

# **BA/BE Inspections and Surveillance**

Arindam Dasgupta, Ph.D.

Deputy Director

Division of New Drugs Bioequivalence Evaluation

Office of Study Integrity and Surveillance

Center for Drug Evaluation and Research

FDA SMALL BUSINESS AND Industry ASSISTANCE

REdI Conference

**September 27 & 28, 2016**



# Disclaimer

**The opinions and information in this presentation are those of the author, and do not necessarily represent the views and/or policies of the U.S. Food and Drug Administration.**

# Agenda

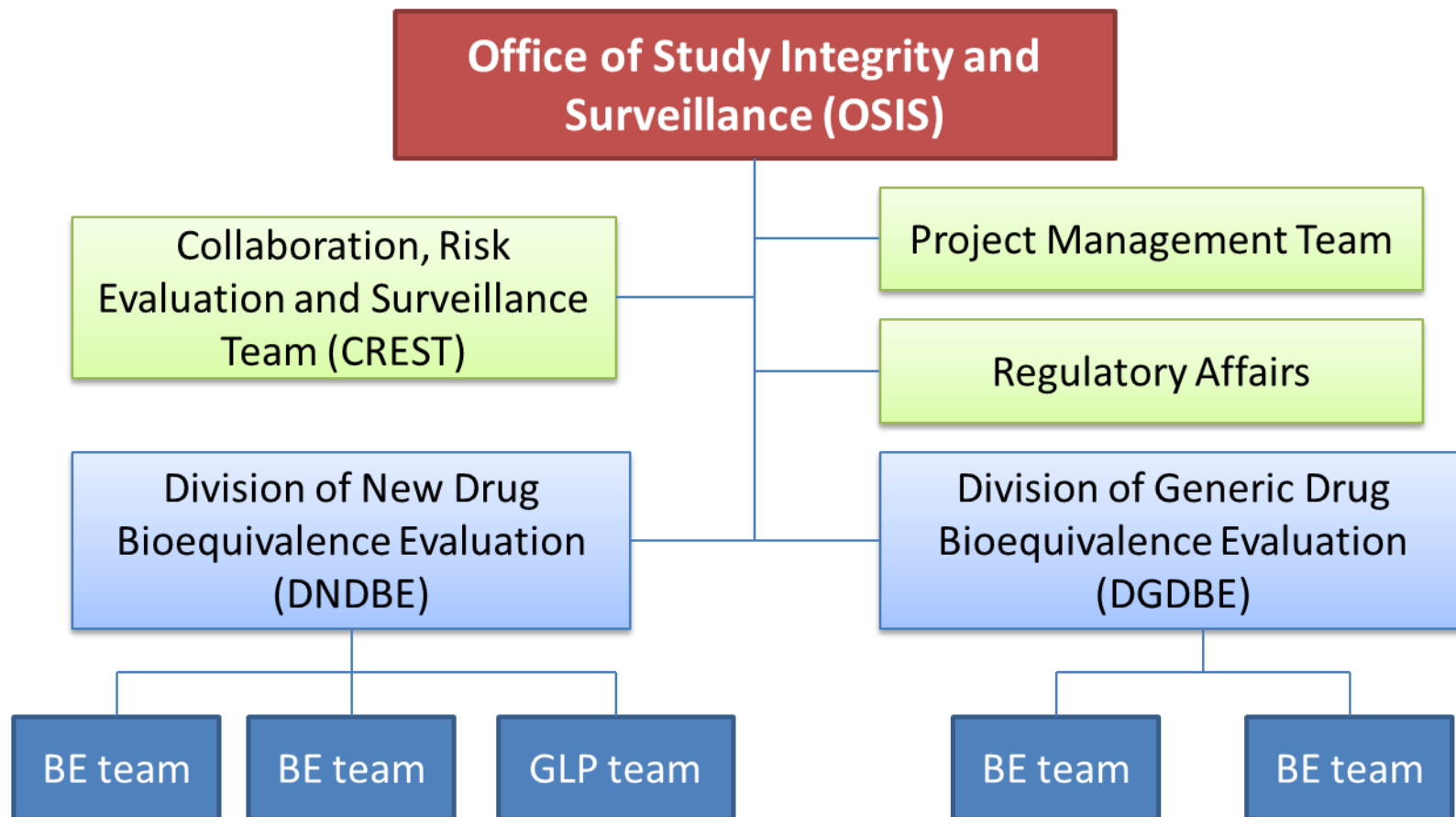
- I. Bioresearch Monitoring Program
- II. OSIS structure and roles
- III. Bioavailability/bioequivalence
- IV. Clinical inspections
  - PK endpoint and clinical endpoint studies
  - Blinding codes
  - Reserve samples
- IV. Analytical Inspections
  - Method validation
  - Study sample analysis



