Generic Inhaled Medications

Generic Advair Inhaler

Generic Advair Inhaler (Seroflo Inhaler) is a combination products containing Fluticasone Propionate and Salmeterol Xinafoate which is used for the treatment of asthma in patients aged 12 years and older. It is also used in the treatment of Chronic Obstructive Pulmonary Disease (COPD).

Financial Interest Disclosure

(over the past 24 months)

Irvin Mayers

Company	Speaker	Advisory	Research
Medimmune			√
Novartis	√	√	√
GSK			√
Boehringer Ingelheim	√	√	√
CADTH		√	
Health Canada		√	

Financial Interest Disclosure

(over the past 24 months)

Irvin Mayers

Company	Speaker	Advisory	Research
AstraZeneca	√	√	√

Objectives

- Describe evaluation process for generics
- Review process for inhaled products
- Review differences between Health Canada, FDA and EMA

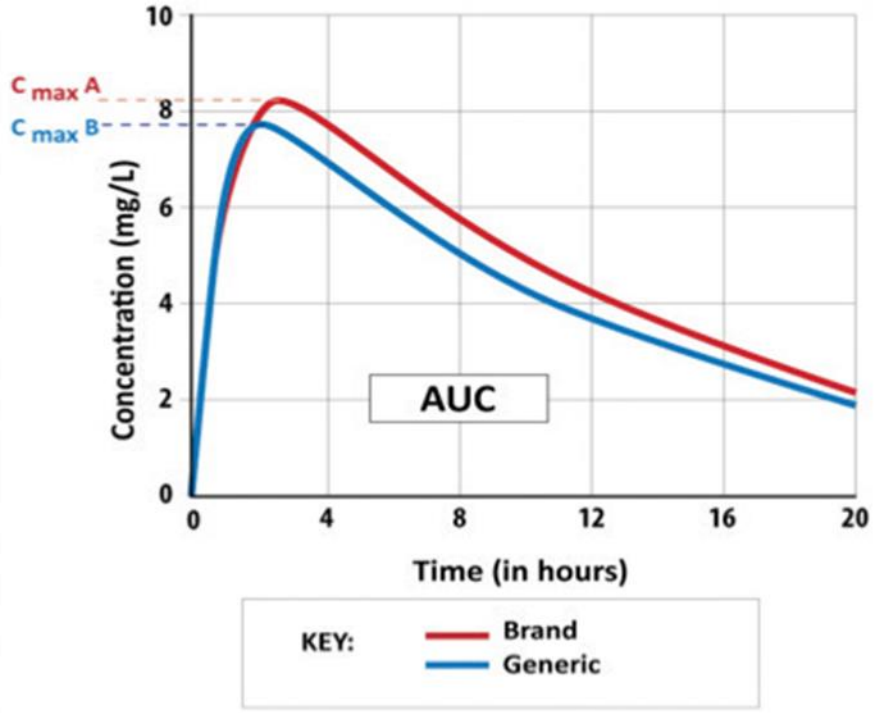
Assessing Bioequivalence

Oral or Intravenous Agents

Bioequivalence

- AUC is blood concentration versus time
  - AUC no less than 80% or no more than 125% of innovator
    - International consensus that differences within this range are not clinically significant

Figure 1: Simulation of a Drug Concentration Versus Time Curve for Two Drug Products

