An Overview of In Vitro BE Studies

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Office of Study Integrity and Surveillance (OSIS) Workshop 2022 – July 19, 2022
Disclaimer

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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
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
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
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

PSGs
Questions?

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