## **FDA's Bioresearch Monitoring Program (BIMO)**

- Comprehensive program of inspections and audits of FDA regulated research
- Assures the quality and integrity of data submitted to FDA
- Protects the human research subjects
- Critical preapproval process for new U.S. products

# OSIS Structure





# Roles of OSIS and OSI under BIMO

## OSIS

- Office of Study Integrity and Surveillance (OSIS) originated from OSI
- **Coordinates and conducts inspections** of bioavailability/bioequivalence and Good Laboratory Practice (GLP) programs
- **Conducts Scientific Reviews** of studies submitted to FDA in support of drug applications.
- **Ensures** data integrity in these drug applications.
- Outreach

## OSI

- Office of Scientific Investigations (OSI)
- **Enforces FDA regulations** (DEPS/CEB) and **Policy** (IO/Policy Staff) for GCP, BA/BE, and GLP programs.
- **Collaborates** with OSIS to evaluate inspectional outcomes and proposes regulatory actions.

# How many of you heard and have an understanding of BA/BE studies?

- Never heard of it before
- Basic understanding
- Intermediate understanding
- Expert

# What is Covered under BIMO?

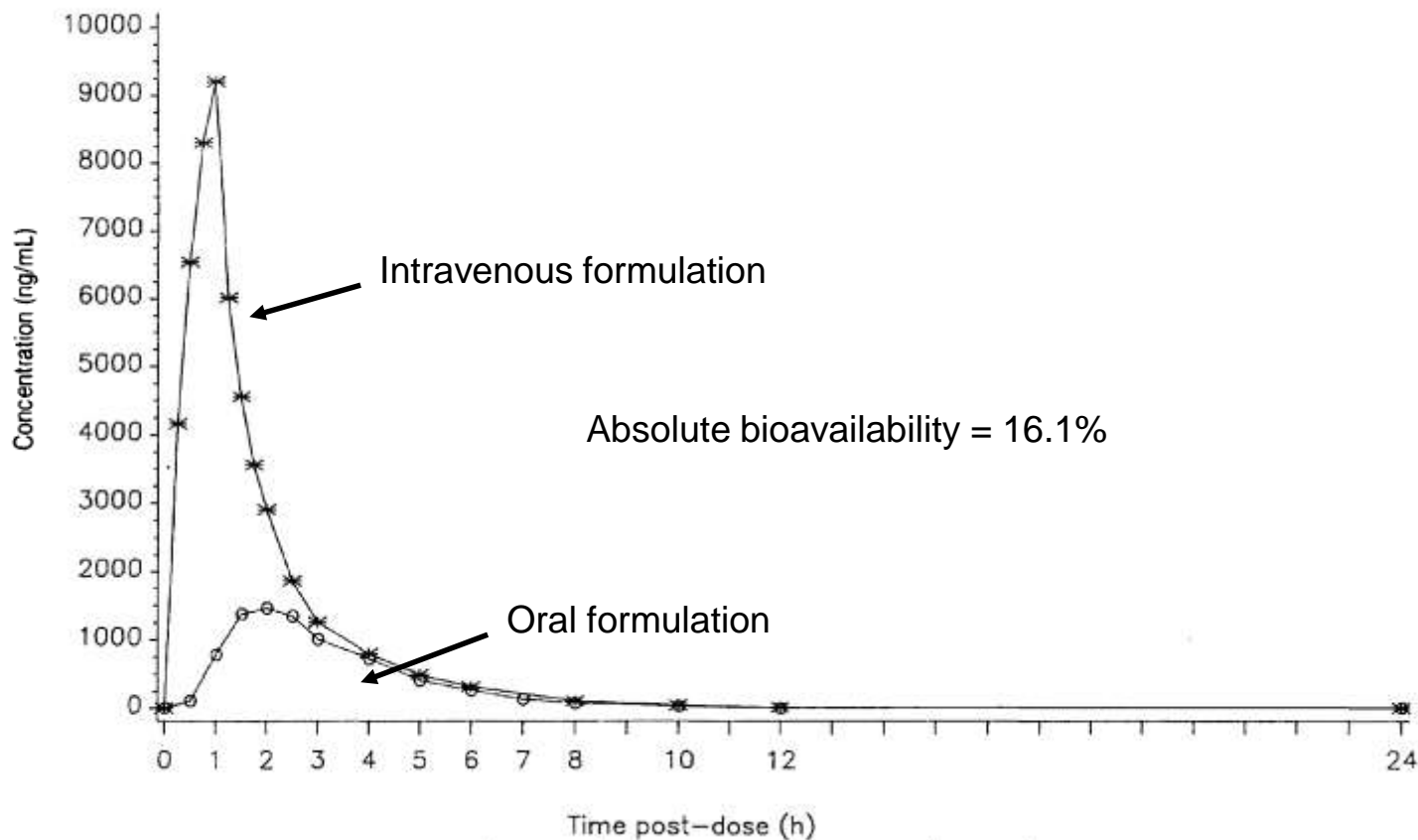
- Bioavailability (BA) and Bioequivalence (BE) studies submitted in support of:
  - New Drug Applications (NDAs)
  - Abbreviated New Drug Applications (ANDAs)
  - Biologic Licensing Applications (BLAs)



