Regulatory and scientific challenges in establishing bioequivalence for generic orally inhaled drug products

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The following presentation reflects the opinions of the author and does not necessarily represent the official position of the US-FDA

Complex Products

GDUFA II (Generic User Fee Amendment II):

- Complex active ingredients
  - Complex mixtures of APIs, peptides
- Complex formulations
  - Liposomes
- Complex routes of delivery
- Complex dosage forms
  - Long acting injectables , transdermals
- Complex drug-device combinations

Locally acting Orally Inhaled and Nasal Drug Products (OINDPs)

Orally Inhaled and Nasal Drug Products

- OINDPs differ from the systemically acting traditional dosage forms in:
  - Most OINDPs are locally acting drugs exerting their therapeutic effects through reaching the sites of action, and their drug delivery does not directly rely on the systemic circulation

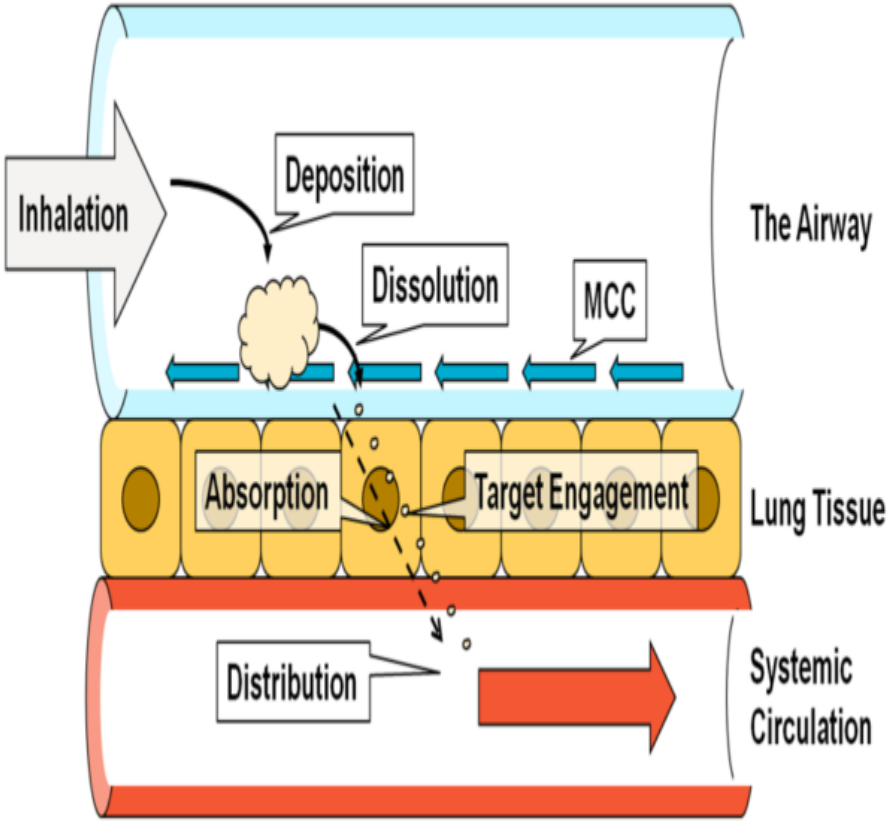

Diagram curtesy of Per Bäckman

Orally Inhaled and Nasal Drug Products

- OINDPs differ from the systemically acting traditional dosage forms in:
  - OINDPs are drug-device combinations which include a formulation integrated with a device, therefore performance depends on the interaction between the formulation and the delivery device

BE evaluation of OINDPs has been considered as one of the most challenging tasks

Nasal Spray

Metered Dose Inhaler (MDI)

Multidose dry powder inhalers

Accuhaler®

Turbuhaler®

Genuair®

Easyhaler®

Twisthaler®

Nexthaler®

Considerations for Generic Locally Acting OINDPs to Demonstrate Therapeutic Equivalence

Equivalent In Vitro Performance

Equivalent Systemic Exposure

Equivalent Local Delivery

Device and Formulation Similarity

Formulation Similarity

- Recommended Qualitatively (Q1) and quantitatively (Q2) the same
- PSG also indicates that Q2 differences may be justified
  - the level of excipient used in the test formulation should not exceed the levels used in the other FDA approved inhalation products
  - the Q2 difference has no impact on bioequivalence, through the in vitro and in vivo BE studies
  - submit pharmaceutical development data, to demonstrate the formulation understanding, and to support how the final test formulation is selected

Device Similarity

Locally acting MDI

- Similar size and shape
- Same basic operating principle
- Same number of doses
- Dose counter

Locally acting DPI

- Similar size and shape
- Same basic operating principle
- Same number of doses
- Dose counter
- Same energy source
  - Passive (breath-actuated)
- Same metering principle
  - Pre-metered single unit-dose (e.g., HandiHaler, capsule),
  - Pre-metered multi-unit-dose (e.g., Diskus, blister strip)
  - Device-metered multi-dose (e.g., Turbuhaler, reservoir)

Device Comparison

- FDA may accept certain design differences if they are adequately analyzed, scientifically justified
  - Threshold Analyses
    - *Labeling Comparison*
    - *Comparative Task Analysis*
    - *Physical Comparison of Delivery Device Constituent Part*
    - Outcomes:
      - No difference
      - Minor Design Differences
      - Other Design Differences

