measures (AUC, Cmax, Cmin) that are related to PD endpoints.
  - Design exposure-response studies that will allow the assessment of the clinical implications of changing formulations or dosing regimens of antiretroviral drugs.

Using PK/PD

- PD endpoints
  - Efficacy
  - Safety

PK/PD Considerations
Pharmacometrics Consultation

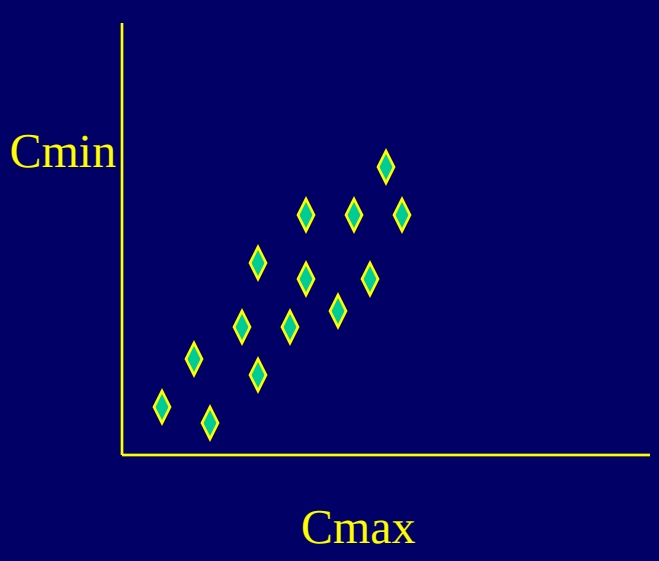
Pharmacometrics Group:
Office of Clinical Pharmacology
and Biopharmaceutics

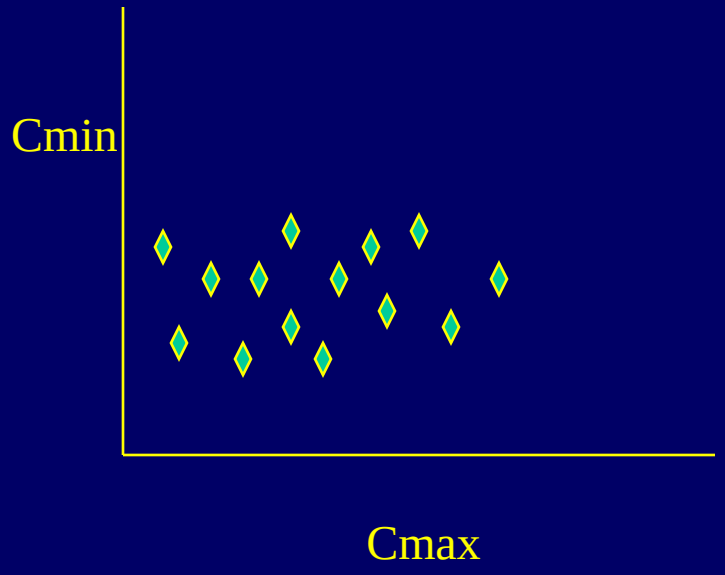
Pharmacokinetic Considerations

- Correlation of exposure measures with one another
- Time of sampling can affect Cmax and AUC
- Diurnal variation
- Shape of concentration vs. time curve
- Identification of Cmin
- Adjustment for protein binding