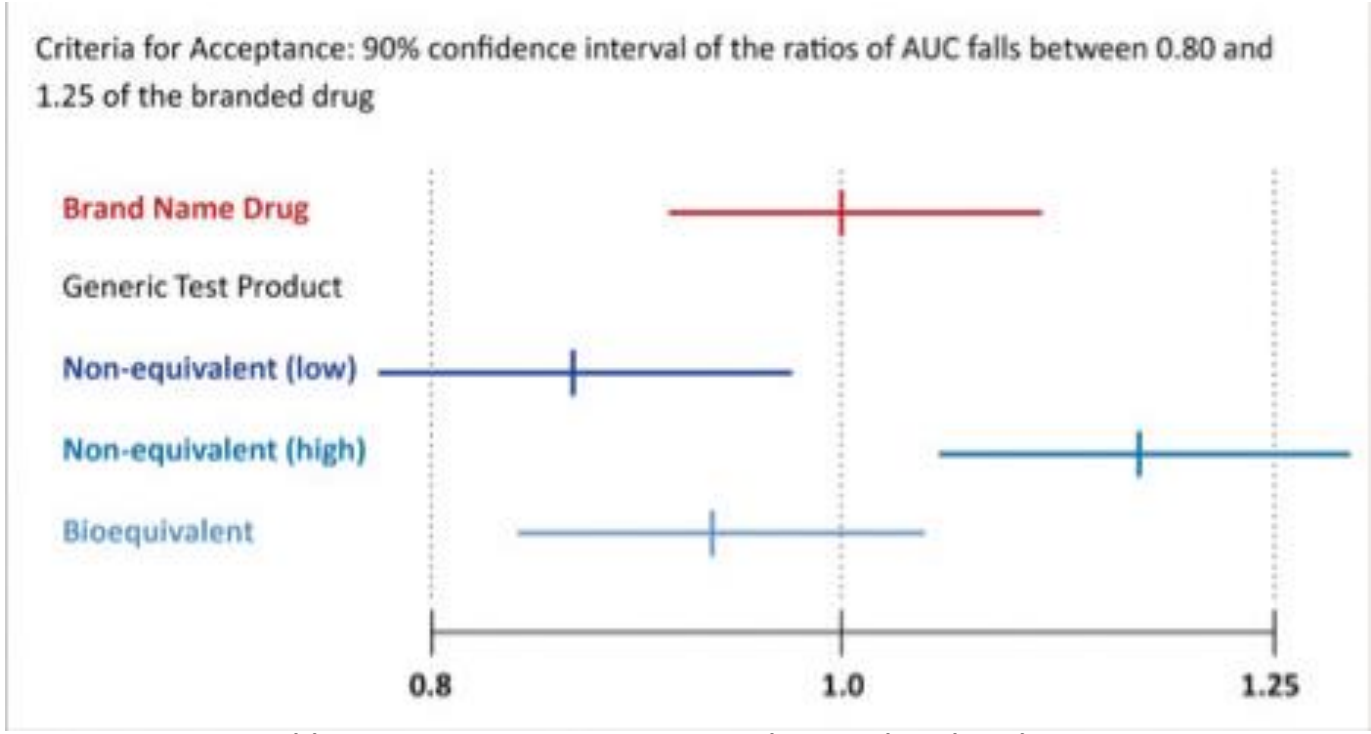


C_{max} maximum plasma drug concentration;
AUC total area under the plasma drug concentration-time curve

1. Canadian Agency for Drug Technologies in Health (CADTH).www.cadth.ca/en/resources/generics
2. Available from: http://www.pharmac.govt.nz/2009/08/25/bpjse_generics_2009.pdf

Bioequivalence

– 90% CI of the AUC must also fall within 80% to 125%.
  - For CI to fall within this range means variance is generally less than 5%.



Available from: http://www.pharmac.govt.nz/2009/08/25/bpjse_generics_2009.pdf

Generic Medications in Canada

- Highly toxic drugs or those with a narrow therapeutic range are known as critical dose drugs.
  - e.g. cyclosporine, flecainide, lithium, sirolimus, tacrolimus, theophylline, warfarin.
  - Health Canada sets different standards for these drugs.
    - Bioequivalence requirements are stricter for critical dose drugs
    - The 90% confidence interval for the AUC ratio should be contained within tighter confidence limits (90% to 112%).

Canadian Agency for Drug Technologies in Health (CADTH).www.cadth.ca/en/resources/generics

Generic Medications in Canada

- The excipients may differ between innovator and generic.
  - Important for patient with allergy or sensitivity to excipient(s).
    - e.g lactose, gluten, sulfites, or tartrazine
- The product may also differ in colour, shape, or markings.
- All generic manufacturers must meet standards for good manufacturing practices (GMP).
  - These include quality standards for ingredients, assays, manufacturing processes, and facilities.

