Summary of the 2010 ISAM/IPAC-RS *Equivalence Considerations for OIPs* Workshop, with a Focus on Patient-Related Aspects

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Presentation Outline

- Background/Genesis of Workshop
- Workshop format
- Breakout session summaries with a focus on patient-related aspects

Genesis of Workshop

- March 2009 Product Quality Research Institute (PQRI) two-day workshop on *Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products*

"the utility of pharmacokinetic studies for evaluating 'local pulmonary delivery' equivalence deserves more attention"

Ref: Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPs): Workshop Summary Report, *" J Aerosol Med Pulm Drug Delivery,* 23, pp. 1-29.

- April 2010 PQRI/RDD 2010 one and one-half day workshop on *Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products*

Workshop Objectives

- Stimulate constructive dialogue about equivalence considerations for OIPs between industry, regulators, academic researchers, and other stakeholders.
- Explore and promote best scientific and regulatory approaches to OPI equivalence determinations, especially within Europe.

Workshop Format

12 October: Plenary Sessions

- Regulatory Perspectives
- Industry and Academic Perspectives

13 October: Breakout Sessions

- Workshop sessions (concurrent sessions, three rotations)
  - Track A: *Considerations for Design of Equivalence Studies*
  - Track B: *In Vivo Tests (PK, PD, Biomarkers)*
  - Track C: *"In Vitro Only" Equivalence*
  - Track D: *Device Design Similarity and Testing Needed to Support Device Changes*
- Plenary Session: Reports from Breakout Sessions

Speaker slides and workshop summaries posted on IPAC-RS Internet site:
http://ipacrs.com/beworkshop.html

Summary to be published later

Attendance Overview

154 registered attendees

- 134 from 63 companies (industry or consulting)8 academicians
- 10 regulators (from Belgium, Germany, Netherlands, Spain, Sweden, UK, US)
- Clinical and CMC disciplines

Companies

- Research Pharma
- Generic
- Device developers
- CRO & Contract testing laboratories
- Components & materials suppliers

Symposium Presentations

Day 1: Two plenary sessions, seven presentations each

➢ Morning Session - Regulatory Perspectives:

- **Generic Medicines: Understanding the Legal Framework in the EU, US, and Canada**
  Mary Devlin Capizzi (DBR, USA)
- **Experience with OIP Equivalence Determinations in the Netherlands - Focus on *In Vitro* Aspects**
  Marjolein Weda (RIVM, Netherlands)
- **MHRA/UK Experience – Focus on *In Vivo*, Design of Clinical Studies, Biomarkers, PK/PD**
  Sanjeeva Dissanayake (MHRA, United Kingdom)
- **MPA/Swedish Experience with OIP Equivalence Determinations**
  Eva Agurell (MPA, Sweden)
- **Spanish Interpretation and Application of the OIP Guideline**
  Alfredo Garcia Arieta (Spanish Agency for Medicines and Health Care Products, Spain)
- **Experience with Canadian Guidance: Similarity and Distinction Relative to European Approach**
  Myrna Dolovich (McMaster University, Canada)
- **An Overview of the FDA Position and Experience with Equivalence of Respiratory Drugs**
  Dale Conner (US FDA/CDER/OGD, Division of Bioequivalence, USA)

Symposium Presentations

Day 1: Two plenary sessions, seven presentations each

➢ Afternoon Session - Industry and Academic Perspectives:

- **Dose-Response and Related Mathematical Considerations**
  Gur Jai Pal Singh (Axar Pharmaceuticals, USA)
- **Synopsis of the RDD/PQRI PK Workshop**
  Dennis O'Connor (Boehringer Ingelheim, USA)
- **Equivalence of OIPs in Europe: Present and Past Approval Principles**
  Anders Fuglsang (Consultant, Former Regulator, Denmark)
- **Subject Populations and Study Designs**
  Richard Ahrens (University of Iowa, USA)
- **Review of the EMEA Guidelines' In Vitro Equivalence Criteria for Cascade Impaction Data**
  Dennis Sandell (S5 Consulting, Sweden)
- **Use of In Vitro vs. In Vivo Data To Conclude Equivalence of Two Inhaled Products**
  Dave Parkins (GSK, United Kingdom)
- **Some Unresolved Issues in the Use of PK for Equivalence of OIPs**
  Günther Hochhaus (University of Florida, USA)

