Current Challenges and Opportunities in Demonstrating Bioequivalence

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Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products
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Outline

• Fundamentals of Bioequivalence (BE) Testing
• Relevance of Conventional (PK) Studies for Documentation of BE of Locally Acting Orally Inhaled Drug Products (OIDP)
• The Current Regulatory Paradigm for OIDP
• In Vitro Evaluations
• In Vivo Evaluations
• Dose Response - Impact on Determination of BE
• Waivers of In Vivo BE Testing
• In Vitro-In Vivo correlation
• Combination Products
Relevant Definitions

- **Pharmacokinetics (PK):** Absorption, distribution, metabolism & excretion (“What the body does to drugs”)

- **PK Endpoint:** A measure of systemic exposure

- **Pharmacodynamics (PD):** The study of biochemical and physiological effects of drugs and mechanisms of their action (“What drugs do to the body”)

- **PD Endpoint:** A measure of biological activity preferably correlated with clinical outcome

- **Clinical Endpoint:** A measure of clinical effectiveness
Fundamentals of Bioequivalence Testing

For Regulatory Submissions in the US
Relevant Regulations

• 21CFR Parts 314 & 320
  – 21 CFR 314.94 (a)(7)
    • Documentation of Bioequivalence
  – 21 CFR 314.94 (a)(8)
    • Comparative Product Labeling
  – 21 CFR 314.94 (a)(9)
    • Chemistry, Manufacturing, and Controls
  – 21 CFR 320.1 (e)
    • Definition of Bioequivalence
  – 21 CFR 320.24 (b)
    • Approaches to Establish Bioequivalence
  – 21 CFR 320.22 (b)
    • Criteria for Waiver of In vivo Bioequivalence Testing
  – 21 CFR 320.36
    • Maintenance of Records of Bioequivalence Testing
  – 21 CFR 320.63
    • Retention of Bioequivalence Samples
Relevant Regulatory Definitions

• **Pharmaceutical Equivalents:** Drug products *in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety*, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates [21 CFR 320.1(c)].

• **Pharmaceutical Alternatives:** Drug products that contain the identical therapeutic moiety, or its precursor, but *not necessarily in the same amount or dosage form or as the same salt or ester*. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates [21 CFR 320.1(d)].
Bioavailability (BA)

- 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 [21 CFR 320.1(a)].

- For systemically available drugs
  - Appearance in the blood of the parent drug/active moiety provides basis for determination of BA
  - May be influenced by
    - Drug substance's solubility, permeability, absorption and elimination properties
    - Formulation related effects

- For drug products that are not intended to be absorbed into the bloodstream, BA may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.1(a)].
Bioequivalence (BE)

The absence of a significant difference in the rate and extent to which the active ingredient or the active moiety in pharmaceutical equivalents or alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [21 CFR 320.1(e)]

• Approaches for Documentation of Bioequivalence
  [21 CFR 320.24 (b)]
  – In vivo studies in humans comparing drug/metabolite concentrations in an accessible biological fluid
  – In vivo testing in humans of an acute pharmacological effect (Pharmacodynamic effect studies)
  – Controlled clinical trials in humans to establish safety and efficacy
  – In vitro methods
  – Any other approach deemed adequate by FDA
Factors Affecting Clinical Response of Oral Products

Formulation

Clinical Response

Patient
Components of the BE Portion of ANDAs for Solid Oral Dosage Forms

• **Pharmaceutical Equivalence (Formulation)**
• **In Vivo Bioequivalence Study(ies)**
  – PK BE Studies [Fasting and Fed (where applicable)]
    • Analytical (Method validation and sample analysis)
    • Blood/Urine Concentration data
    • BA metrics data ($\text{AUC}_{0-t}$, $\text{AUC}_{0\text{-inf}}$, $\text{C}_{\text{max}}$)
    • Statistical Analysis
• **In Vitro Study(ies)**
  – In vitro dissolution or other studies based on validated methods
Basic PK BE Study

• Drug Products
  – Test (T) and Reference (R)

• Dose
  – Generally the highest approved strength, with exceptions

• Subjects
  – Healthy volunteers (Mix of Gender, Race ..)

