Scientific Considerations for Establishing Bioequivalence of Generic Drug Products

Bing V. Li, Ph.D.
Division of Bioequivalence I
OGD/CDER/FDA

April 23, 2015
Rockville, MD

Disclaimer

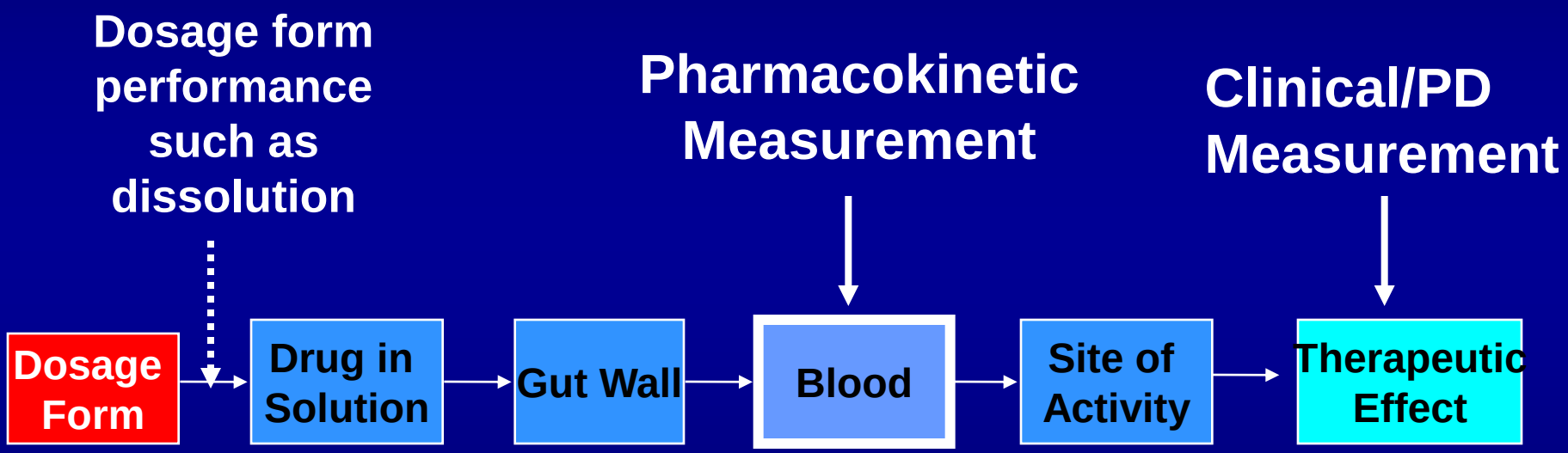
Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

What is Bioequivalence (BE) ?

The absence of a significant 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 administrated at the same molar dose under similar conditions in an appropriately designed study…" [21 Code of Federal Regulation (CFR) § 320.1]

No significant difference in the rate and extent when the drug becomes available at the site of drug action

