

## **Discussion Points**

### **For the “Track B” Breakout Session: In Vivo Tests (PK, PD and Biomarkers)**

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Inhaled Products For Local Action*  
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## **PK and Lung Deposition in Determination of Equivalence of Local Delivery**

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### **Pharmacokinetic<sup>1</sup> Evaluation**

- **Early Bioavailability (30 min)**
- **Charcoal-block**

### **Response**

- **A combination of EBA and CB would provide evidence for local delivery**
  - For low oral A drugs, CB may not be necessary**
  - For other drugs EBA + CB may be sufficient, if no oromucosal absorption (unless the label recommends mouth rinse)**

## PD/Clinical Outcomes of Equivalence of Local Delivery

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- Efficacy**
  - **Bronchodilators**
    - Bronchoprotection model more useful than the bronchodilation model
  - **Corticosteroids**
    - Steroid-naïve patient preferred, patients on low dose steroids may also be useful. If difficult to recruit appropriate patients tapering patients off the steroid regimens may be considered.
    - Biomarker relevant to the mode of action of drug
      - Exhaled Nitric Oxide (eNO) reflective of anti-inflammatory effect
      - Sputum Eosinophils also reflective of anti-inflammatory effect
    - FEV<sub>1</sub> (Asthma stability model) may also be affected by inflammation
- Safety: Not necessary if BE includes PK equivalence**

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## Dose Response

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- Possibility**
  - Possible for beta-agonists
  - May be possibility for ICS based on suitable models
- Acceptability: Overall slope, Statistical significance**
- The marketed strength may represent the recommended single maximum dose**
  - Bio-IND (For doses exceeding the max. labeled dose)
  - Specially made test products for delivery of lower doses

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## Applicability to BE of Combination Products (1)

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### PK Evaluations

- Both actives
- Multiple comparisons for both with and without charcoal

### PD Evaluations

- Separate assessment for each active drug, if PD study is required.
- Design and objectives of PD-studies depending on outcomes of PK-studies

## Applicability to BE of Combination Products (2)

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### If one active meets BE, the other fails?

- Repeat all testing on the revised product to show both active meet BE criteria – one view point
- Do PD on the failed (PK) component – another view point  
based on the pertinent EU-Guideline approach

## **Additional View Points**

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- Direct application of BE criteria used for solid oral to inhaled products?**
  - Variability
  - Relevance of low systemic exposure
  - Systemic exposure differences that were established to be safe from same reference products in different types of devices (MDI vs DPI)
- Why should sponsor be asked to conduct comparative in vitro and PK studies, if acceptable PD studies trump these failures?**