# What it is Bioavailability?

- From a regulatory perspective under 21 CFR 320.1(a):
  - **Bioavailability** is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
  - BA estimates the relative fraction of an orally administered dose that is absorbed into the systemic circulation compared to a reference material (i.e., solution, suspension, or intravenous dosage form).

# Absolute Bioavailability



# What is Bioequivalence?

- From a regulatory perspective under 21 CFR 320.1(e):
  - **Bioequivalence** is defined as 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 administered at the same molar dose under similar conditions in an appropriately

**Pharmaceutical equivalent** - same active ingredient, same dosage form, same route of administration, and identical in strength or concentration.

**Pharmaceutical alternative** - same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths.

# Determination of Bioequivalence

- Commonly rely upon the concentration of active moiety in the systemic circulation to demonstrate BE
- Two products are considered bioequivalent if similar concentration-time profiles are achieved for the same dose

# BE Study Endpoints

# BE Study Endpoints

- Bioequivalence can be demonstrated in ways other than comparing the concentration of the active moiety in a biological fluid.
- Common BE endpoints include:
  - Pharmacokinetic (PK) endpoint based on blood, plasma or serum.
  - PK endpoint based on urinary excretion.
  - Pharmacodynamic (PD) endpoint.
  - Clinical endpoint.

# BE Study Endpoints (1)\*

- PK endpoint based on blood, plasma or serum
  - In vivo test in humans in which the concentration of the active moiety in whole blood, plasma, serum or other appropriate biological fluid is measured as a function of time [21 CFR 320.24(b)(1)(i)].

\*In decreasing order of accuracy, sensitivity, and reproducibility

## BE Study Endpoints (2)

- PK endpoint based on urinary excretion
  - In vivo test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time [21 CFR 320.24(b)(2)].
  - Not appropriate if urinary excretion is not a significant mechanism of elimination.



# BE Study Endpoints (3)

- PD endpoint
  - In vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility [21 CFR 320.24(b)(3)].
  - May apply to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution and has an acute pharmacologic effect.

