An Overview of In Vitro BE Studies

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Learning Objectives

- Understand why an in vitro study may be used to establish bioequivalence (BE)
- Identify resources to aid with in vitro BE study selection and development
- Describe types of in vitro BE studies

21 CFR Part 320

21 CFR 320.24(a) - Bioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. **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.**

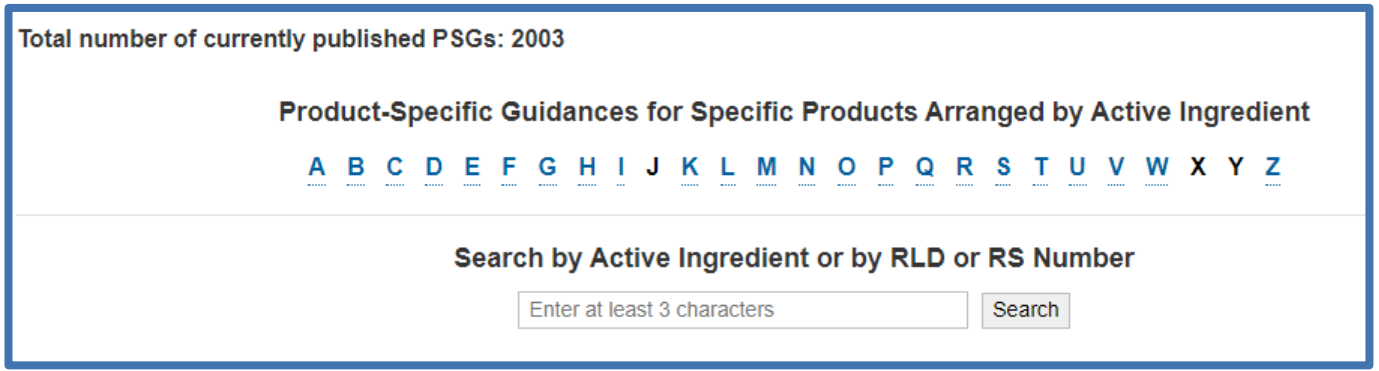
Why In Vitro?

- In vivo BE studies
  - Expensive
  - Time-consuming
- In vitro BE studies
  - Can reduce risk of harm
  - May be the best method to determine BE

Key Resources

Product-Specific Guidances (PSG)

- PSGs provide recommendations to support ANDA drug development
- Over 2000 PSGs available



Reference Standard

- Identify the appropriate reference listed drug (RLD) from the Orange Book
  - See also: Purple Book
- Can use a different reference standard in some cases

Types of In Vitro BE Studies

Common In Vitro BE Studies

- In vitro permeability testing (IVPT)
- In vitro release testing (IVRT)
- In vitro binding testing
- Size distribution studies
  - In vitro globule size distribution study
  - Particle size distribution/determination (PSD) study
  - In vitro liposome size distribution study
- In vitro aerosol studies (5- or 6-test battery)

Other In Vitro Studies

- In vitro dissolution testing for BE determination
- BCS dissolution testing
- BCS solubility testing
- BCS permeability testing
- In vitro NG/G tube study
- In vitro microbial kill rate study

BCS-based biowaiver

IVRT and IVPT

IVRT and IVPT

- Semi-solid topical dermatological drugs
  - In vitro BE approaches: IVRT and IVPT
  - In vivo BE approach: clinical endpoint
  - IVRT can be used for other formulations