Canadian Agency for Drug Technologies in Health (CADTH).www.cadth.ca/en/resources/generics

Generic Medications in Canada
The Holy Grail for Generics

- Interchangeability is not the same thing as bioequivalence.
  - Health Canada determines bioequivalence based on comparative bioavailability
  - Each province or territory determines interchangeability based on its own policies or regulations.
    - Interchangeability very important for marketing drugs
      - Also concern to patients when they get “new” drug

Canadian Agency for Drug Technologies in Health (CADTH).www.cadth.ca/en/resources/generics

Special Classes Where AUC is not Enough

- Ointment/Creams
  - Systemic absorption does not reflect activity at site of action
- Subsequent Entry Biosimilars (SEBs)
  - Biological agents have large, complex structures
    - There is inherent variability manufacturing process
  - An identical, generic drug is not possible
- Inhaled Medications
  - Systemic absorption is related to side effect profile and may not reflect effect at site of action

Chingcuanco et al., Bioequivalence of Biosimilar Tumor Necrosis Factor- Inhibitors Compared With Their Reference Biologics. A Systematic Review. Ann Intern Med. 2016; 165:565-574.

Inhaled Drugs for the Treatment of Asthma of COPD

Bioequivalence Oral or Inhaled

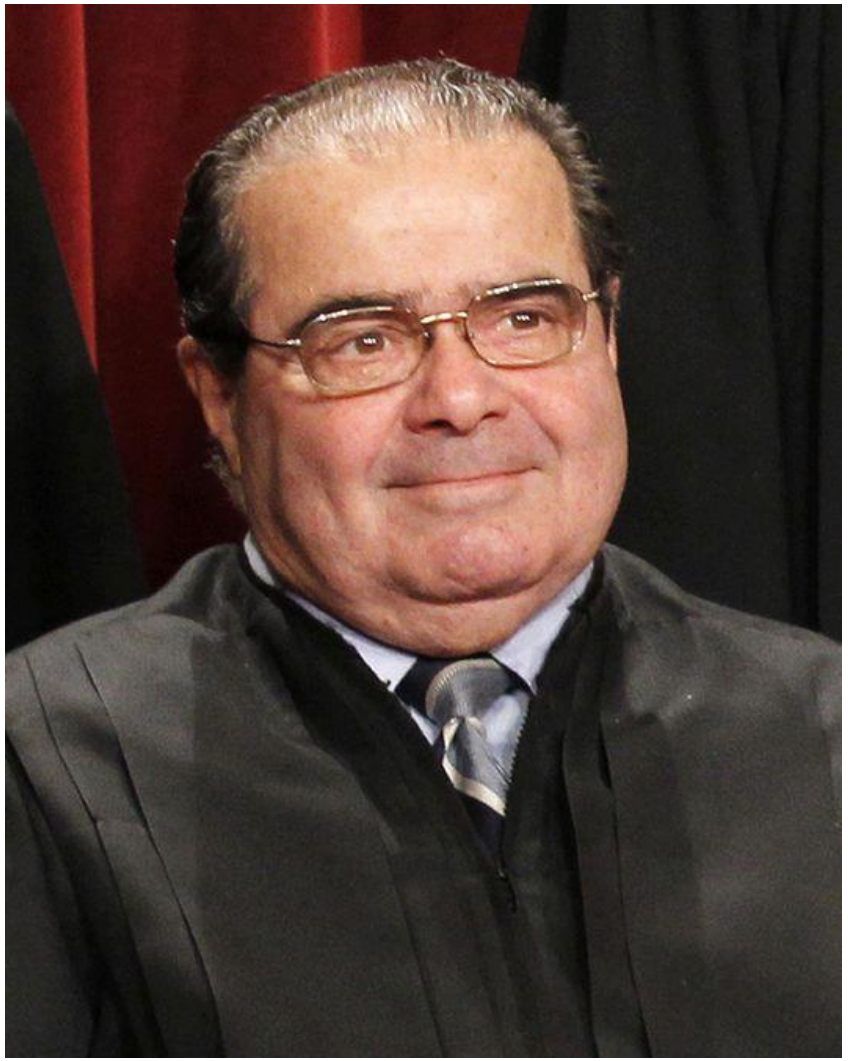
- Area under curve reflects multiple factors
  - Release of the active ingredient from the drug
  - Absorption from the GI tract
  - Presystemic metabolism
  - Distribution
  - Elimination
- Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data
- Bioequivalence can be demonstrated through other comparative testing
  - Comparative pharmacodynamic (PD) studies
  - pharmaceutical properties
- Comparative clinical testing supports therapeutic equivalence between tests and reference products