# BE Study Endpoints (4)

- Clinical endpoint
  - Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence [21 CFR 320.24(b)(4)].
  - May apply to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

# BE Study Designs

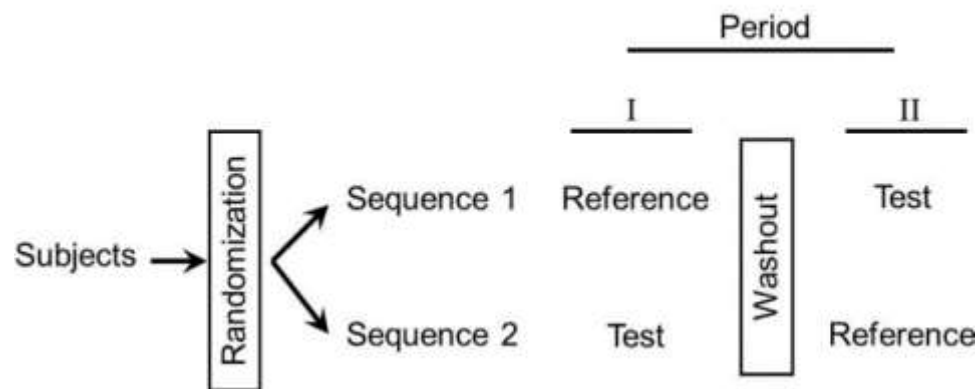
# General Considerations

- Population
  - Normal healthy subjects (n=18-36)
    - # of subjects enrolled depends on drug variability (↑ variability = ↑ subject enrollment).
  - Subjects with the target disease
    - If drug has considerable toxicities.
- Fed/fasted state
  - If food affects drug absorption.
- Single dose vs. multiple dose
  - Single dose most sensitive to detect differences in formulations.
  - Multiple dose if comparison at steady state is necessary.

# Common Study Design

- Single-dose, randomized, crossover, open-label, fasted state
  - Each subject receives Test and Reference products in separate dosing periods.
  - Length of time between dosing periods (washout) depends on elimination half life of the drug.
  - Subjects/investigator are generally not blinded to treatment allocation
  - Assignment to dose sequence is random

## Standard 2×2 Crossover design



Note: Other designs including parallel are also possible.

# Clinical Endpoint Studies

- Typically include clinical portions only.
  - Subjects are dosed with Test and Reference drug products, pharmacodynamic evaluations are conducted before and after drug dosing.
- Clinical portions are usually conducted at the same facility.

# Clinical Endpoint Studies

- Pharmacodynamic (PD) assessments
  - Drugs not intended for systemic absorption, or measurement in the blood is not feasible
  - Usually blood samples are not collected
  - Examples:
    - Albuterol inhaler on bronchodilation (PD endpoint)
    - Anti-infective cream on impetigo (clinical endpoint)
  - Usually double-blinded design

# PK Endpoint Studies

- Usually include clinical and analytical portions
  - Clinical portion
    - Subjects are dosed with Test and Reference drug products, blood samples are collected.
  - Analytical portion
    - Blood samples are analyzed for drug concentration using pre-defined criteria.
  - Both portions may be conducted at the same facility or different facilities