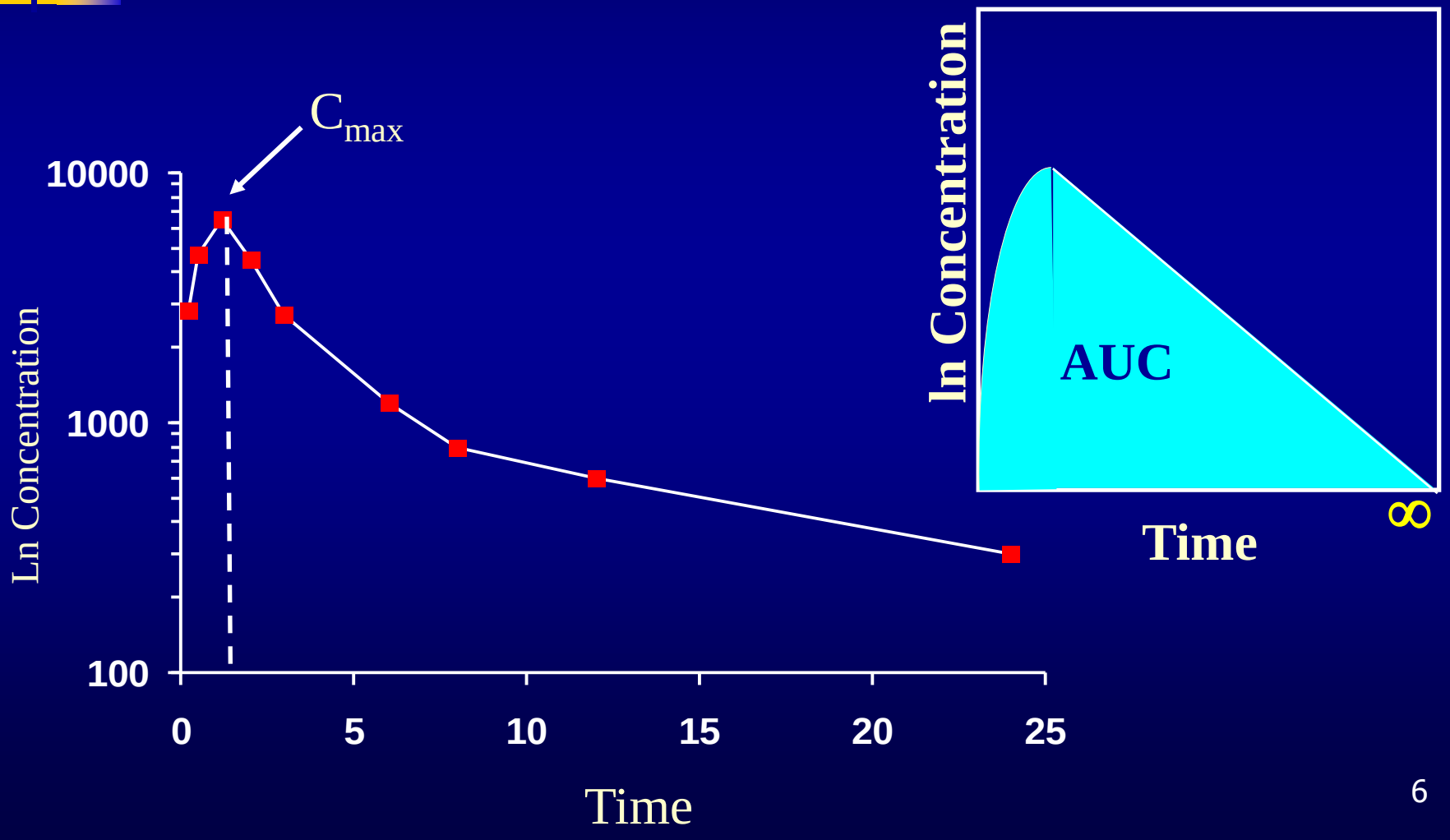
Model of Oral Dosage Form Performance Systemically Acting Drug