Available from: http://www.pharmac.govt.nz/2009/08/25/bpjse_generics_2009.pdf

Generic Inhalers

- AUC for inhaled products may not accurately reflect biological activity of the product
- Health Canada convened expert panel to give advice regarding inhaled products
  - Scientific Advisory Committee: Respiratory and Allergy Therapeutics (SAC-RAT)
    - The only worse acronym was proposed name honoring deceased US supreme court justice

Worst Acronym on Record



Antonin **S**calia **S**chool **o**f **L**aw

Orally Inhaled Products (OIPs)

- There is not consensus between different regulatory agencies regarding approval of SMEs
  - EMA uses Stepwise Approach
    - Step 1: In vitro equivalence
    - Step 2: Lung deposition and systemic exposure
    - Step 3: pharmacodynamic and/or clinical trials

Orally Inhaled Products (OIPs)

- FDA uses Aggregated weight-of-evidence approach
  - Pharmaceutical equivalence
  - In Vitro tests
  - Pharmacokinetic study
  - Clinical trial
- Need to complete all tests successfully for approval

SAC-RAT ICS Guidance

- The committee focused on bioequivalence
- Underlying explicit assumption that all other relevant guidance criteria regarding inhaled therapeutic agents had been met
- The language of generic medications
  - Innovator or Reference product
    - Also known as Canadian Reference product
  - Subsequent Market Entry (SME) or Test product

GUIDANCE FOR INDUSTRY

Pharmaceutical Quality of Inhalation and Nasal Products. Adopted 2006

- Sampling of Physical properties to be tested
  - Particle size
    - Median and distribution characterized
  - Physical characterization
    - Test for pMDI should include solubility, size, shape, density, rugosity, charge, and crystallinity of the drug substance and/or excipients
  - Extractables and leachables
  - Delivered dose uniformity & fine particle mass over patient flow rate range
  - Shaking requirements
  - Drug delivery rate and total drug delivered

GUIDANCE FOR INDUSTRY

Pharmaceutical Quality of Inhalation and Nasal Products. Adopted 2006

- The properties to be tested vary depending upon mode of inhalation
  - Pressured MDI
  - Nebulization
  - Dry Powder inhaler
    - Shaking test needed for pMDI but not DPI
      - “demonstrate that the shaking instructions provided to the consumer are adequate”.
    - Interaction with spacer not possible for DPI
  - Physical characterization needed for all inhalation products
    - tests for dry powder inhalers should include particle size distribution of the carrier (if present), bulk and tapped density, particle morphology (shape, texture and surface properties), melting point, electrostatic charge, porosity, specific surface area, hygroscopicity and moisture content

GUIDANCE FOR INDUSTRY

Pharmaceutical Quality of Inhalation and Nasal Products. Adopted 2006

- Each of the physical property elements has a set of associated requirements
  - *e.g. "Delivered dose uniformity and fine particle mass over patient flow rate range"*
    - … "demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates (through the delivery device) achievable by the intended patient population, at constant volume".
    - "The range of flow rates should be justified in relation to clinical studies or published data for the same delivery device. "
    - "The minimum (e.g., 10th percentile), median, and maximum (e.g., 90th percentile) achievable rate" should be evaluated.