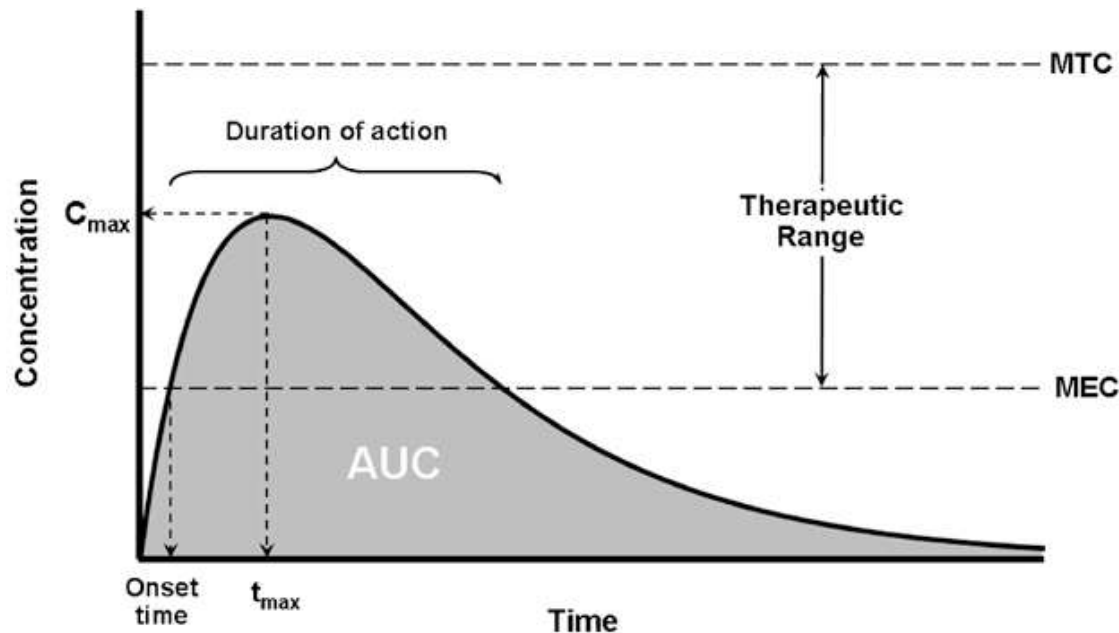


# PK Endpoint Studies (cont.)

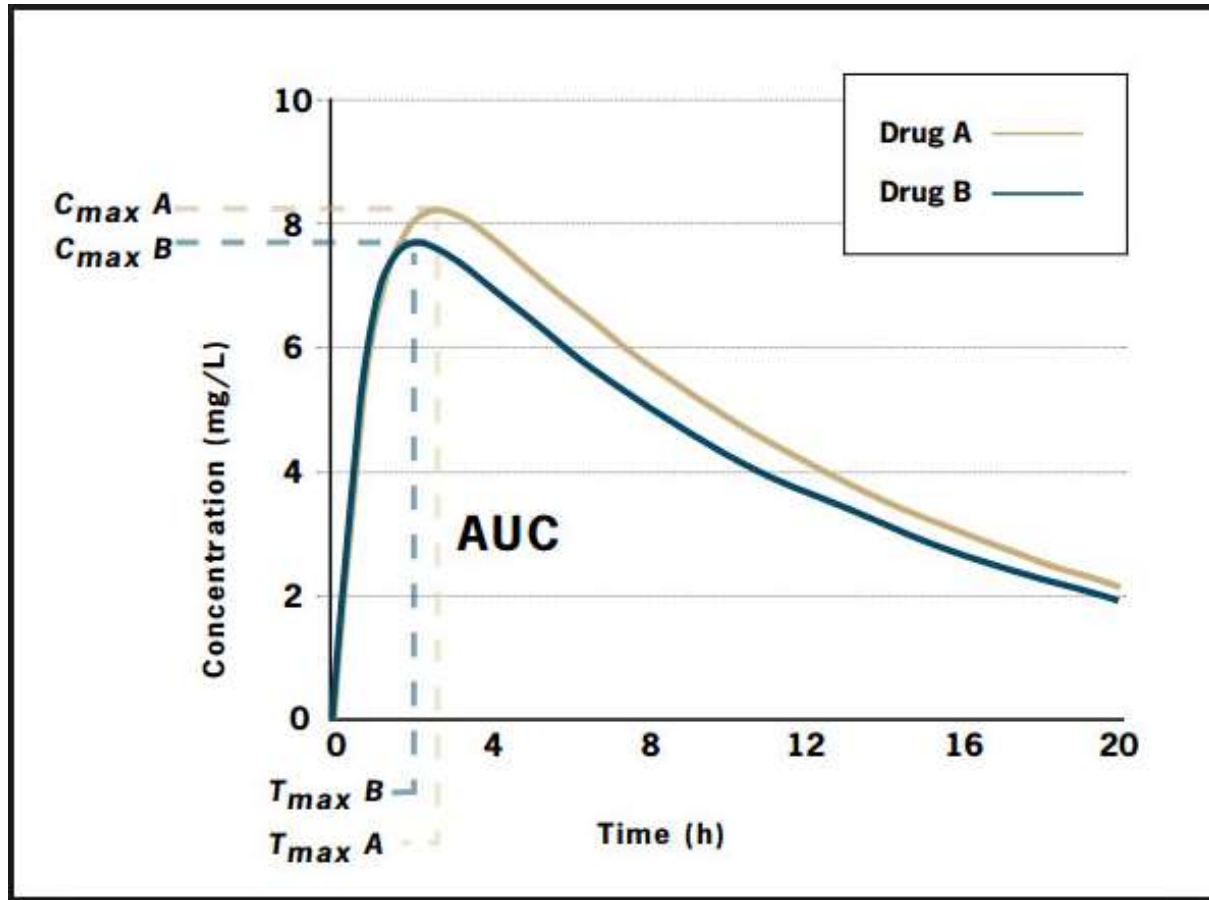
- Serial samples of a biologic fluid (plasma, serum, urine) are collected from subjects just before and at various times after dosing.
- The samples are analyzed for drug and/or active metabolite concentrations.
- The concentration data are used to generate a drug concentrations-time profile (i.e., a systemic exposure profile).