Draft Guidance for Industry : Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, January 2017

Device Comparison

- In instances when *other than minor* differences are identified:
  - Consider re-design of the device to minimize differences from the RLD
  - Potential need for additional information and/or data to support the ANDA submission
  - Contact FDA through a pre-ANDA submission/controlled correspondence *before* conducting comparative use human factors studies

- There may be some differences in the internal design, such as the air channel geometry and dimension. These internal differences should not affect bioequivalence, through the in vitro and in vivo BE studies

Considerations for Generic Locally Acting OINDPs to Demonstrate Therapeutic Equivalence

Equivalent In Vitro Performance

Equivalent Systemic Exposure

Equivalent Local Delivery

Device and Formulation Similarity

Equivalent In Vitro Performance

Locally acting MDI

- Equivalent Emitted Dose
- Equivalent APSD
- Equivalent Spray Pattern
- Equivalent Plume Geometry
- Equivalent Priming and Re-priming

Locally acting DPI

- Equivalent Emitted Dose
- Equivalent APSD
- Comparable device resistance

Equivalent In Vitro Performance

- Method validation
  - Complete validation package
  - Validation criteria pre-defined in SOP
  - Use the method that is representative of the method used in the pivotal study
  - Use unexpired reference product

Considerations for Generic Locally Acting OINDPs to Demonstrate Therapeutic Equivalence

Equivalent In Vitro Performance

Equivalent Systemic Exposure

Equivalent Local Delivery

Device and Formulation Similarity

Equivalent Systemic Exposure

Locally acting MDI

- Based on PK (AUC and Cmax) data
- PK study conducted on ALL strengths

Locally acting DPI

- Based on PK (AUC and Cmax) data
- PK study conducted on ALL strengths

PK study serves two purposes:

1) Rate and extend of the drug getting into the systemic circulation - systemic toxicity
2) Evidence to support bioequivalence

Equivalent Systemic Exposure

- Drug level in the systemic circulation may difficult to be detectable or maybe highly variable
  - Validated analytical method with adequate sensitivity
- Early onset of the PK profile
  - Study design should be robust to quantify the early onset and Cmax
- RLD batch-to-batch PK variability
  - Has been observed
  - Contact FDA for guidance to discuss alternative approaches before conducting study
  - Possible contributing factors:
    - API/Product storage condition and stability
    - Inactive ingredients: source and quality
    - Aging of the batches
  - Rule out other sources of the intrinsic PK variabilities
    - Sensitive analytical method
    - Robust study design
    - Adequate user training

Considerations for Generic Locally Acting OINDPs to Demonstrate Therapeutic Equivalence

Equivalent In Vitro Performance

Equivalent Systemic Exposure

Equivalent Local Delivery

Device and Formulation Similarity

Equivalent Local Delivery

Locally acting MDI

- PD endpoint study or comparative clinical endpoint study

Locally acting DPI

- PD endpoint study or comparative clinical endpoint study

Equivalent Local Delivery: PD study

- For short acting beta-agonists (i.e., albuterol) MDI
  - Bronchodilatation – direct measure of lung function
    - High variability in response data
    - Depending on the study proposal and data, dose-scale approach for bronchodilatation studies may be insensitive to difference in relative bioavailability
  - Bronchoprovocation – measure lung function after exposure to challenge agent (i.e., methacholine)
    - may provide more sensitive means of demonstrating BE between a test and reference albuterol MDI product
  - Modeling/simulation approach could help to identify the most sensitive approach demonstrating dose-response

Equivalent Local Delivery
PD/Comparative Clinical endpoint BE studies

- Changes in formulation, manufacturing, and device often occur during drug development process
  - Recommend to use the to-be-marketed drug product in the comparative clinical endpoint study
  - Have a plan for bridging study if the comparative clinical endpoint study is not conducted on the to-be-marketed drug product

Conclusions

- Establishing bioequivalence for OINDPs is considered as one of the most challenging tasks for generic products
- BE assessment of OINDPs takes into account
  - Device and formulation
  - In vitro drug product performance
  - in vivo studies of systemic exposure
  - in vivo studies of local delivery
- Opportunities are available for communications with FDA on innovative technologies in OINDP area

FDA Drug Information
@FDA_Drug_Info

Follow

#FDAapproves first generic version of Advair Diskus (fluticasone propionate and salmeterol inhalation powder): go.usa.gov/xE87m.

1:21 PM - 30 Jan 2019

Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, announced in a press release:

> "Today's approval of the first generic drug product for one of the most commonly prescribed asthma and COPD inhalers in the US is part of our longstanding commitment to advance access to lower cost, high-quality generic alternatives."

Jan 31, 2019 APPROVAL **FDA Approves Wixela Inhub (fluticasone propionate and salmeterol inhalation powder, USP), First Generic of Advair Diskus**

FDA Approves Generic Inhalation Treatment for Asthma, COPD

JANUARY 30, 2019

The FDA has approved the first generic version of Advair Diskus (GlaxoSmithKline), a fluticasone propionate and salmeterol inhalation powder product.

From: xxxx
Sent: Saturday, March 23, 2019 3:06 PM
To: CDER DRUG INFO <DRUGINFO@fda.hhs.gov>
Subject: One Million Thanks!!!

Re: FDA approves first generic Advair Diskus

Acknowledgement

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