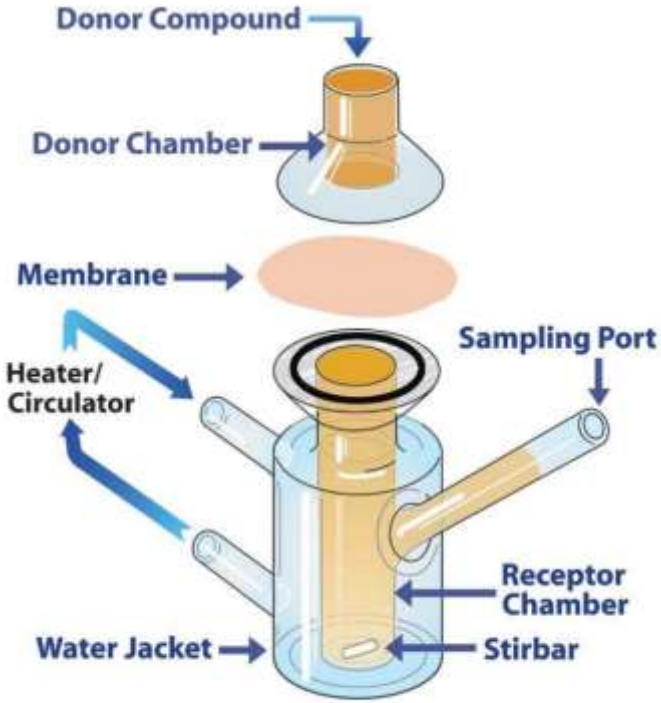


Image courtesy of PermeGear

IVRT and IVPT

IVRT

- Synthetic membrane
- Consistent
- Infinite dose
- Release rate
- Not expected to correlate or predict vivo BA/BE

IVPT

- Human skin
- Variable
- Finite dose
- Flux profile
- Expected to have in vitro-in vivo correlation

IVRT and IVPT

- Both
  - Method development
  - Method validation
- IVRT
  - Study
- IVPT
  - Pilot study
  - Pivotal study

A	B	A
B	A	B

B	A	B
A	B	A

IVRT and IVPT

- Example: acyclovir 5% topical cream
  - In vitro
    - Q1 and Q2 sameness
    - Q3 – physical and structural tests
    - IVRT **and** IVPT
  - In vivo
    - Clinical endpoint

IVRT and IVPT

- Resources
  - United States Pharmacopeia (USP) General Chapter <1724> , Semisolid Drug Products – Performance Tests
  - FDA/CRCG 2021 workshop
  - In Vitro Bioequivalence Data for a Topical Product: Bioequivalence Review Perspective (Dr. Suman Dandamudi, 2017)

In Vitro Binding Testing

In Vitro Binding Testing

- 21 CFR §320.23(b)(2)
- Phosphate or bile acid-binding drugs (GI)
- Equilibrium (pivotal) and kinetic testing
- Measure unbound analyte(s) in filtrate

In Vitro Binding Testing

Equilibrium

- ± acid pre-treatment*
- 8+ concentrations of phosphate/bile salts
- Incubate till equilibrium

Kinetic

- - or ± acid pre-treatment*
- 2 concentrations of phosphate/bile salts
- 8+ lengths of time

*For specific pH(s), please refer to the PSGs.

In Vitro Binding Testing

- Example: sucralfate oral suspension
  - Only in vitro recommended
    - Equilibrium binding study with bovine or human serum albumin
    - Equilibrium binding study with bile salts
    - Kinetic binding study with bile salts
    - In vitro enzyme (pepsin) activity study

In Vitro Aerosol Studies

In Vitro Aerosol Studies

Inhaled

1. Single actuation content (SAC)
2. Aerodynamic particle size distribution (APSD)
3. Spray pattern
4. Plume geometry
5. Priming and repriming

Nasal

1. SAC
2. Droplet size distribution by laser defraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Priming and repriming

Draft Guidance

In Vitro Aerosol Studies

- Both in vitro **and** in vivo commonly recommended
- Example: albuterol sulfate, aerosol, metered; inhalation
  - In vitro: 5-test battery for inhaled aerosols
  - In vivo: PK study

Size Distribution Studies

Size Distribution Studies

- Globule, particle, or liposome size distribution studies
- Help ensure uniformity and consistent dosing
- Different formulation types
- Varying methods

Size Distribution Studies

- Example: Cyclosporine ophthalmic emulsion
  - In vitro
    - Q1 and Q2 sameness
    - Q3 comparable
      - **Globule size distribution**, viscosity, pH, zeta potential, osmolality, surface tension
  - In vivo
    - Clinical endpoint
- Resource: Assessment of Complex Drug Product – Physicochemical Characteristics to Support In Vitro BE Studies (Dr. Asif Rasheed, 2020)

Challenge Questions

Challenge Question #1

Which of the following statements is NOT true?

A. Reference standards can be identified using the Yellow Book.

B. Acceptable study types are described in the product specific guidances.

C. If a reference listed drug is unavailable, FDA may select a new one to serve as a reference standard.

D. The Purple Book details licensed biological products.

Challenge Question #2

Which of the following are components of in vitro aerosol studies?

A. Single actuation content

B. Spray pattern

C. Plume geometry

D. All of the above

Summary

- In vitro BE studies
  - can be conducted with or instead of in vivo BE studies
  - can vary greatly and are highly dependent upon the drug and formulation

Closing Thought

Questions?

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