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

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International Conference
*European Equivalence Considerations for Orally Inhaled Products For Local Action*
Frankfurt, Germany, 12-13 October 2010

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PK and Lung Deposition in Determination of Equivalence of Local Delivery

- **Pharmacokinetic 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**

- **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$_1$ (Asthma stability model) may also affected by inflammation

- **Safety:** Not necessary if BE includes PK equivalence

**Dose Response**

- **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
Applicability to BE of Combination Products (1)

- **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)

- **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

- 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?