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

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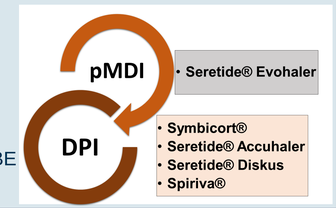
PURPOSE

- Generic orally-inhaled 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 evidences (similar to FDA's).

BioPharma Services Inc. (BPSI)

has a proven track record and extensive experience with PK- BE studies for OIPs.

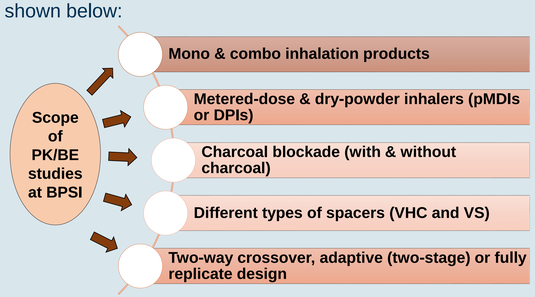


OBJECTIVE(S)

1. Highlight the prominent PK properties of some OIPs.
2. Investigate the variability of OIPs in PK/BE clinical trials.
3. Summarize BPSI experience, designs and challenges in PK/BE.
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 (Volumatic spacer); **both**:

    → reduced total systemic exposure by 38% and 68%, respectively compared to no spacer use (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 (C_{max} and T_{max}) & extent (AUC_t) of absorption.
  - C_{max} → as early as 6 min with salmeterol, formoterol, budesonide and tiotropium; the T_{max} was around 1h for fluticasone.
  - **Partial $AUC_{0\text{-}30}$** → surrogate for efficacy if very quick lung absorption precludes significant gut absorption (e.g. salmeterol).
- **Charcoal Blockade** resulted in:
  - ***Formoterol:*** reduced enteral 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_{WR})*** 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.

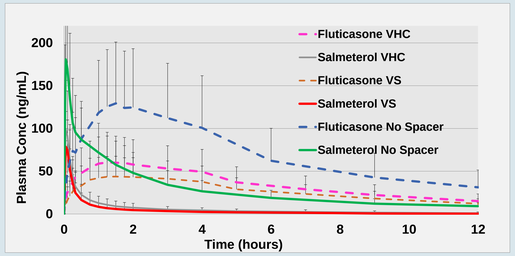


Fig 1. PK profiles of fluticasone & salmeterol upon inhalation of Seretide® Evohaler pMDI using different spacers.

Table (1): PK parameters (mean ±S.D.) of different inhalation drugs

Inhalation Drugs	$AUC_{0\text{-}30}$ (pg.h/mL)	AUC_t (pg.h/mL)	AUC_{inf} (pg.h/mL)	C_{max} (pg/mL)	T_{max} (H)	Lambda (1/H)	$T_{1/2}$ (H)
Budesonide	230±160	1290±747	1330 ±755	665±479	0.2±0	0.198±0	3.8± 1
Formoterol	4±2	39 ± 24	47 ± 25	12 ± 8	0.1± 0	0.08 ± 0	10 ± 3
Fluticasone	NA	1400 ± 565	1500 ±586	193 ± 68	0.9 ±0	0.07±0	13±2
Salmeterol	64 ±20	406± 116	455± 120	247±142	0.06 ±0	0.05 ±0	14 ±4
Tiotropium	NA	45 ±26	85 ±69	9 ±5	9 ±0	0.03 ±0	40±35

*AUC_t is $AUC_{0\text{-}72}$

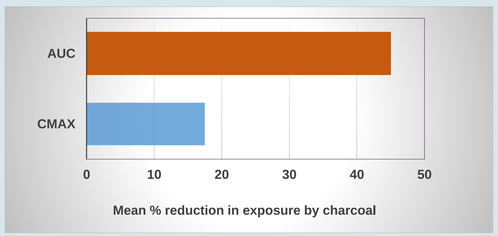


Fig 2. Mean reduction in PK parameters by means of charcoal blockade on formoterol absorption from Symbicort® DPI

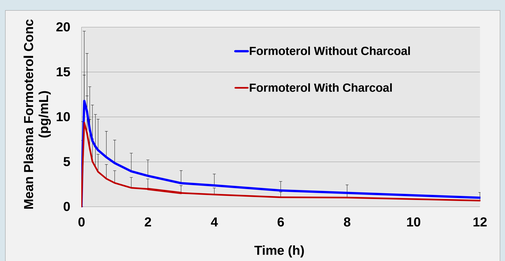


Fig 3. PK profiles showing the effect of charcoal blockade on formoterol absorption upon inhalation of Symbicort® DPI

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 bioanalytical 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

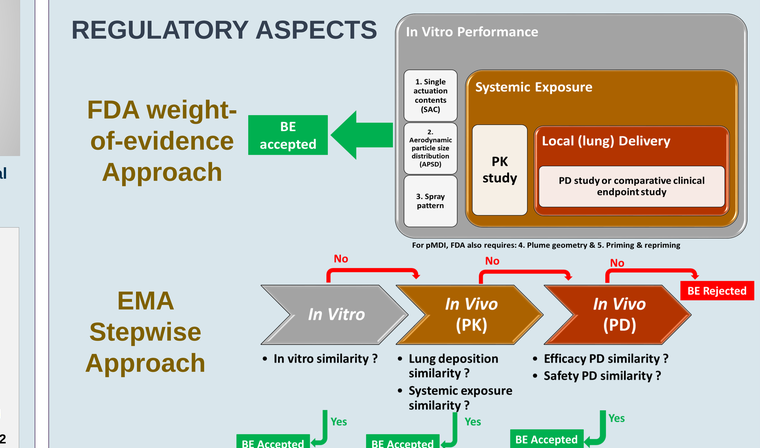
(Comforts & concerns - BPSI experience):

- **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 in coordination with actuation.

  → **DPI,** rapid, forceful and deep inhalation.
- **High variability**: batch-to-batch variability.; hooked on formulation and active agent; sample size and study design (adaptive, replicate and 2 –way crossover).

REGULATORY ASPECTS



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