# Concentration-Time Profile

- Area under the concentration curve (AUC):
  - The extent of exposure following drug administration.
- Peak drug concentration ( $C_{max}$ ):
  - The highest concentration achieved following drug administration.



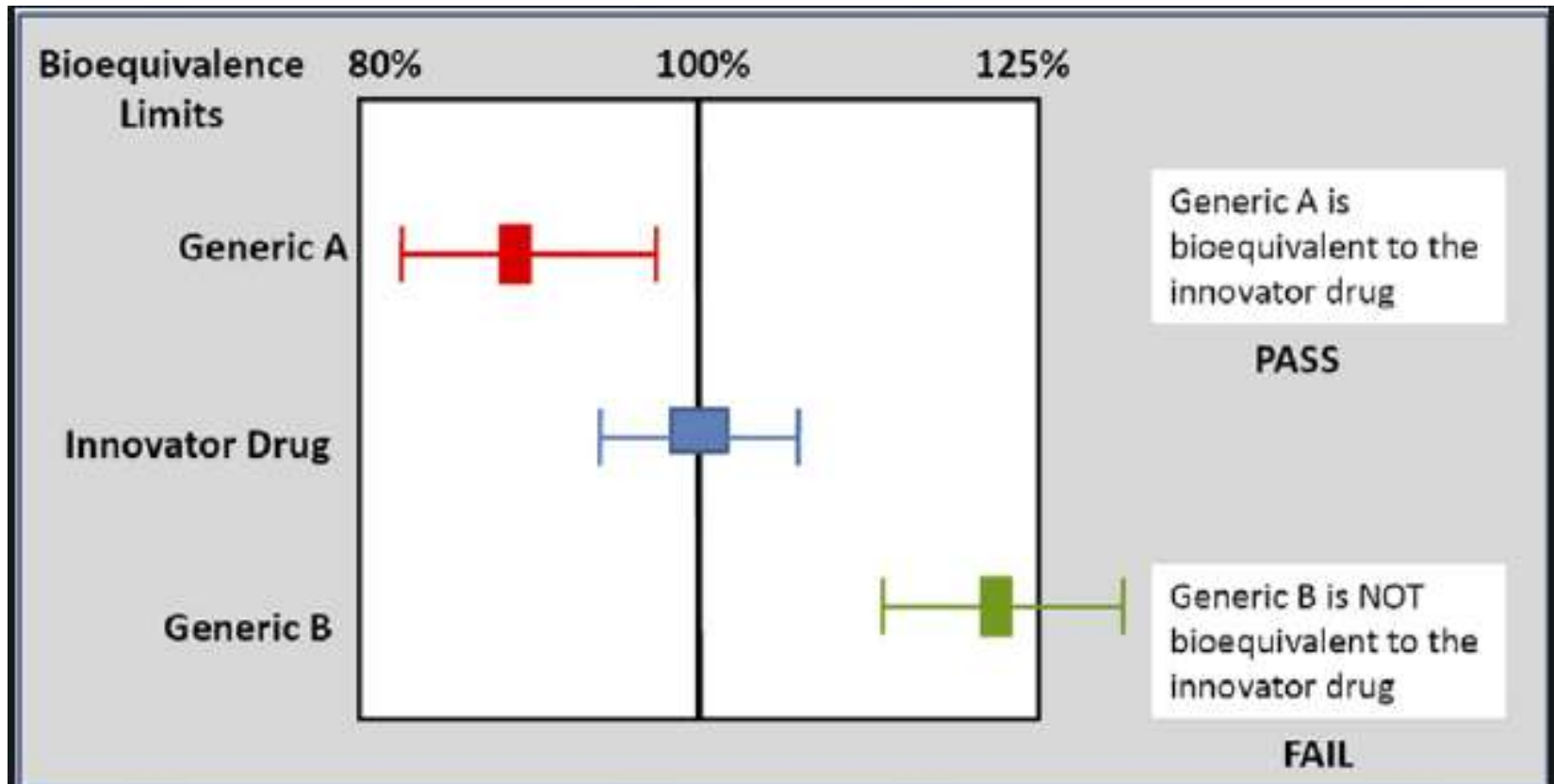
# Example of Bioequivalent Drug Profiles