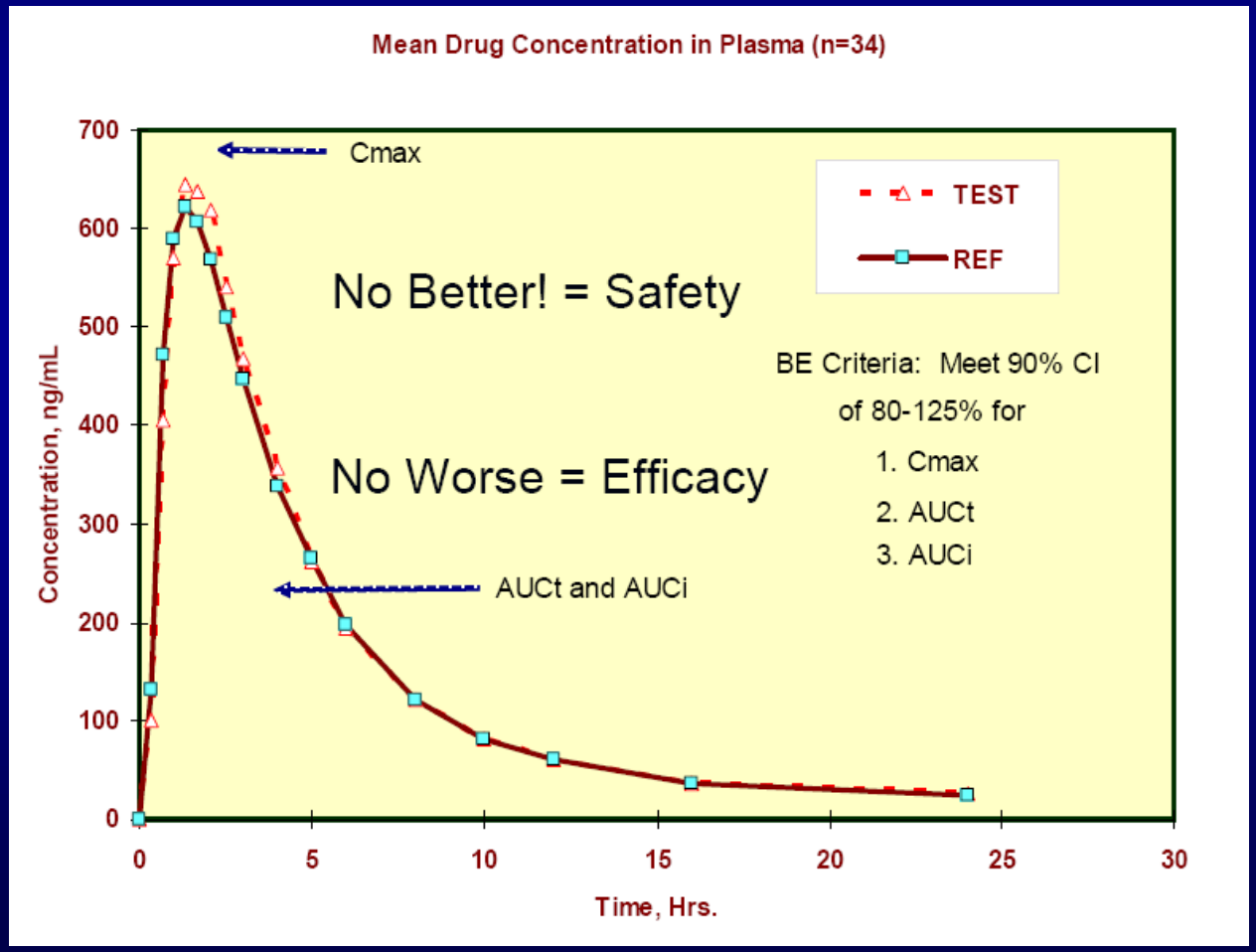
Approaches to Determining Bioequivalence (21 CFR 320.24)

- *In vivo* measurement of active moiety or moieties in biologic fluid
  - "PK study"
- *In vivo* pharmacodynamic comparison
  - "PD study"
- *In vivo* limited clinical comparison
  - "Bioequivalence study with clinical endpoints"
- *In vitro* comparison
- Any other approach deemed appropriate by FDA

Plasma Concentration Profile



Therefore, BE can be pictured as:

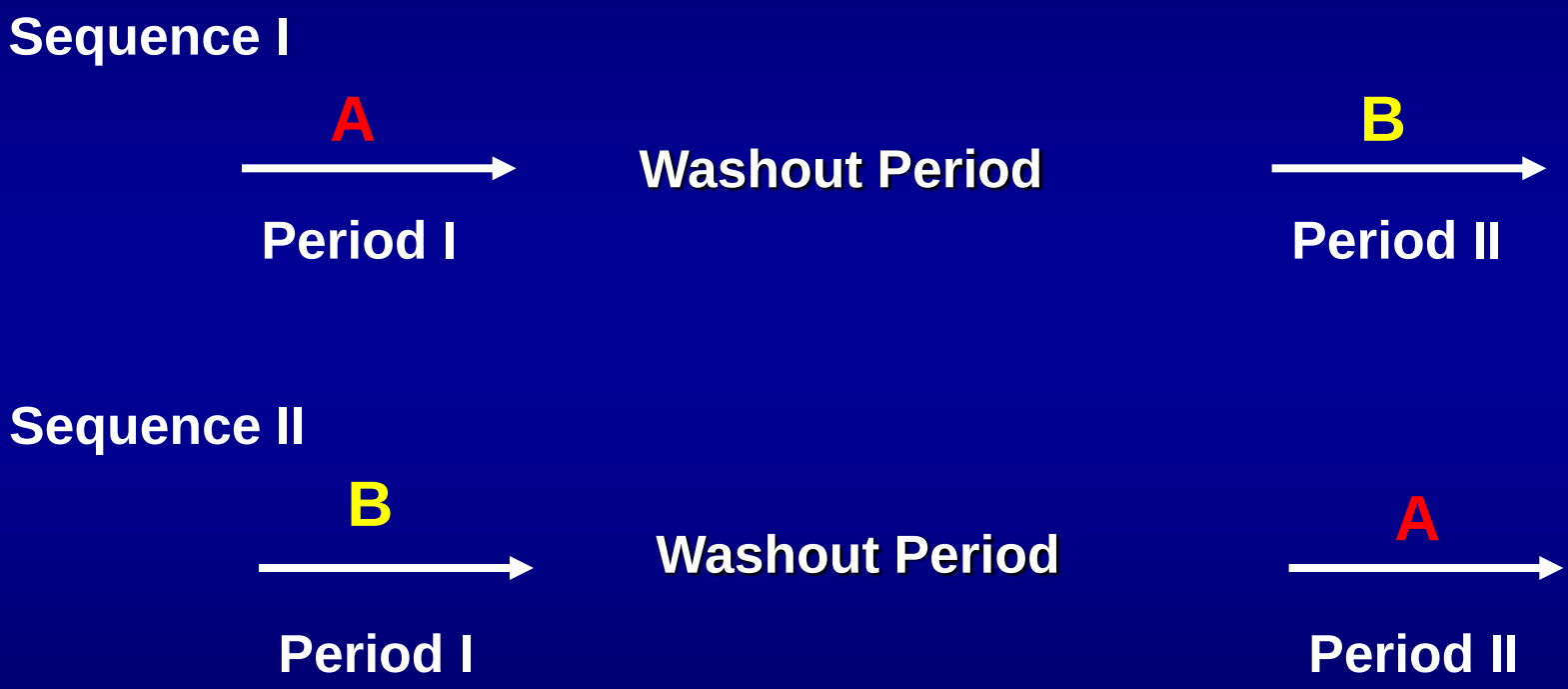


Components of an in vivo BE Study

- Human study
- Bioanalytical
- Statistical

Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration, March 2003

Study Design:
2-way Single Dose Crossover



A = Test Drug

B = Reference Listed Drug (RLD)

Study Design: Alternatives

- Parallel design single-dose
  - Long half-life drugs
- Replicate design single-dose
  - Highly variable drugs

PK Study Populations

- 18 years or older, healthy subjects from general population
- Why healthy subject but not patient?
  - 1). The physical processes of drug absorption are usually the same in patients as they are in healthy subjects. Healthy subjects can adequately characterize any difference in formulations
  - 2). Certain factors in patients may confound BE determination

Patients are used only when the drug is not safe to administer to healthy subjects

Single Dose vs. Multiple Dose Study Designs

- Single-Dose Design
  - Single-dose studies almost always are more sensitive
- Multiple-Dose Design
  - Multiple doses on healthy subject: safety concern
  - Multiple-dose study design is only recommended in patients who are already receiving a stable dose

PK Study Conditions

- Generally, both Fasting and Fed studies are recommended
- Fed study may be exempted under the following conditions for IR product:
  - 1). If the RLD label recommends the product to be taken on empty stomach ONLY: no fed study is needed
  - 2). If the drug product belongs to Biopharmaceutics Classification System I (BCS I) drug, BE studies may be waived (biowaiver)
- MR Product: Both fasting and fed BE studies are recommended
- Occasionally, sprinkle study is recommended if the RLD label instructed that the drug be taken in sprinkled vehicle

Parent vs. Metabolite

- Measurement of parent drug is generally recommended because the parent drug is more sensitive to the change in formulation
- Metabolite is measured under the following two circumstances:
  - 1). Parent drug levels are too low to measure:
    - BE on data of metabolite
  - 2). Metabolite formed through pre-systemic metabolism + contributing meaningfully to the safety and efficacy of the drug product:
    - measure both parent and metabolite
    - BE on data of parent
    - metabolite data as supportive evidence

Components of in vivo BE Study

- Human Study
- Bioanalytical
- Statistical

Bioanalytical Study Considerations

- Pre-study Method Validation
  - Precision and Accuracy
  - Linearity
  - Limit of Quantitation (LOQ)
  - Stability
  - Selectivity
- Within Study Sample Analysis:
  - Detailed raw data
  - Within study validation
  - Reassay

Reassay is an issue!

