

OSIS' Role in Conducting Inspections and Remote Regulatory Assessments (RRAs) of Abbreviated New Drug Application (ANDA) In Vitro Bioequivalent (BE) Studies

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Disclaimer

This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Learning Objectives



- Describe types of in vitro BE studies
- Describe the process Office of Study Integrity and Surveillance (OSIS) utilizes in conducting inspections and Remote Regulatory Assessments (RRAs) of sites that perform in vitro ANDA BE studies

What is an In vitro BE study?

§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.

(a) FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products.

In vivo test is preferred.....however

(b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

.....

(5) A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.

What is an in vitro BE study?

..... continued



- When mentioned in a Product Specific Guidance(PSG). PSG is a guidance which describes FDA's current thinking.
- When it supports a BE determination.
- When it allows biowaivers.
- When used as supportive information along with in vivo data.

Commonly Inspected in vitro BE Studies



- Bile Acids binding studies
- Phosphate binding studies
- Aerosols and spray product characterization testing
- In vitro permeation test
- In vitro release test

Who inspects the study conduct of In vitro BE tests



- In vitro test for pharmaceutical quality – Office of Inspections and Investigation (OI) and Office of Pharmaceutical Quality (OPQ)
- In vitro test for BE determination – OSIS
(Reserve sample provisions of 21 CFR Part 320 apply)

Over Arching Questions for In Vitro (BE) Studies



- Determine if the study submitted to the Agency was repeated with a new study number or amendment.
- If the study was outsourced, assess if the contract research organization was aware that the conducted in vitro studies are pivotal bioequivalence studies.
- Investigate whether the firm has drug accountability records for receipt, storage, and use of the test and RLD drug products used in the study.
- Document if the firm has a SOP for handling drug products (Test/Reference) used in the study.

Elements that may be reviewed by an investigator



- Determine the condition of samples received
- Verify sample accountability
- Review equipment used in the study
- Review method development summary

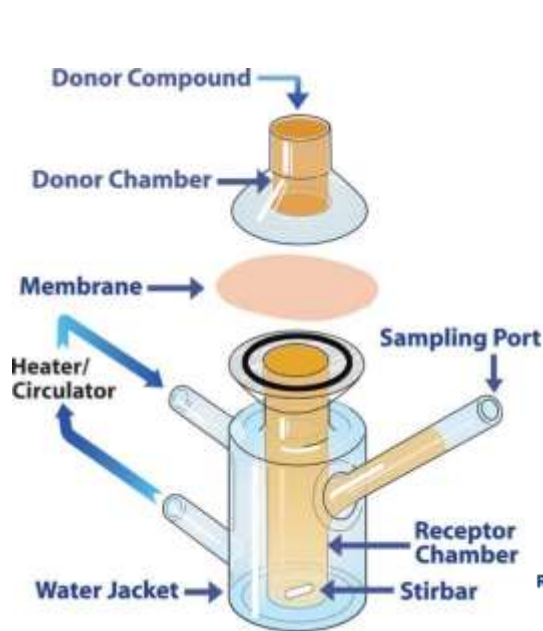
Elements that may be reviewed by an investigator..... ...continued

- Assess the adequacy of method validation used
- Verify the validation used is the same as that was submitted to the agency
- Review the results of sample analyses
- Document reserve samples were randomly selected, retained, and stored

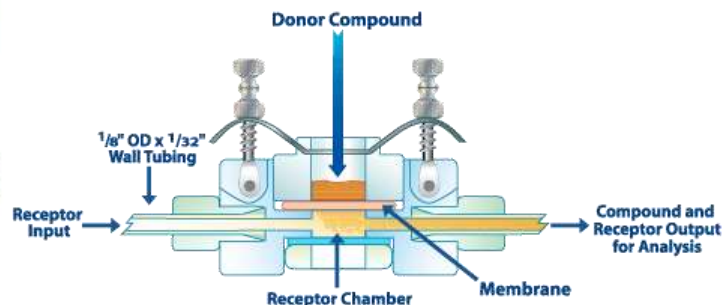
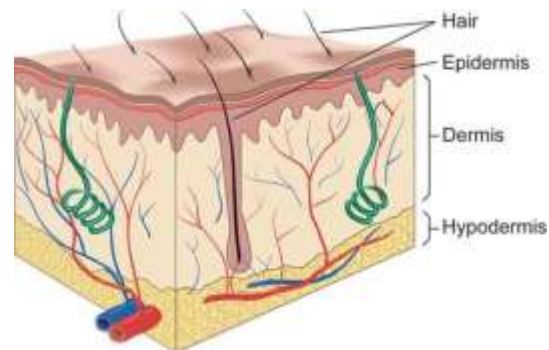
**OSIS Inspection strategy also depends on the
specific in vitro BE test**

**Example: In vitro permeation study
Franz Cell Diffusion Study**

In Vitro Permeation Test (IVPT)



Cell images courtesy of PermeGear



Inspection strategy also depends on the specific in vitro BE test: E.g., Franz Cell Diffusion Study

1. Verify that test and reference products tested on Franz diffusion cell system in a random or unbiased order.
2. Determine if a multi-station Franz diffusion cell system was used in the study, were both the test and reference samples tested in each run.
3. Document whether the same experimental conditions (membrane, filter, buffer, etc.) used in both method validation and IVRT sample testing.
4. Verify that an appropriate filter membrane adsorption study was performed during method validation.

Franz Cell Diffusion Study.....continued

5. Document if the samples were collected at time points specified in the protocol.
6. Verify that the stability data from method validation support the sample handling conditions during the study.
7. Assess whether the samples aliquot collected during testing stored under conditions according to protocol before sample analysis.