• Study Design:
  – Randomized, two-treatment, two-period crossover or replicate (3 or 4 period)
2x2 Crossover Treatments
(T=Test R=Reference)

Healthy Volunteers
Period I

Still Healthy Volunteers
Period II

Washout
Plasma Concentration Profiles of Test and Reference Products (An Example)
PK BE Evaluation

• Metrics
  – AUC (AUC\textsubscript{0-t}, AUC\textsubscript{0-inf}) – Total Exposure
    • Area under plasma concentration vs. time curve
    • Represents extent of drug absorption
    • Trapezoidal rule for computation
  – C\textsubscript{max} – Peak Exposure
    • Single peak plasma concentration
    • Represents rate of drug absorption
PK BE Evaluation
(Statistical Analysis)

• Analysis of Variance (ANOVA)
  – Ln-transformed AUC$_{0-t}$, AUC$_{0-\text{inf}}$ and C$_{\text{max}}$ data
  – Subject, Treatment, Period, Sequence, Subject (Sequence) as factors in the ANOVA model

• 90% Confidence Intervals
  – Acceptable limits: 80.0-125.0%
  – Two one-sided tests procedure to determine
    • If T is significantly less bioavailable than R
    • If R is significantly less bioavailable than T
    • A significant difference defined as 20% at $\alpha = 0.05$
Relevance of PK Studies for Documentation of BE of Locally Acting Orally Inhaled Drug Products (OIDP)
Disposition of Solid Oral Dose

Dose to Patient

Target Sites

GI Tract

Liver

Systemic Circulation

Vena porta

Metabolism

Renal Elimination

Fecal Elimination

Conc. vs Time

BE
Disposition of Aerosolized Dose

- Dose to Patient
- Lung Deposition
  - Systemic Circulation
    - Metabolism
      - Vena porta
      - Renal Elimination
  - Liver
- GI Tract
- Fecal Elimination

- BE Metric(s)
- Stat. Analysis
- Accept. Criteria
- Population Linearity

- Equivalence
- Biomarker
Current Regulatory Paradigm

“Weight of Evidence”

Formulation & Device

In Vitro Performance

Systemic Exposure

Local Delivery

What Evidence?

Weight Distribution!!
Components of the BE Portion of ANDAs

**Oral Drug Products**
- Pharmaceutical Equivalence
- $Q_1$ and $Q_2$ sameness* of formulations is not essential
- In Vitro Dissolution
- Systemic Exposure (PK)
- Clinical studies for drugs acting locally in the GI tract – rare
- Statistical Evaluation of BE (ANOVA)
- Stability Testing:  
  - Assay & In vitro Dissolution

**Orally Inhaled Products**
- Pharmaceutical Equivalence
- $Q_1$ and $Q_2$ sameness* of formulations **is essential**
- In Vitro Performance Studies
- Systemic Exposure (PK Preferred)
- PD/Clinical Studies to determine Equivalence of Drug Delivery to the Local Site of Action (Lung)
- Statistical Evaluation of BE (PK-ANOVA, PD/Clinical?)
- Stability:  
  - Assay, Delivered Dose/Actuation and Fine Particle Fraction (Impactor-Sized Mass)

* $Q_1$: The test and reference products contain the same inactive ingredients
  
  $Q_2$: Concentration or amount of each inactive ingredient in the test product is within $\pm 5\%$ of that present in the reference product
Orally Inhaled Drug Products

• Pharmaceutical Equivalence
  – Drug (Albuterol vs. Albuterol Sulfate)
  – Device (MDI vs. DPI)
Metered Dose and Dry Powder Inhalers

Propellant Driven MDI

Dry Powder Inhaler
Dry Powder Inhaler Devices

- Twisthaler
- Diskus
- Aerolizer
- Handihaler
- Turbuhaler
Factors Affecting Clinical Response of OIDP