Breakout Sessions

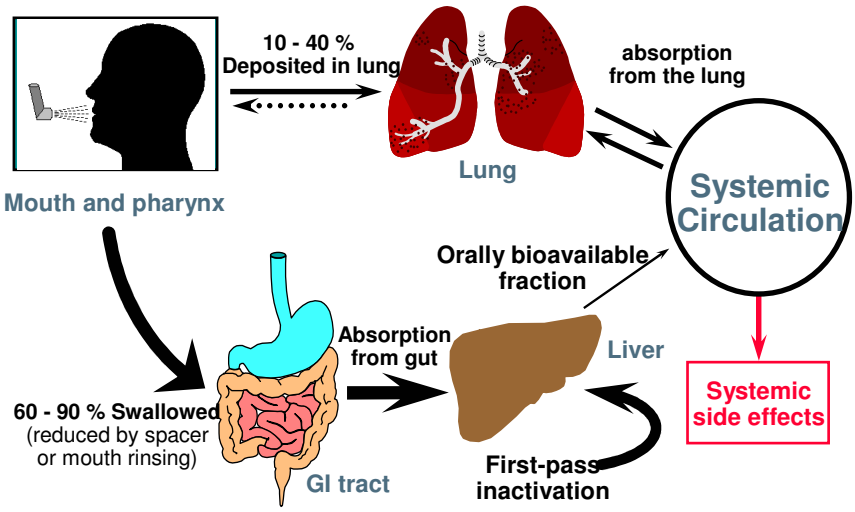
Day 2: Breakout sessions, three rotations

- **Track A: Considerations for Design of Equivalence Studies**
  Moderators:
  Colin Reisner (Pearl, USA)
  Richard Ahrens (University of Iowa, USA)
  Sanjeeva Dissanayake (MHRA, United Kingdom)
- **Track B: In Vivo Tests (PK, PD, Biomarkers)**
  Moderators:
  Gur Jai Pal Singh (Axar, USA)
  Robert Hermann (Cr-Appliance, Germany)
  Dale Conner (FDA, USA)
  Parameswaran Nair (McMaster University, Canada)
- **Track C: "In Vitro Only" Equivalence**
  Moderators :
  Myrna Dolovich (McMaster University, Canada)
  Bill Doub (FDA, USA)
  Dave Parkins (GSK, United Kingdom)
  Marjolein Weda (RIVM, Netherlands)
- **Track D: Device Design Similarity and Testing Needed to Support Device Changes**
  Moderators :
  Tim Chesworth (AstraZeneca, United Kingdom)
  Paul Lafferty (Medical Technology Consulting, United Kingdom)
  Robert Price (University of Bath, United Kingdom)

Patient-Related Topics

- EMA Stepwise Approach to BE
- Healthy Volunteers vs. Patients
- Pediatric Populations
- Relevance of Incomplete Charcoal Block
- Alternate Sizing Techniques
- Spacer/Holding Chambers
- Patient Handling - Device/Patient Interface
- Risk and Quality Management Systems

Fate of Inhaled Drugs



Courtesy of Gunther Hochhaus, Ph.D., University of Florida, adapted from Meibohm (2000)