# How is BE Determined?

- For PK endpoint:
  - Cmax and AUC undergo statistical analysis to determine if PK endpoints demonstrate bioequivalence.
  - Test and Reference products are considered bioequivalent when the 90% CI of the geometric mean ratios (T/R) of Cmax and AUC are within 80% to 125% (0.80 to 1.25).
- For PD endpoint:
  - Percent change from baseline observed with test vs. reference vs. placebo

# How is BE Determined?



# When is a BE Study Necessary?

- For NDAs:
  - When the to-be-marketed formulation is different than the formulation used in Phase 3 clinical trials to support safety and efficacy.
  - When changes are made to the marketed formulation (tablet already approved, sponsor wants to market a capsule, suspension, or extended release formulation).

# When is a BE Study Necessary?

- For ANDAs
  - Compares the generic versus reference formulations.
  - If the concentration of the drug in the biological fluid is the same, it is assumed that the generic formulation will demonstrate the same safety and efficacy as the innovator product.

# **OSIS INSPECTIONS**



# Goal of Inspections

- Evaluate BA/BE data submitted to ANDAs, NDAs, BLA applications
  - Study conduct, documentation
- Ensure data Integrity
  - Verify records on-site vs. submissions to FDA
  - Evaluate scientific rigor in bioanalytical measurement of drug concentrations
  - Identify deficiencies impacting study quality, subject protection
  - Assess overall quality of the work and the firm's compliance to FDA's expectations (under surveillance approach)
- Verify corrective actions from previous deficiencies
- Conduct outreach – Regulations and guidance

# Inspection Process

- Opening meeting
  - Introductions
  - Credentials
  - Announcement of studies/scope
- Facility tour
  - Laboratories, instruments
- Data audit
  - Paper and electronic records
  - Instrument/IT Systems/Personnel/Reserve samples
  - Staff interviews
- Close-out meeting
  - Issuance of Form FDA 483 (Inspectional Observations), if needed
  - Discussion items

# Form FDA 483



- FDA investigator discusses inspectional findings with the firm's management.
- If in the investigator's judgment findings are considerable and significant, he or she may issue Form FDA 483, "Inspectional Observations."
- The inspected firm may voluntarily respond to Form FDA 483 within 15 business days of its issuance.