- All reassay samples should be reassayed per an SOP that is established prior to sample analysis
- The SOP should have objective criteria for identifying samples to be reassayed
- The SOP should have objective criteria for the reporting of the reassay values

Guidance for Industry: Bioanalytical Method Validation (Revised), Sept, 2013

We suspect PK repeats (which we discourage) when we see the following

- "Anomalous values"
- "Unassignable cause"
- "Incongruous values"
- "Sample reanalyzed to obtain confirming value"
- "High value between two low values"
- "Low value between two high values"

Components of in vivo BE Study

- Human Study
- Bioanalytical
- Statistical

Data Analysis

- Significantly different level is **20%**

  Two One-sided Tests Procedure:

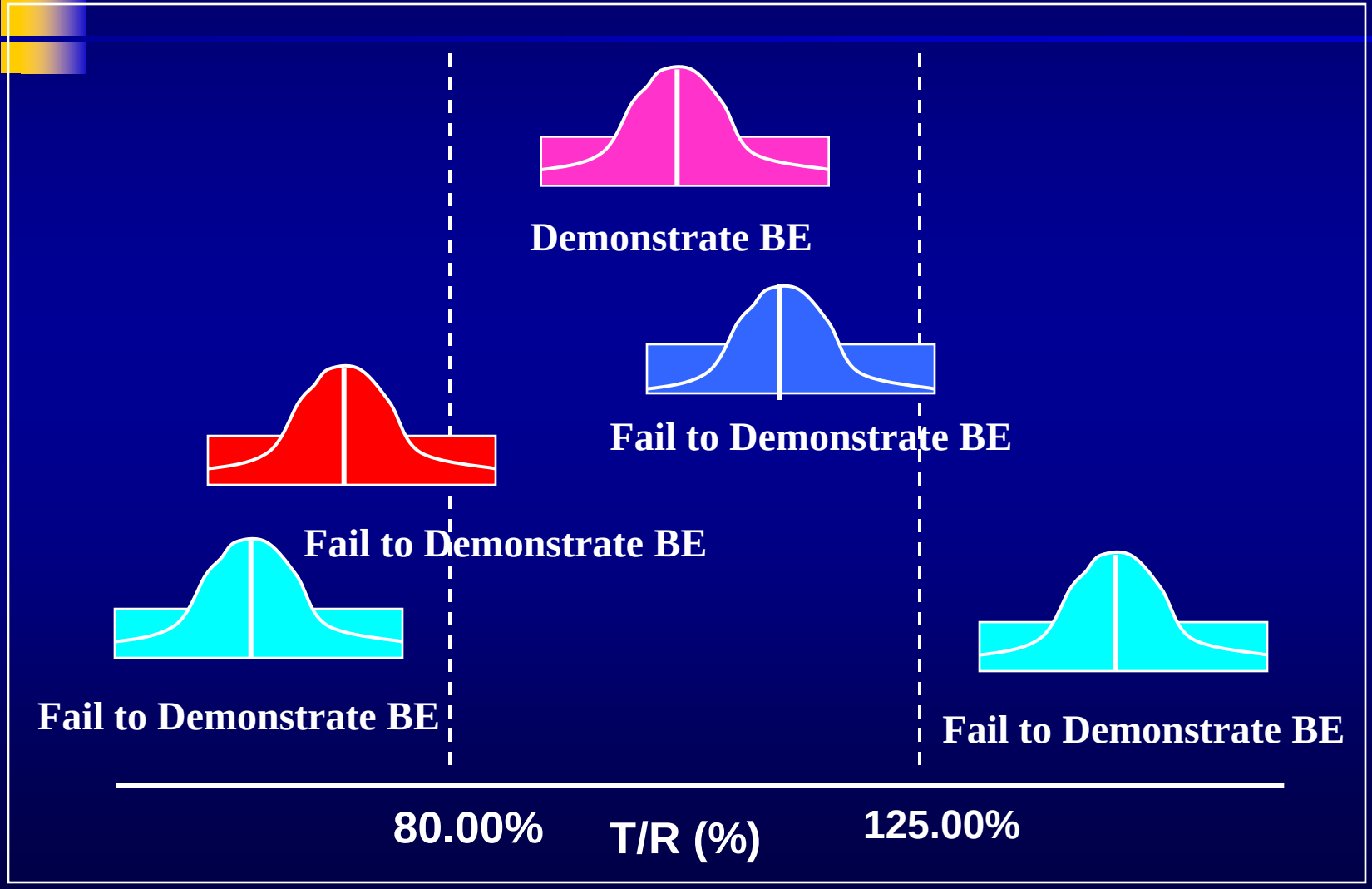
  - (1) Test (T) is not significantly less than Ref (R)
    - 90% Confidence interval on T/R > 80%
  - (2) Ref is not significantly less than Test
    - 90% Confidence interval on R/T > 80%
    - or 90% Confidence interval on T/R < 125%

