Comforts and Concerns in PK-based Bioequivalence Studies of Inhalation Products.

Noha Rayad and Juan He
BioPharma Services Inc. Toronto, Canada

http://www.biopharmaservices.ca/
https://www.linkedin.com/company/biopharma-services-inc/

**PURPOSE**
- Generic orally-administered products (OIPs) are warranted as safe, effective and affordable medications.
- Regulatory agencies: far from harmonized: require in vitro, in vivo PK, and/or PD studies to demonstrate bioequivalence (BE)/therapeutic equivalence (TE) to innovator products.
  - FDA → weight-of-evidence approach (PK is one component).
  - EMA → a stepwise approach (PK with charcoal blockade).
  - Health Canada → aggregated evidence (similar to FDA’s).

**OBJECTIVE(S)**
1. Highlight the prominent PK properties of some OIPs.
2. Evaluate the variability of OIPs in PK/BE clinical trials.
4. Identify the safety profiles (in terms of AEs).
5. Highlight regulatory guidelines for these complex generics.

**METHOD(S)**
- Drugs studied were fluticasone, salmeterol, budesonide, formoterol, tiotropium bromide and combinations thereof.
- PK-BE studies were conducted on total of 580 NHVs; design/scope shown below.

**RESULT(S)**
- **Spacer for pMDIs**
  - VHC (AeroChamber plus valved holding chamber) & VS (Vacuum spacer); both:
    - reduced total systemic exposure by 38% and 68%, respectively compared to no reporter (fig 1).
    - showed high inter-subject CV%: yet ISCV% was slightly lower for VS compared to VHC.
  - VHC was superior to VS in terms of:
    - Absorption (46% higher exposure; fig 1).
    - Passing BE criteria.
- **Study Design, PK profiles & BE comparisons**
  - Design: 2-way crossover; replicate design for HVD; and two stage design (for attaining sufficient statistical power).
  - T and R comparison → based on rate (Cmax and Tmax) & extent (AUC) of absorption.
  - Cmax → as early as 6 min with salmeterol, formoterol, budesonide and tiotropium; the Tmax was around 1 h for fluticasone.
- **Charcoal Blockade** resulted in:
  - Formoterol: reduced oral absorption of a proportion of inhaled drug (fig 2 and 3).
  - Budesonide: almost same exposure as without charcoal.
- **Variability**
  - Inter-subject variability for AUC and Cmax (range)
    - 55-65% for fluticasone, salmeterol, budesonide and formoterol.
    - 70-80% for tiotropium DPI.
  - Within-subject variability (S&W) of reference product/Cmax
    - 35% to 60 for fluticasone, salmeterol, budesonide, formoterol, and tiotropium.
  - BE → widened 90% CIs (per replicate design).
- **Safety**
  - AEs → all studied OIPs displayed mild - moderate AEs in severity: well tolerated in NHV.

**CONCLUSION(S)**
- For demonstrating BE → consistent inhalation technique, lung disposition and PK variability are highly dependent on subjects’ training, formulation & device (for consistent lung delivery).
  - Fully replicate BE design, widened 90% CIs for Cmax
  - Adaptive design, if uncertainty about variability/sample size.
  - Sensitive analytical methods helped in achieving BE.
  - Spacer → reduced total systemic exposure by targeting the medication deeper into the lungs; consistent absorption achieved by VHC spacer.
  - Charcoal blockade → significantly reduced total absorption especially for drugs with inherent high gut bioavailability.

**RECOMMENDATIONS**
*Comforts & concerns - BPSI experience:*
- Subjects & staff training and standardized inhalation technique were optimized for lung deposition of drug and reduced variability: such that:
  - MDI, a steady and gentle inhalation: focused on formulation and active agent; sample size and study design (adaptive, replicate and 2-way crossover).
- DPI, rapid, forceful and deep inhalation.
  - High variability: batch-to-batch variability: on formulation and active agent; sample size and study design (adaptive, replicate and 2-way crossover).

**REGULATORY ASPECTS**
- In Vitro Performance
  - Systemic Exposure
    - PK study
    - Local (Bragg) Delivery
    - PK/Bragg study
    - Formulation & device (for consistent lung delivery).
  - FDA weight-of-evidence Approach
  - EMA Stepwise Approach

- CRO
  - In Vivo
    - In Vivo (PK)
    - In Vivo (PD)
    - Safety
  - BioPharma Services Inc. Toronto, Canada