<http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm237624.htm>

# Form FDA 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER [REDACTED]		DATE(S) OF INSPECTION March 12-18, 2015	
Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>		FEI NUMBER [REDACTED]	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: [REDACTED]			
FIRM NAME [REDACTED]		STREET ADDRESS [REDACTED]	
CITY, STATE AND ZIP CODE [REDACTED]		TYPE OF ESTABLISHMENT INSPECTED Contract Research Organization	
<p>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE, IF YOU HAVE ANY QUESTIONS. PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</p> <p>DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:</p> <p>The observation was made during the inspection of the following bioanalytical studies and associated method validations: [REDACTED] and [REDACTED] and [REDACTED]</p> <p>1. Freeze-thaw, bench-top and extract stability stability evaluations of [REDACTED] and [REDACTED] in plasma in [REDACTED] study [REDACTED] were not performed using freshly prepared calibrators and/or QCs.</p> <p>2. Not all aspects of study conduct were adequately documented to allow complete study reconstruction. Specifically:</p> <p>a. Thawing of [REDACTED] samples in ice-water bath during sample processing for method validation study [REDACTED]</p> <p>b. Verification that sample processing started within 1 hour of withdrawal of samples from freezer for [REDACTED] and [REDACTED] for method validation study [REDACTED]</p> <p>c. During stability evaluations for [REDACTED] and [REDACTED] [REDACTED] sample processing sheets did not document the preparation of fresh calibrators and/or QCs.</p>			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE [REDACTED]	EMPLOYEE(S) NAME AND TITLE (Print or Type) [REDACTED]	DATE ISSUED March 18, 2015

# Changes to the BE Inspection Program

- FDASIA (Food and Drug Administration Safety and Innovation Act)
  - expands FDA's authority and strengthens the agency's ability to safeguard and advance public health
  - Includes user fee programs PDUFA V, GDUFA (Generics), and BSUFA (Biosimilars)

Reference:

<http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FDASIA/ucm20027187.htm>

# **Clinical and analytical Site Inspections**

# Clinical Site Inspections

- Inspections cover:
  - Education, training, and experience of principal investigator and staff
  - Adequacy of facilities
  - Subject safety
  - Informed Consent
  - Case Report Forms
  - Dosing
  - Drug product accountability & storage
  - Biological sample collection, processing, and storage
  - Adverse events
  - Protocol adherence
  - Correspondence with sponsors/monitors
  - Reserve samples
  - Sealed blinding code (if double blind)
  - Randomization

# How many of you heard and have an understanding about reserve samples for BE studies?

- Never heard of it before
- Basic understanding
- Intermediate understanding
- Expert and know the regulations and guidance related to it





# Reserve Samples for BE Studies

- Required under 21 CFR 320.38 and 320.63, which allows FDA to detect and deter fraud in BE studies.
- FDA has authority to collect reserves.
- Reserve samples are representative of the actual drug products used in the study.
- Randomly selected and retained by clinical site, and **NOT** by the sponsor, packager, manufacturer or study monitor.
- Sufficient quantity to permit FDA to perform 5X all of the release tests.
- Retained from each shipment.

# Reserve Samples (cont.)

- Multisite study-reserves retained across all sites
- Maintained in original container and stored under condition prescribed in the label
- Access limited to authorized personnel
- Retained for at least 5 years following the date on which the application is approved, or if the application is not approved, at least 5 years following the completion of the study
- Stored at the clinical site or an independent third party (cannot be returned to sponsor)

# Blinding Codes

- Clinical site maintains a sealed code for blinded studies
- Identifies the administered treatment and reserve samples
- Retain blinding code from initial receipt until the inspection
- Blinding code should NOT be collected by the monitor or returned to the sponsor

# Analytical Site Inspections

- Inspections cover:
  - Education, training, and experience of principal investigator and staff
  - Adequacy of analytical site
  - Analytical method validation
  - Acceptance criteria during in-study validation
  - Receipt and storage of samples
  - Repeat analysis of samples
  - Equipment logs, SOPs
  - Correspondence with sponsors
  - Confirmation of data included in final study report
  - Reserve samples (for in vitro studies)

# Analytical Methods

- Small molecule drugs
  - High performance liquid chromatography
  - Mass spectrometry (LC-MS/MS, etc.)
  - Dry blood spots
- Large molecule drugs (usually biologics)
  - Enzyme-linked Immunosorbent Assay (ELISA, ECL, GyroLab)
  - Immunogenicity (anti-drug antibodies [ADA], neutralizing antibodies [NAbs])
  - Cut-points
  - Sensitivity and drug tolerance

# Questions?

**Please complete the session survey:**

**[surveymonkey.com/r/DRG-D1S4](https://surveymonkey.com/r/DRG-D1S4)**

# Final Thoughts

When we are auditing studies, we are essentially looking to reconstruct the study based on available documents/raw data.

So when you prepare for an FDA inspection, please be mindful of that.