- Bioequivalence acceptance criteria:

  90% Confidence Interval (CI) is **80.00-125.00%** for ratio of the test/reference of three PK parameters $LnAUC_t$, $LnAUC_{inf}$, and LnC_{max}

Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001

Possible Outcome of BE Studies



Example of Data Output

Drug A Tablets Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 12345				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng.hr/ml)	6926.21	7073.05	**0.98**	**88.52-108.32**
AUC∞ (ng.hr/ml)	7272.94	7442.56	**0.98**	**88.79-107.55**
Cmax (ng/ml)	1014.78	1067.66	**0.95**	**87.18-103.62**

Can *in vivo* bioequivalence study be waived?

Yes!

Waivers of BE Study

1. The BE study can be waived for the drug products when their in vivo bioequivalence is self-evident

This waiver assumes that release of the drug substance from the drug product is self-evident

- Solutions: Oral/Parenteral/Inhalation/Topical
- Excipients in formulation do not affect the drug absorption

Waivers of BE Study

2. Waivers can be granted for the different strengths of the same product

Example:

- BE is demonstrated on the highest strength product
- The highest strength and lower strengths are proportionally similar in their formulations
- All strength products demonstrate acceptable and comparable dissolution

Example of Formulation Proportionality

Components	150 mg/tab (% w/w)	300 mg/tab (% w/w)
Active ingredient	150.0 (71.94%)	300.0 (71.94%)
Corn Starch, NF	15.0 (7.19%)	30.0 (7.19%)
Alginic Acid, NF	20.0 (9.59%)	40.0 (9.59%)
Ethyl Cellulose, NF	8.0 (3.84%)	16.0 (3.84%)
Microcrystalline Cellulose, NF (Avicel PH-102)	12.5 (6.00%)	25.0 (6.00%)
Sodium Lauryl Sulfate, NF	0.5 (0.24%)	1.0 (0.24%)
Magnesium Stearate, NF	2.5 (1.20%)	5.0 (1.20%)
Tablet tablet Weight (mg)	208.5	417.0

Waivers of BE Study

3. Waivers based on Biopharmaceutics Classification System (BCS)

What is the BCS?

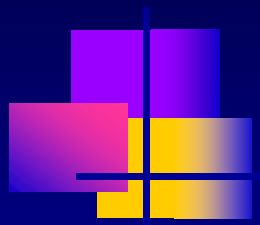
- The BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability

Biopharmaceutics Class	***Solubility***	***Permeability***
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies For Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification system, August, 2000