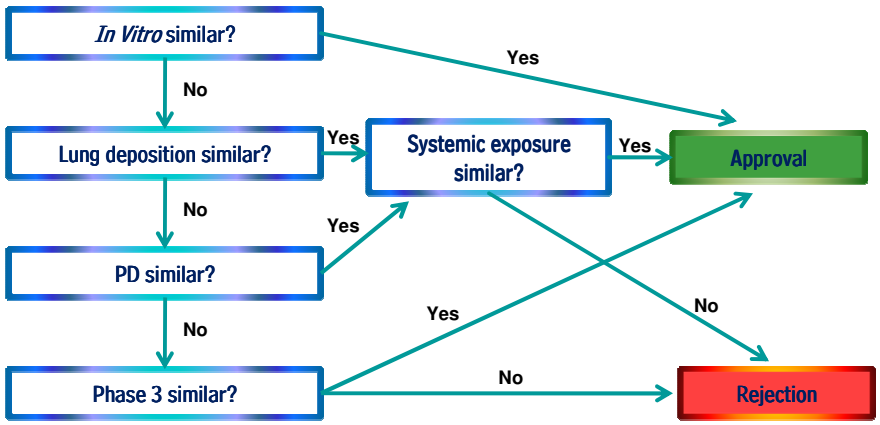
Regulatory Landscape

Status of Current Guidelines/Guidances For *In Vitro/In Vivo* BE of Orally Inhaled Products

Country	Guideline/Guidance	Status
EMEA	Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Treatment of Asthma in Children and Adolescents	Guideline, January, 2009
Canada	Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Second Entry Short-acting Beta$_2$-agonists Metered Dose Inhaler Submission Requirements for Subsequent Market Entry Inhaled Corticosteroid Products for use in the Treatment of Asthma	Guideline, February, 1999 Draft guidance, August, 2007
USA	Informal Only for Inhalation Products – Presentations given at Regulatory and Scientific Conferences. FDA seeking proposals.	

From Shah et al, *Challenges in Meeting International Requirements for Clinical Bioequivalence of Inhaled Drug Products* March 2009 PQRI workshop on *Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products*

EMA Guideline: Stepwise Approach



Ref: **Experience with OIP Equivalence Determinations in the Netherlands - Focus on *In Vitro* Aspects**
Marjolein Weda (RIVM, Netherlands)

EMA Guideline: Stepwise Approach – *In Vitro* Similar?

Comparative impactor analysis is allowed as a surrogate for therapeutic equivalence when a set of criteria is fulfilled:

- Same **drug substance** (same salt, ester, hydrate, etc)
- In cases where the **drug is in the solid state**, differences in crystalline structure and/or polymorphic form must have no influence on dissolution and aerosol particle behavior
- In cases where **different (or different amounts) of excipients** are used, differences must have no influence on aerosol particle behavior and patient inhalation behavior
- In cases where **different (or different amounts) of excipients** are used, there should be no change in the safety profile

EMA Guideline: Stepwise Approach – *In Vitro* Similar?

Comparative impactor analysis is allowed as a surrogate for therapeutic equivalence when a set of criteria is fulfilled:

- Identical **dosage form** (pMDI vs. pMDI)
- Target **delivered dose** is similar (± 15%)
- Inhalation device must have the same **resistance to airflow** (± 15%); applicable to DPIs
- **Inhaled volume** for the required dose is similar (± 15%)
- **Handling** of the inhalation device in order to deliver the same dose is similar

In summary, many comparative *in vitro* tests are needed to support the evidence of therapeutic equivalence, not just cascade impactor analysis.

Track A: *Considerations for Design of Equivalence Studies*

General Considerations:

- *What is of fundamental importance when designing an equivalence study?*
- *When is pediatric data required and why?*

Safety Considerations:

- ***When is assessment in the pediatric population required?***

Pediatric Populations

Track A: *General Considerations for Design of Equivalence Studies*

- ***When is pediatric data required and why?***

  Consensus: Pediatric data may be required in certain circumstances, particularly for generic DPIs.

  Likely to be required where relative performance of devices (in terms of APSD) differs across the flow rate range.

  Debate: A more conservative view was expressed that similarity of devices (look, mechanism, operation) is required to waive the requirement for pediatric data.

Pediatric Populations

When is pediatric data required and why?