Draft HC Guidance

- SAC-RAT developed proposed guidance to assist sponsors filing submissions for subsequent market entry (SME) ICS preparations for use in the treatment of asthma
- No validated model to test therapeutic equivalence of SME product to the Canadian Reference product
- ICS will be used in adult and pediatric patients as per label indication
  - Pediatric specific problems should be considered
    - Sensitivity to excipients
    - Need for SME device to be compatible with existing spacers

Asthma
Draft Study Design

- Powered on anti-inflammatory effects of ICS
- Randomized placebo-controlled trial
- Three parallel arms
  - SME, Canadian Reference, Placebo
  - Crossover possible but problems with washout
    - Significant number of subjects will not recover eosinophil counts following washout

Asthma
Draft Study Population

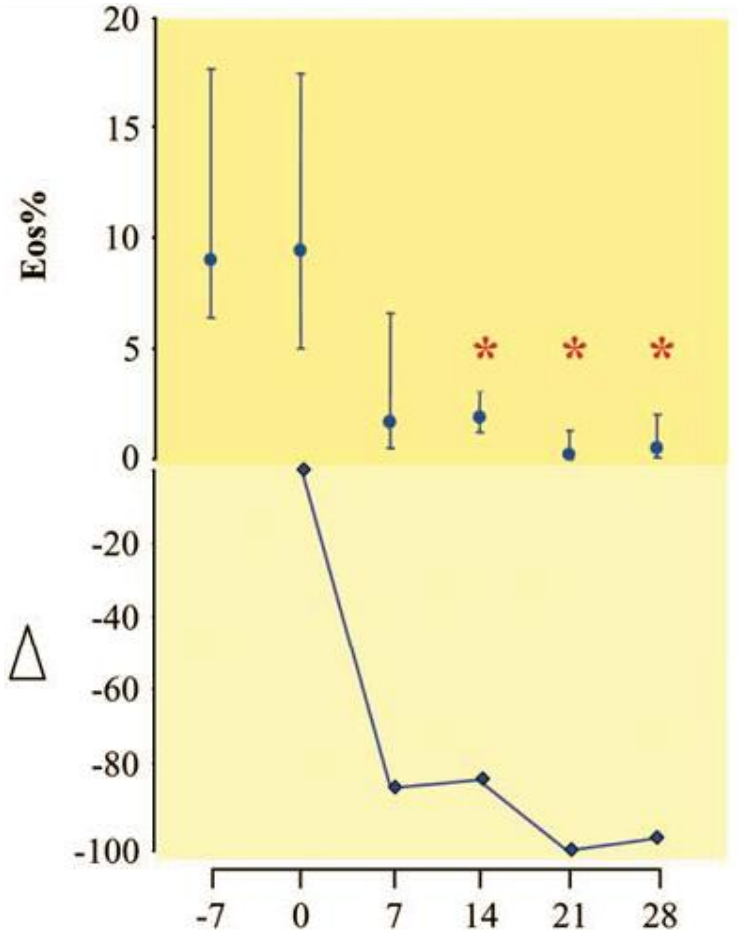
- Mild, stable asthma
  - Asthma defined by ATS standard definitions
  - Unethical to withhold effective active controller medication for prolonged period
- Steroid naïve
  - At least 6 weeks free of ICS
- Evidence of airway inflammation
  - Induced sputum eosinophils of at 3%
    - Alternate inflammatory markers can be negotiated

Asthma
Draft Study Design

- Study duration at least 3 weeks if parallel
  - Need time to reach therapeutic plateau
- Use lowest single dose of ICS of Canadian Reference product
  - Ensure that dose below therapeutic plateau
    - Still on the steep slope of dose-response curve
- Co-primary endpoints
  - Inflammatory outcome
  - Pre-bronchodilator FEV_1

Airway Eosinophils
Dose response to ICS

- Patients with eosinophilic bronchitis
- Treated with escalating doses of fluticasone
  - 50, 100, 200,and 400 μg/d each for 7 days
  - Largest percent decrease noted with fluticasone 50 μg/day



