In-vitro approaches as alternatives to clinical studies for OINDPs

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Development of *in-vitro* approaches to reduce need for clinical studies

- PSGs for corticosteroid-containing OINDPs recommend clinical endpoint studies
  - Mylan's Gx fluticasone propionate – salmeterol xinafoate inhalation powder was approved on this basis in 2019
- PSG for mometasone furoate nasal suspension revised in 2019 to include PSD of drug in suspension (e.g. by MDRS) (with PBE test for equivalence) as alternative to CE studies
  - Apotex Gx approved on this basis (see Liu et al, AAPS J (2019) 21:14)
- PSG for beclomethasone dipropionate suspension aerosol revised in 2019 to include option to discuss alternative supportive in-vitro studies which:
  - "may include, but are not limited to, (i) more predictive APSD testing using representative mouth-throat models and breathing profiles, (ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates, (iii) dissolution, and (iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes…….quantitative methods and modeling (for example, physiologically-based PK and computational fluid dynamic studies) and alternative in vivo PK BE studies".

Additional in-vitro characterization approaches

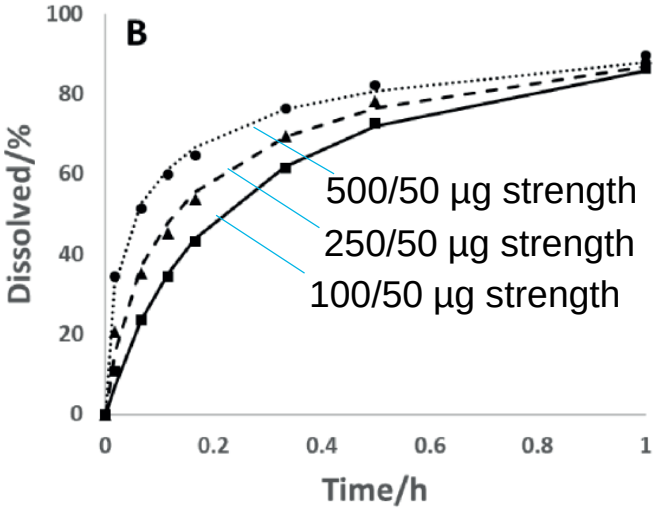
- More extensive physico-chemical characterization can provide greater confidence in *in-vitro* similarity
- There is scope for further research to understand relevance of *in-vitro* characterization for *in-vivo* drug product performance
  - e.g., measurement of API particle size in drug product
    - Does the technique measure a representative sample of the particle size distribution?
    - Does the sample preparation technique disperse agglomerates in a relevant way?

In-vitro dissolution of corticosteroids

- Recent publications highlight contrasting approaches in FDA-funded research
  - In Vivo-Relevant Transwell Dish-Based Dissolution Testing for Orally Inhaled Corticosteroid Products (Sakagami *et al*, Pharm Res (2019) 36: 95)
  - Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products (Price *et al,* The AAPS Journal (2020) 22:47)
- For compounds (e.g. fluticasone propionate) exhibiting dissolution rate-limited absorption, it is clear that use of sink conditions (e.g. in USP 2 apparatus) enables observation of *in-vivo* relevant discrimination between formulations
  - Transwell-type systems under non-sink conditions in the donor phase show permeation-limited kinetics
- Minimizing *in-situ* agglomeration during dose collection is also critical

In-vitro dissolution testing and mechanistic PK modeling of fluticasone propionate from Advair Diskus

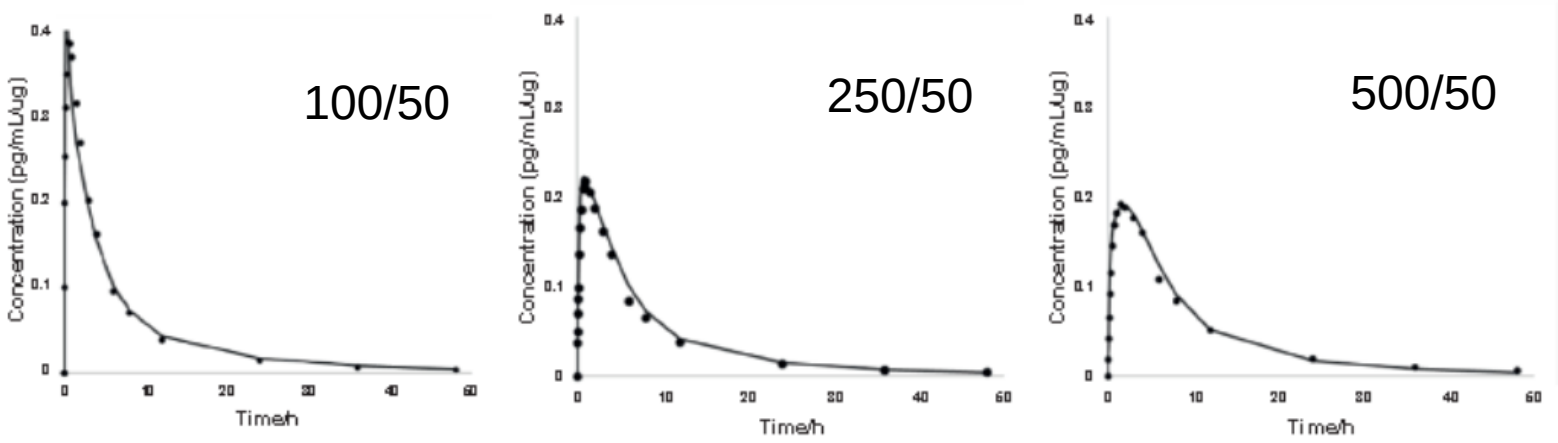
- Dissolution method
  - 0.5 – 8 µm aerosolized fraction collected using modified NGI
  - USP 2 (paddle) apparatus, PBS + surfactant media



Backman and Olsson, RDD 2020

In-vitro dissolution testing and mechanistic PK modelling of fluticasone propionate from Advair Diskus

Simulated vs observed PK concentration – time profiles (dose-normalized)



Backman and Olsson, RDD 2020

Mechanistic PK modelling potentially allows

- Estimation of local concentrations (site of action)
- Sensitivity analysis vs product variables

Conclusions

- There is scope for further research to support development of BE guidance for OIPs without requirement for clinical equivalence studies.
- Understanding relevance of additional physical characterization techniques for *in-vivo* performance is important
- In-vitro dissolution is a key technique for low solubility compounds, potentially providing focused product characterization: evidence of rate of absorption at the site of action
  - Greater understanding and standardization of dissolution techniques is required
  - Use of *in-vitro* dissolution data in mechanistic *in-vivo* models is potentially valuable
  - “i-BCS” classification of molecules for inhaled delivery needed to inform guidance development