- Although there is some debate, for novel OIPs there is agreement that safety / efficacy should be evaluated in children
- For a generic OIP, EMA guideline states:
  - In children pulmonary deposition studies are not appropriate. Pharmacokinetic studies as a surrogate for efficacy only imply efficacy, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence in children to warrant their use. Imaging studies in children are also not appropriate.
  - In children safety data cannot be extrapolated from data generated in adults with asthma or from a surrogate adult population.
  - If the *in vitro* criteria for equivalence are not fulfilled (with some additional caveats), clinical development of the product in children will be required.

Pediatric Populations

When is pediatric data required and why?

- In children pros/cons of PK vs. PD essentially same as in adults. Hence PK for efficacy in children should be as scientifically valid.
- Is extrapolation (for efficacy and safety) from adults valid?
  - Although airways geometry in adults vs. children varies, can two products which are equivalent in adults be inequivalent in children?
    - If T & R are pMDIs, unlikely (although both with and without spacer comparisons required)
    - Where relative delivery from two DPIs varies across the pressure drop/flow rate range, adult equivalence may not reflect pediatric comparison - Pediatric data important
    - Where relative delivery from two DPIs does not vary across the pressure drop/flow rate range, extrapolation from adults likely to be valid (assuming no handling issues)

Ref: **MHRA/UK Experience – Focus on *In Vivo*, Design of Clinical Studies, Biomarkers, PK/PD**
Sanjeeva Dissanayake (MHRA, United Kingdom)

Pediatric Populations

When is pediatric data required, and why?

- Swedish Medical Products Agency (MPA) opinion:
  - ***When TE demonstrated in adults using:***
    - **Quality data**: ***if needed*** perform handling study in children including efficacy and safety parameters.
    - **PK data** – ***if needed*** perform handling study in children including efficacy and safety parameters.
    - **Clinical data** (non-inferiority, assay sensitivity) in adults – clinical studies in children needed?

Ref: **MPA/Swedish Experience with OIP Equivalence Determinations**
Eva Agurell (MPA, Sweden)

Healthy Volunteers vs. Patients

Track A: *General Considerations for Design of Equivalence Studies*

- ***What is of fundamental importance when designing an equivalence study?***

  Consensus: Universally agreed that **assay sensitivity was the key**. Whatever is required should be permissible in terms of enriched populations, dose, dose separation, duration, and population.

  Consensus: **Development of half-strength T presentations not appropriate** for such studies. However, regulatory authorities may occasionally request such development.

  Consensus: **Volunteers acceptable for PD safety**; patients usually required to evaluate efficacy (asthma or COPD population, not both). **Healthy volunteer reasonable surrogate for systemic exposure.**

Healthy Volunteers vs. Patients

Healthy Volunteers vs. Patients:

- Study (healthy or patients) should detect relevant differences in formulation/device with highest resolution
- The higher the central deposition (e.g., asthmatics), the lower the power to detect formulation differences
- Differences in lung function across asthmatics will increase the variability
- As a result, healthy volunteers should be considered
  - What flow rates?
  - Combination of healthy volunteers and patients?

Ref: **Some Unresolved Issues in the Use of PK for Equivalence of OIPs**
Günther Hochhaus (University of Florida, USA)

Track B: *In Vivo Tests (PK, PD, Biomarkers) (1)*

- PK and Lung Deposition in Determination of Equivalence of Local Delivery
  - *Early Bioavailability (EBA - 30 min)*
  - *Charcoal block (CB)*

***Consensus*: A combination of EBA and CB would provide evidence for local delivery**

- For low oral available drugs, CB may not be necessary
- For other drugs EBA + CB may be sufficient, if there is no oromucosal absorption (unless the label recommends mouth rinse)

Relevance of Incomplete Charcoal Block

Does incomplete adsorption of API by charcoal (charcoal block) have important ramifications?

