

PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products

Workshop Agenda

Day 1

Moderator Dennis O'Connor, B.S.
Boehringer Ingelheim Pharmaceuticals, Inc.

8:30 AM **Introduction**
Janet Woodcock, MD
U.S. Food and Drug Administration

8:45 AM **Current Challenges and Opportunities in Demonstrating Bioequivalence**
Gur Jai Pal Singh, Ph.D.
Watson Pharmaceuticals

This presentation will provide an overview of the current challenges and opportunities in establishing bioequivalence (BE) for OIPs. Beginning with a review of the fundamentals of establishing bioequivalence of multisource products, the presentation will present an understanding of the FDA paradigms for demonstrating BE in OIPs, discuss the complexities in the evaluation of in vitro, pharmacokinetic, and pharmacodynamic studies, and describe the challenges in the application of BE approaches for OIPs compared with conventional solid oral dosage forms including post approval changes, BE waivers, and establishment of an IVIVC.

9:30 AM **The FDA Critical Path Initiative – Clinical Considerations**
Badrul Chowdhury, M.D., Ph.D.
U.S. Food and Drug Administration

This presentation will cover clinical and pharmacodynamic study considerations as relevant to the Critical Path Initiative including novel pharmacodynamic study designs, biomarker strategies, multiple strength and combination products, and clinical study designs for OIPs for local action, for example asthma and chronic obstructive pulmonary disease (COPD). The larger portion of this talk will focus on clinical study designs and biomarkers.

10:00 AM Break

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Moderator Michael Riebe, Ph.D.
Merck Research Laboratories

10:15 AM **The FDA Critical Path Initiative – *In Vitro* Techniques and *In Vivo* Imaging Technology**

Anthony J. Hickey, Ph.D.
University of North Carolina

This presentation will examine the role that assessment of aerodynamic particle size distribution, aerosol deposition, imaging techniques, and modeling and simulation of product performance/drug delivery could or should play in bioequivalence testing and will review current attempts at establishing possible IVIVCs for locally acting OIPs.

10:45 AM **Bioequivalence of Inhaled Corticosteroids**

Guenther Hochhaus, Ph.D.
University of Florida

This presentation will discuss the use of pharmacokinetic tools for the bioequivalence testing of inhaled glucocorticoids. PK studies may have the ability to answer the three main questions relevant for the bioequivalence of this and other inhalation drug classes:

- How much is deposited in the lung? How much is absorbed orally (only relevant for drugs with significant oral bioavailability)?
- How fast is it absorbed?
- Where is it deposited (central vs peripheral lung)?

11:15 AM **Device Design Similarity**

David Parkins, Ph.D.
GlaxoSmithKline

The proprietary nature of devices may prevent the manufacturers of multisource inhalation products from marketing the same device as used in the originator products. Furthermore, changes during the development of a new device may necessitate additional data. This presentation will explore the device design characteristics which may be critical to *in vitro* and *in vivo* performance.

11:45 PM Lunch

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Moderator Mei-Ling Chen, Ph.D.
U.S. Food and Drug Administration

1:00 PM **International Regulatory Approaches to Bioequivalence**
Marjolein Weda, Ph.D.
National Institute for Public Health and the Environment, The Netherlands

This presentation will review EU approaches to bioequivalence as outlined in the Draft Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP. Consideration will be given to the rationale for *in vitro* tests and the use of PK and/or imaging studies for establishing bioequivalence.

1:30 PM **Challenges in Meeting International Requirements for Bioequivalence of Inhaled Drug Products**
Tushar Shah, M.D.
Teva Pharmaceuticals

Given the diversity in the available international requirements for the approval of OIPs, meeting the requirements for demonstrating bioequivalence (BE) globally is challenging. This presentation will describe the following challenges: different BE limits; different study designs; different biomarkers; and whether dose-response is or is not needed.

2:00 PM **Statistical Approaches for Particle Size Distribution Data**
David Christopher, M.S.
Schering-Plough

This talk will consider approaches to multivariate equivalence with particular attention to particle size profiles. There are three options that have been considered. The first is the chi-square method developed by an FDA Working Group for analysis of cascade impactor profiles. The second is a multivariate population BE method of Chervoneva and Hauck, developed originally for small dimension cases. The third is f2 developed for dissolution profiles. The application of all three options for cascade impactor profiles will be discussed with consideration for where this work next needs to go.

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2:30 PM Quality by Design for Orally Inhaled Drug Products

Lawrence Yu, Ph.D.