Formulation

Device

Patient

Clinical Response
Evaluation of Comparative In Vitro Performance
Determinants of In Vitro Performance

Formulation Life Sectors
Beginning, Middle & End

Metering Device Actuator
Aerosol Plume
In Vitro Performance Tests

• Quantity of drug delivered and its consistency with product labeling
  – Single Actuation Content (SAC) Through Container Life
  – Priming and Prime retention (Repriming)

• Plume Characteristics
  – Particle Size Distribution
    • Cascade impaction, laser diffraction*
  – Spray Pattern (Where applicable)*
  – Plume Geometry (Where applicable)*

PSD by Cascade Impactor (CI)

The illustration is based on hypothetical data.

S = Stem, A = Actuator & F = Filter

The illustration is based on hypothetical data.
Evaluation of Comparative In Vivo Performance
Equivalence of Systemic Exposure
(PK BE Studies)

• **Dose**
  – Single/multiple actuations

• **Subject Training**

  ![Breath Coordination](image1)
  ![Inspiratory Flow Rate](image2)

• **Blood Concentration Profiles**
  – Low (possibly negligible) blood concentrations at the recommended maximum daily doses
  – Erratic plasma concentration profiles
Equivalence of Local Delivery

- **Bronchodilators**
  - **Beta Agonists**
    - Short acting
      - Albuterol
    - Long Acting
      - Formoterol
  - **Cholinergic Agents**
    - Ipratropium bromide
- **Anti-inflammatory Agents**
  - Corticosteroids

Lack of Single Marker – Unlike Blood Conc. for Systemic Exposure Assessment

Bronchodilation – FEV₁
Methacholine Challenge (PC₂₀)
Dose Response and its Impact on Determination of Bioequivalence
Assessment of Bioequivalence

Based on:

*Response axis*

or

*Dose axis*
Pharmacokinetic Studies

Response Scale T/R: 0.80
Dose Scale T/R: 0.80
Pharmacodynamic Studies
Reference Product Dose = ED$_{50}$

**Dose (Multiples of ED$_{50}$*)**

**PD Response (% E$_{max}$)**

Response Scale T/R: 0.80
Dose Scale T/R: 0.67

* Dose required to produce 50% of the maximum achievable response
Pharmacodynamic Studies
Reference Product Dose >ED$_{50}$

Dose Scale T/R: 0.26

Response Scale T/R: 0.80

* Dose required to produce 50% of the maximum achievable response
Waivers of In Vivo BE Testing

• **Oral Products**
  – Acceptable in vivo BE study(ies) of the highest strength or lower strength (due to safety concerns)
  – Formulation proportionality between the lower and the higher strengths
  – Comparative in vitro dissolution of the lower and the higher strengths of the test products

• **OIDP - Complexity in Application of the Oral Product Approach**
  – The general lack of linearity/dose proportionality in the pharmacodynamic response
  – Probable difference in the in vitro performance of the lower and higher strength products
In Vitro-In Vivo Correlation

• Oral Products
  – Considerable wealth of literature
  – Established models to determine in vivo dissolution from PK data – Type “A” correlations, occasionally

• OIDP
  – Little information - few rank order relationships
  – Device Dependency
  – Correlation of in vitro measurements with PK data complicated by absorption from non-pulmonary sites
  – Lack of models to correlate in vivo lung deposition with clinical (PK and/or PD) data
Combination Products!
Advair®*

First Treatment Day

- ADVAIR DISKUS 100/60 twice daily (N = 87)
- Salmeterol 50 mcg twice daily (N = 86)
- Fluticasone propionate 100 mcg twice daily (N = 85)
- Placebo (N = 77)

Last Treatment Day (Week 12)

- ADVAIR DISKUS 100/60 twice daily (N = 73)
- Salmeterol 50 mcg twice daily (N = 49)
- Fluticasone propionate 100 mcg twice daily (N = 65)
- Placebo (N = 26)

*Product Labeling
Thank You