Franz Cell Diffusion Study.....continued

9. Determine if the recovery and mass-balance calculations were conducted in accordance with firm's established procedures.
10. Verify that each experiment was performed after adequate equilibration of diffusion cell.
11. Document whether the firm has an SOP for testing.
12. Assess if repeat testing conducted was justifiable.

Reserve Sample Retention for In Vitro BE Studies*



1. Document if the firm retained randomly selected and appropriately identified reserve samples of the test and reference drug products used to conduct in vitro BE studies.
2. Determine whether the firm retained adequate quantity of test and reference drug products as reserve samples.
3. Investigate if the firm stored the test and reference drug products in an area segregated from the area where testing was conducted.

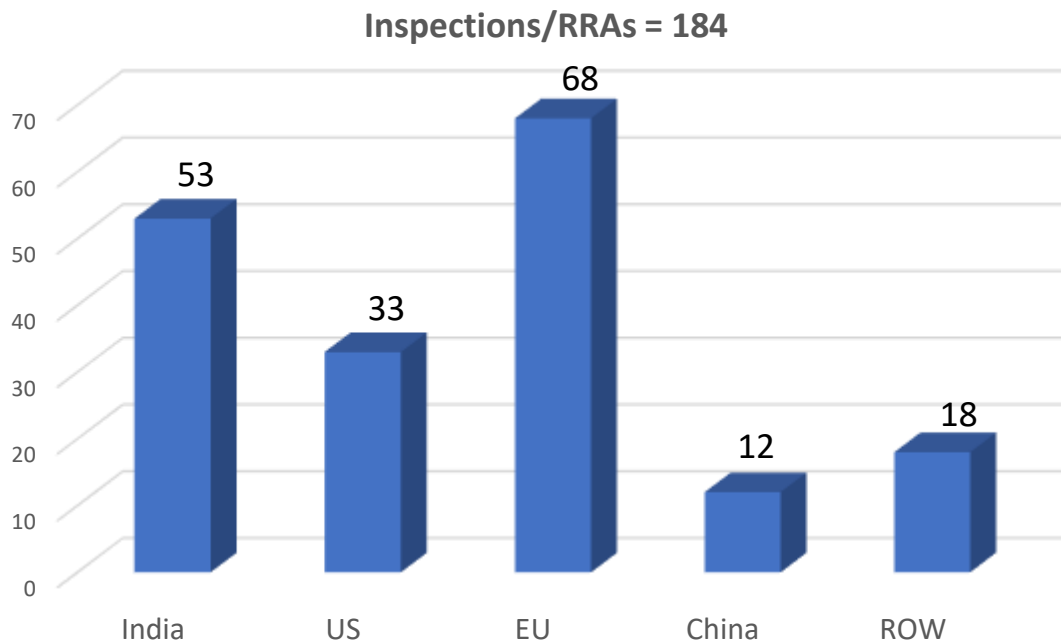
* 21 CFR 320.63 – Retention of bioequivalence samples (ANDAs)

Reserve Sample Retention...continued



4. Document if the firm stored the test and reference drug products under storage conditions consistent with product labeling.
5. Verify whether the firm stored the test and reference drug products in a secure and controlled environment with limited to authorized personnel.
6. Document if the reserve samples of test and reference drug products were stored in their original containers.
7. If the reserve samples were stored at a third-party site, investigate if they were independent from the applicant.

Distribution of Inspections and RRAs by Countries (2019-2024)



Top three in vitro BE tests inspected

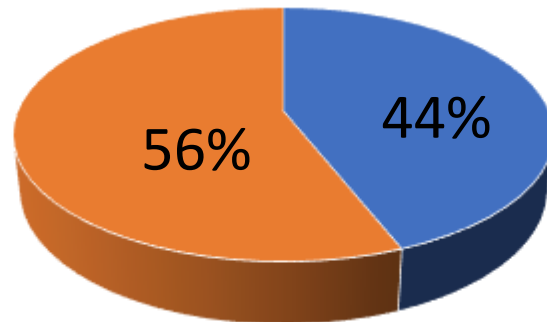


1. In vitro release/permeability
2. Equilibrium kinetic binding studies
3. Particle size distribution

Percent No Action Indicated (NAI) vs. non-NAI (2019-2024)



184 Inspections or RRA's Performed



■ Concerns ■ No Concerns

Includes observations and discussion items

Most frequent citation was reserve sample violation

Summary



The following topics were covered:

- Definition and types of in vitro BE studies
- Elements covered during inspection or RRA of a firm performing in vitro BE studies
- Elements covered specifically for in vitro BE test (Franz diffusion study)
- Reserve sample requirements

Challenge Questions



Challenge Question #1

Which FDA Office is responsible for inspecting the study conduct of in vitro BE studies?

- A. Office of Generic Drugs
- B. Office of Study Integrity and Surveillance
- C. Office of Pharmaceutical Quality
- D. None of the above

Challenge Question #2

What regulation contains the provisions for conducting in vitro BE study?

- A. 21 CFR Part 210
- B. 21 CFR Part 211
- C. 21 CFR Part 320
- D. All of the above

Closing Thought



We hope you can use the provided information to prepare your firm for an FDA inspection of ANDA in vitro BE studies.

Resources



- [Product-specific guidances for generic drug development](#)
- [21 CFR Part 320 – Bioavailability and Bioequivalence](#)
- [Handling and Retention of Bioavailability BA and Bioequivalence BE Testing Samples](#)

Thank you