U.S. Food and Drug Administration

This presentation will review the opportunities to construct a design space for Orally Inhaled Products. The focus will be on describing potential critical quality attributes (CQA) for OIPs and discussing whether linking those CQA to clinical performance is necessary. In addition, this presentation will describe how product and process understanding together with the appropriate control strategies might obviate the need for bioequivalence studies for formulation or device changes (i.e., regulatory flexibility) and the special requirements for combination products.

3:00 PM Break

3:15 PM Extended Breakout Sessions

Session 1: *In Vitro* Approaches to Demonstrating Bioequivalence

Facilitators:

David Christopher, M.S., Schering-Plough

Richard Dalby, Ph.D., University of Maryland

Bing Li, Ph.D., U.S. Food and Drug Administration

During this breakout session, the participants will discuss the current state of the art with respect to in vitro testing, the challenges and barriers in the use of in vitro testing for the assessment of BE, and the opportunities and future direction for the use of in vitro studies to demonstrate BE. This session will also examine when in vitro tools would be useful for determining bioequivalence during development and what is needed to demonstrate an IVIVC (relationship) for inhaled products.

Session 2: Biomarker Strategies

Facilitators:

Richard C. Ahrens, M.D., University of Iowa

Dale Conner, Pharm.D., U.S. Food and Drug Administration

Partha Roy, Ph.D., U.S. Food and Drug Administration

In this breakout session, participants will discuss the characteristics of biomarkers that make them acceptable for demonstrating BE, clinically acceptable differences in biomarker performance, the requirements for validating novel clinical endpoints, the appropriateness of measuring response on a dose scale or a response scale, the acceptance of different biomarkers in different global regions, and the relevance of different biomarkers for different disease.

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Session 3: Imaging Techniques

Facilitators:

Anthony J. Hickey, Ph.D., University of North Carolina

Beth Laube, Ph.D., Johns Hopkins University School of Medicine

Sau Lee, Ph.D., U.S. Food and Drug Administration

In this breakout session, participants will discuss appropriate uses of Imaging in OIP development. Questions to be considered include where can imaging be used most appropriately in the development of OIPs, how imaging was used in the transition from CFCs to HFAs, what recommendations can be made on appropriate study designs, and what opportunities are there to use imaging in the construction of an IVIVC.

Session 4: In Vivo Approaches to Establishing Local Delivery Equivalence

Facilitators:

Gur Jai Pal Singh, Ph.D., Watson Pharmaceuticals

Leslie Hendeles, Pharm.D., University of Florida

Badrul Chowdhury, M.D., Ph.D., U.S. Food and Drug Administration

Sandra Suarez, Ph.D., U.S. Food and Drug Administration

In this breakout session, participants will discuss pharmacodynamic responses to assess BE, clinical trial designs including how to develop acceptable, clinically meaningful, acceptance criteria and relevant clinical endpoints, use of dose response, the unique requirements for multi-strength and combination drug products, and the use of pharmacokinetic studies as a measure of local delivery equivalence.

Session 5: Device Design Similarity

Facilitators:

Geena Malhotra, B.Pharm., Cipla LTD

David Parkins, Ph.D., GlaxoSmithKline

Prasad Peri, Ph.D., U.S. Food and Drug Administration

The proprietary nature of devices may prevent the manufacturers of multisource inhalation products from marketing the same device as used in the brand products. Furthermore, changes during the development of a new device may necessitate the development of additional data. In this breakout session, participants will discuss the device design characteristics which may be critical to *in vitro* and potentially *in vivo* performance. Patient interchangeability will be discussed.

5:00 PM

End of Day 1

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Day 2

8:30 AM Breakout Sessions (Repeated with feedback from Day 1)

Repeat of Session 1:
In Vitro Approaches to Demonstrating Bioequivalence

Repeat of Session 2:
Biomarker Strategies

Repeat of Session 3:
Imaging Techniques

Repeat of Session 4:
In Vivo Approaches to Establishing Local Delivery Equivalence

Repeat of Session 5:
Device Design Similarity

10:00 AM Break

10:30 AM Breakout Sessions (Repeated with feedback from Day 1)

Repeat of Session 1:
In Vitro Approaches to Demonstrating BE

Repeat of Session 2:
Biomarker Strategies

Repeat of Session 3:
Imaging Techniques

Repeat of Session 4:
In Vivo Approaches to Establishing Local Delivery Equivalence

Repeat of Session 5:
Device Design Similarity

12:00 PM Lunch

PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products

1:30 PM	Review of Breakout Session 1
2:00 PM	Review of Breakout Session 2
2:30 PM	Review of Breakout Session 3
3:00 PM	Break
3:15 PM	Review of Breakout Session 4
3:45 PM	Review of Breakout Session 5
4:15 PM	Closing Remarks
4:30 PM	End of Day 2