- Hypothetical charcoal block study where adsorption is incomplete:
  - 100 μg drug dose
  - 10% drug delivery to the lung, 90% to GIT
  - Pulmonary BA 100%, oral BA depends on API
  - Assume charcoal block 96% effective
- If oral BA is **40%** (e.g., BDP), **87%** of estimated "pulmonary" dose is absorbed via lungs:
  - 10 μg absorbed via lungs
  - 1.4 μg absorbed via GIT

  (90 μg x 4% not adsorbed by charcoal x 40% oral BA)
- If oral BA is **10%** (e.g., budesonide, terbutaline) , **97%** of estimated "pulmonary" dose is absorbed via lungs

Ref: **MHRA/UK Experience – Focus on *In Vivo*, Design of Clinical Studies, Biomarkers, PK/PD**
Sanjeeva Dissanayake (MHRA, United Kingdom)

Relevance of Incomplete Charcoal Block

Does incomplete adsorption of API by charcoal (charcoal block) have important ramifications?

However, even in worst case (e.g., BDP), differences in pulmonary vs. GI deposition for T vs. R product will be reflected in the PK profiles because of different absorption rates via the lungs/GIT.

- **BE would be very unlikely in this scenario**

In summary, efficiency of charcoal block should be validated. However, differential pulmonary and GI absorption rates will mitigate the confounding influence of incomplete charcoal adsorption (> 96%)

Ref: **MHRA/UK Experience – Focus on *In Vivo*, Design of Clinical Studies, Biomarkers, PK/PD**
Sanjeeva Dissanayake (MHRA, United Kingdom)

Track B: *In Vivo Tests (PK, PD, Biomarkers) (2)*

Additional Viewpoints:

- ***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?***

Track C: *"In Vitro Only" Equivalence*

Alternate Sizing Techniques:

- Likelihood of acceptability of alternative *in vitro* methods (e.g., alternative particle sizing techniques) incorporating
  - ***Simulation using patient-relevant flow patterns***
    - Useful to incorporate but not sure about methodology
    - What flow rate(s) to use for DPIs and is flow rate or acceleration in flow rate the important parameter?
  - ***Induction port design***
    - A lot of passion in the discussion on ports…..
  - ***Electronic lung***
    - Does permit use of patient profiles but expensive compared to a standard impactor
  - ***Acceleration profiles***
    - Acceleration in flow rate may be important for some DPIs

Spacers/Holding Chambers

What kind of data should be provided for a spacer/holding chamber?

- Test product will follow the summary of product characteristics (SPC) of the reference product: **if a spacer is included in the reference product** SPC**, the test product is likely to be used with the same spacer**, according to the same instructions.
- The same principles apply as for the comparative pMDI testing program: **start with *in-vitro* comparison.** If equivalence cannot be demonstrated: *in-vivo* studies are required.
- *In-vitro* study: **spacer should be treated as prescribed by the spacer manufacturer** (and applied by the patient), e.g. washed with soap solution/drip-drying, or no pretreatment.
  - Setting up the test in a clinically relevant manner:
    - Time delay between actuation/inhalation (e.g. 2 seconds)
    - Tidal breathing (unless to be used in one breath)

Ref: **Experience with OIP Equivalence Determinations in the Netherlands - Focus on *In Vitro* Aspects**
Marjolein Weda (RIVM, Netherlands)

Spacers/Holding Chambers

EMA 2009 Guidance on Clinical Requirements for Demonstrating Therapeutic Equivalence - asthma, COPD adults, pediatrics (Sections 4.1.3 and 6.2):

- required to be available for use with all pMDIs, and always with children;
- drug available (ED) from spacer affected by materials of manufacture, time delay between actuation and inhalation of pMDI, washing/preparation; patient interface;
- if data collected with one or more specific spacers, approval of OIP only with those spacers;
- test product characterized under same conditions as reference - no spacer, specific spacer.