BCS Biowaiver

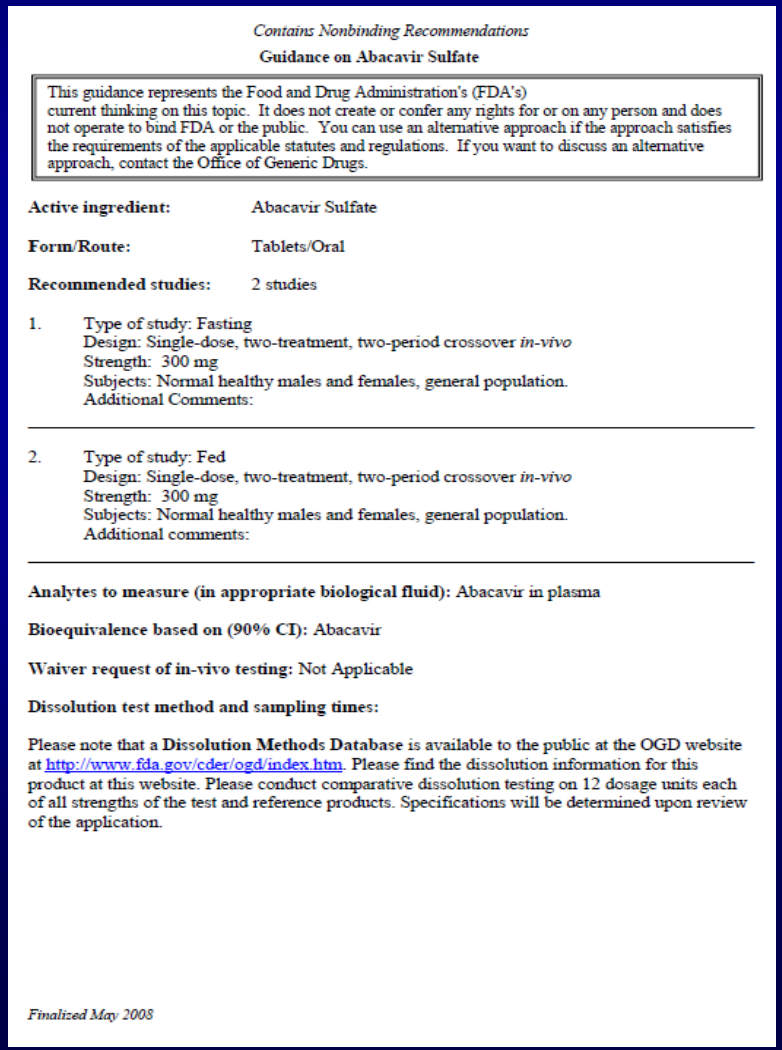
- Drug substance is highly soluble and highly permeable (BCS 1) and is stable in the gastrointestinal tract
- The drug is not considered have a narrow therapeutic range
- Test and Reference products are pharmaceutically equivalent
- Test product exhibits rapid dissolution profile (>85% in 30 min)
- Excipients used in test product are not likely to effect drug absorption



References and Database

Product-Specific Recommendations for Generic Drug Development

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Total count 1277 as of April 2015
- First source for BE study



Contains Nonbinding Recommendations

Guidance on Abacavir Sulfate

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Abacavir Sulfate

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 300 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments:

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 300 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments:

Analytes to measure (in appropriate biological fluid): Abacavir in plasma

Bioequivalence based on (90% CI): Abacavir

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Finalized May 2008

Common Technical Document Summary Tables

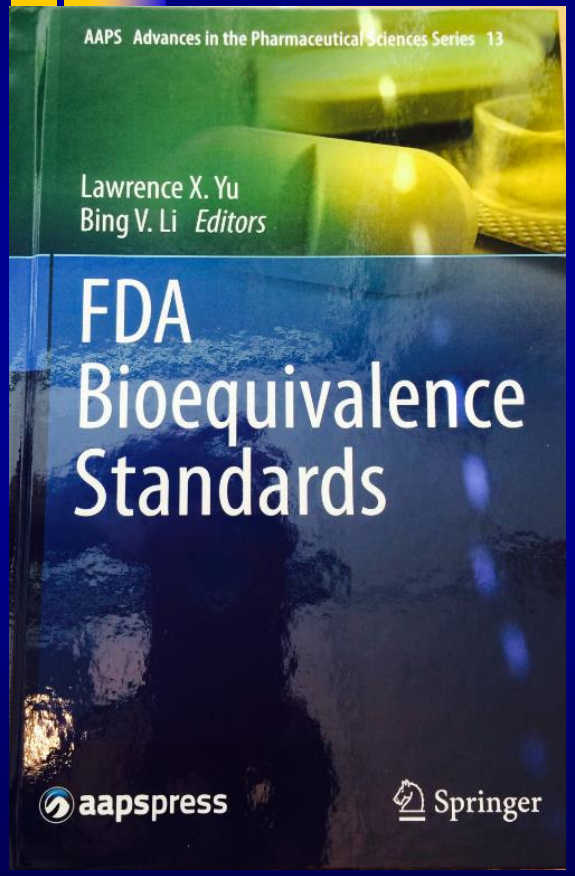
- http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm120955.htm
- These summary tables provide a standard format for data to be submitted to the Office of Generic Drugs in a concise format consistent with current recommendations.

Example:

Table 2 Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (units/mL)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T1/2 (hr)	Kel (hr-1)	
Study #	Fasting study title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range) Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#
Study #	Fed study title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range) Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#

FDA Bioequivalence Standards



- Springer 2014
- AAPS Advances in the Pharmaceutical Sciences Series
- Features a comprehensive selection: 16 chapters of the most current regulatory sciences in the bioequivalence area
- FDA scientists who themselves develop regulatory policies and conduct regulatory assessment of bioequivalence studies contributed all of the chapters