Pharmacokinetic Considerations

- Correlation of exposure measures with one another





Pharmacokinetic Considerations

- Time of sampling can affect Cmax and AUC

  Example: Typical Cmax observed at 1 hour

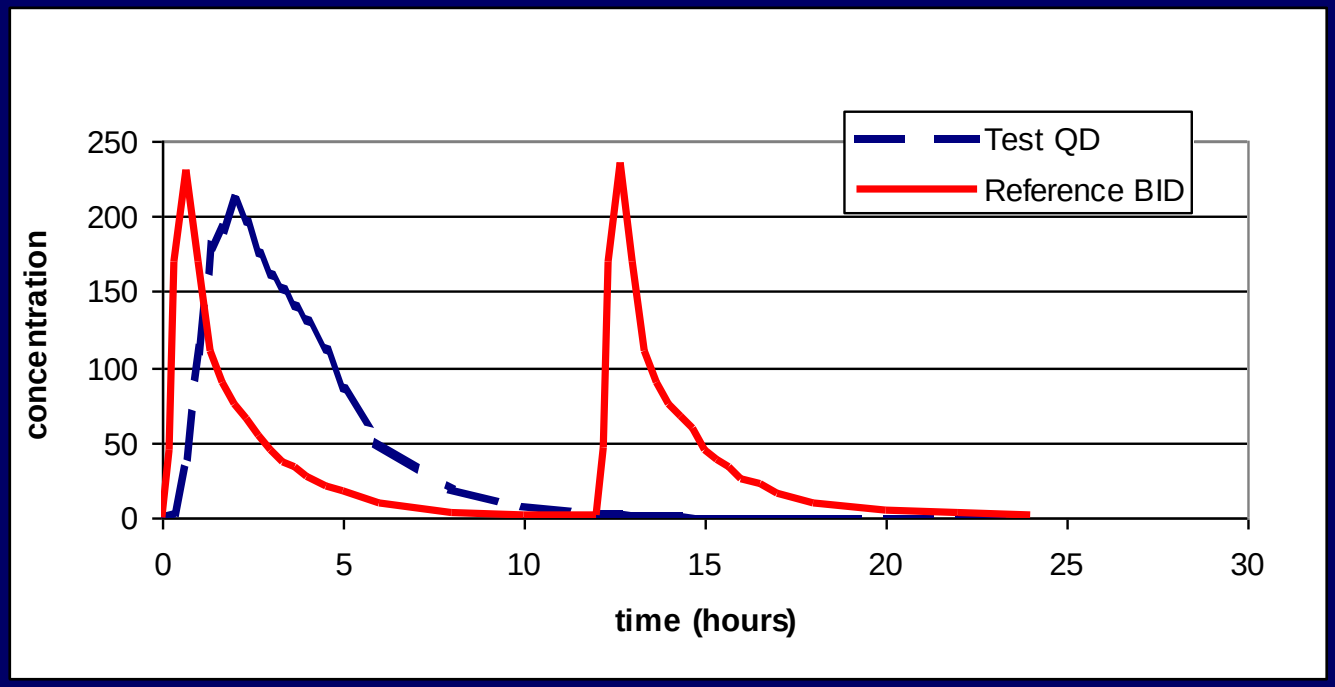
  – Sample at 0, 0.5, 1, 2, 4, 6 hours
    - Cmax = 5100
  – Sample at 0, 0.5, 1.5, 2.5, 4, 6 hours
    - Cmax = 4000
  – Sample at 0, 2, 4, 6 hours
    - Cmax = 3000

Pharmacokinetic Considerations

- Diurnal variation
  - usually estimate $AUC_{0\text{-}24}$ as
    - $AUC_{0\text{-}8}$ x 3
    - $AUC_{0\text{-}12}$ x 2
  - Estimation assumes that PK profile is the same in the morning and evening.
  - There is some evidence that this estimation is not appropriate, but do not have data for most drugs.

Pharmacokinetic Considerations

- Shape of concentration vs. time curve



Pharmacokinetic Considerations

- Identification of Cmin
  - high variability
  - arithmetic mean vs. geometric mean vs. median

    example:
    - arithmetic mean = 145
    - geometric mean = 102
    - median = 121
  - time of sample collection
    - different dosing intervals

Pharmacokinetic Considerations

- Adjustment for protein binding
  - Assume all patients have the same fraction of drug bound to protein?

  Example:
  - Drug that is 99% (average) protein bound
  - Patients 1 and 2 have Cmin = 1000
  - Patient 1: 99.5% bound, 0.5% unbound, corrected Cmin = 5
  - Patient 2: 98% bound, 2% unbound, corrected Cmin = 20

Pharmacodynamic Considerations

- Suppression of virus: Different doses or regimens may have similar efficacy early in treatment, but may diverge at later times.

Additional Considerations

- Mechanism of action
- Other exposure measures
- Multiple drug therapy
- Compliance
- Consumption of other agents or food
- Active metabolites
- Response in naïve vs. previously treated patients

PK/PD Considerations

- If we do establish a PK/PD relationship, does it apply to all situations?
  - 3 drug classes
  - All drugs within a class
  - All populations

Outline

- Terminology
- Bioequivalence
- Scenarios with antiretroviral drugs
  - New formulations
  - Alternative dosing regimens
  - Drug interactions
  - Dosing pediatric patients
- PK/PD Considerations
- Standard of Evidence

Standard of Evidence

- Under different scenarios, there may be different standards of evidence.

New formulation

Change in dosing regimen

PK enhancer

Drug interaction

Standard of Evidence

- The standard of evidence differs for regulatory decisions vs. managing an individual patient.