Ref: **Experience with OIP Equivalence Determinations in the Netherlands - Focus on *In Vitro* Aspects**
Marjolein Weda (RIVM, Netherlands)

Patient Handling - Device/Patient Interface

- *Patient Handling - Device/Patient Interface:*
  - Correct operation and inhalation technique key to therapeutic outcome
  - Diversity of design means critical steps varies from device to device
  - Handling studies show that rates of patient/device critical errors can vary from device to device
  - A common mishandling error for DPIs is for patient to inhale unnecessarily slowly
  - Although the instruction leaflet is not the sole source of training, patients do find it useful

Ref: **Use of In Vitro vs. In Vivo Data To Conclude Equivalence of Two Inhaled Products**
Dave Parkins (GSK, United Kingdom)

Track D: *Device Design Similarity and Testing Needed to Support Device Changes*

- *Comments on Device Survey:*

- Lack of consistency in responses
  - More work required to investigate this
  - Did respondents answer based on what they would do or what they believed should be done?
- *Risk Management does not appear to be informing decision making*
- Desire to see sub-analysis of responses e.g. by region, background, experience
- Interest in comparing survey responses to actual approaches that were taken by the scenario writers

Track D: *Device Design Similarity and Testing Needed to Support Device Changes*

- *OINDP Change Guidelines:*

- *Existing change guidelines and standards are insufficient*
- *Desire for more specific OINDP change guidelines*
  - Flexible not prescriptive
  - Based on Risk Management principles (ISO 14971 and ICH Q9)
  - Approach to change based on assessment of impact on Critical Quality Attributes
  - Appropriate technical input e.g. linking testing to clinically relevant parameters
  - Need to consider who should draft this guideline? How should it be co-ordinated?

Track D: *Device Design Similarity and Testing Needed to Support Device Changes*

- *Risk and Quality Management Systems:*

- Consensus in the future relies on *use of Risk Management and QMS*
  - How to earn trust and get regulatory buy in?
  - Are regulators prepared to allow manufacturers to oversee their own activities subject to a different type of regulatory control?
  - Who/How to create framework for increased self-regulation?

Acknowledgements

The Organizing Committee

Carole Evans (Inspire, Co-Chair)
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Ilse Peterson (DBR)
Colin Reisner (Pearl)
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Terry Tougas (BI)
Pat Watson (BI)

Back-up Slides

Additional Discussion Topics from the Breakout Sessions

Track A: *Considerations for Design of Equivalence Studies (1)*

General Considerations:

- When are pharmacodynamic safety / efficacy studies required, and why?
- Definition of equivalence margins for 'effect-axis' comparisons / Effect axis or dose axis (relative potency) comparison?

Track A: *Considerations for Design of Equivalence Studies (2)*

Efficacy Considerations:

- What are the basic elements of a PD study?
- If you are developing a SABA formulation, which study model would you choose to use?
- Is the choice of models different for a LABA?
- If you are developing an inhaled corticosteroid, which study model would you choose to use?
- Advantages/disadvantages of Exhaled nitric oxide, AMP or mannitol challenge, sputum eosinophilia

Track A: *Considerations for Design of Equivalence Studies (3)*

Safety Considerations:

- PK defines requirement for safety studies
- What are the safety parameters that need to be assessed for development of beta-agonists, antimuscarinic agents and inhaled steroids?
- What are the appropriate populations for safety assessments of beta-agonists, antimuscarinic agents, and inhaled steroids?

Track B: *In Vivo Tests (PK, PD, Biomarkers)*

- PD/Clinical Outcomes of Equivalence of Local Delivery
  - Efficacy (e.g., Bronchodilators, Corticosteriods)
  - Safety
- Dose Response
- Applicability to BE of Combination Products
  - PK/PD Evaluations
  - If one active meets BE, the other fails?

Track C: *"In Vitro Only" Equivalence*

Themes that came up during discussion:

- Distinguishing testing for 'similarity' versus 'therapeutic equivalence'
- 'Clinical relevance and ability to model what happens *in vivo*' versus 'characterization of product performance'
- '*In vitro* only' is an option, but not a common one; limits are conservative