Kelly et al., J Allergy Clin Immunol 117:989-94, 2006

Asthma
Biological Activity

- Clinical Efficacy
  - Inflammatory marker
    - Both SME and Canadian Reference product should have 50% reduction in eosinophils compared with Placebo
    - This ensures that both products are biologically active in the subjects chosen
  - FEV_1
    - Mean FEV_1 of SME and Canadian Reference product are at least 10% greater than placebo

Asthma
Therapeutic Equivalence

- Standard definition
  - The 90% confidence interval of the relative mean FEV_1 (based on the log transformed data) of the SME to the Canadian Reference product should be within 80-125%
  - The 90% confidence interval of the relative mean eosinophil count (based on the log transformed data) of the SME to the Canadian Reference product should be within 80-125%

Trial Design LABA/SABA Suggestion for EMA

- Unique trial design for each class of product
  - Assess safety parameters in fasting state to avoid food effect.
  - Single dose studies may be acceptable for SABA's and LABA's.
  - Safety effects are generally not seen with approved and lower doses of these products.
    - Doses greater than maximal approved dose may need to be assessed to observe known class effects
    - Evaluate vital signs (including heart rate and blood pressure), ECG (particularly QTc interval), serum potassium, and blood glucose.

Evans C et al., J Aerosol Med Pulm Drug Delivery 25: 2012; 1-23.

Trial Design LAMA Suggestion for EMA

- Consider local adverse events (e.g., dry mouth).
- Minimal evidence to support feasibility of demonstrating dose–response for safety variables.
- PK similarity (upper limit of 90% CIs for the Test/Reference (T/R) ratio is 125%) is desirable.
- Consider alternative approach to PD safety
  - Assess biochemistry, hematology and ECG at maximal effect (fasting state),
  - Acceptability of this approach needs to be discussed with regulators on a case by case basis.

Evans C et al., J Aerosol Med Pulm Drug Delivery 25: 2012; 1-23.

FDA Draft Guidances for Generic OIPs

- ICS/LABA fixed dose combinations have been released over the last 5 years
  - Fluticasone proprionate/Salmeterol Xinafoate
  - Budesonide/Formoterol Fumarate dehydrate
  - Fluticasone Furoate/Vilanterol Trifenatae
  - Moetasone Furoate/Formoterol Fumarate
- The guidances are product specific
- There are also product specific guidances for LAMAs and LABAs

FDA Approach Fluticaosone Proprionate/ Salmeterol Xinafoate (Advair™)

- Proposed guidance for generic Advair™ dry powder
  - *In vitro* testing
    - Single actuation content (SAC)
      - Test at flow rates of 30 L/min, 60 L/min and 90 L/min.
      - Drawn 2 L air through the delivery system.
      - Test at beginning, middle and end of lifecycle of device
    - Aerodynamic particle size distribution (APSD)
      - Use flow rates of 30 L/min, 60 L/min and 90 L/min.
      - The volume of air drawn through the delivery system should be 4 L.
      - Test at beginning and end of lifecycle of device

FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate Sept 2013

FDA Approach
Generic Advair™

- Device
  - Passive (breath-actuated) device
  - Pre-metered multi-dose format 60 doses
  - External operating procedures consisting of (1) Open, (2) Click, (3) Inhale, and (4) Close
  - Similar size and shape to the R product
  - Comparable device resistance to the R product
  - Dose counter
- Formulation
  - The T and R products qualitatively and quantitatively.
  - Sponsor should provide pharmaceutical development data
    - in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the T and R products.

FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate Sept 2013

FDA Approach
Generic Advair™

- Pharmacokinetic study
  - Fasting, single-dose, two-way crossover
  - Normal healthy males and non-pregnant females.
  - After inhalation rinse mouth and spit. Do not swallow
  - Measure Fluticasone propionate and salmeterol in plasma.
  - Equivalence based on AUC and C_{max} for fluticasone propionate and salmeterol.
    - The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00–125.00%.
      - T=Test and R=Reference products

FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate Sept 2013

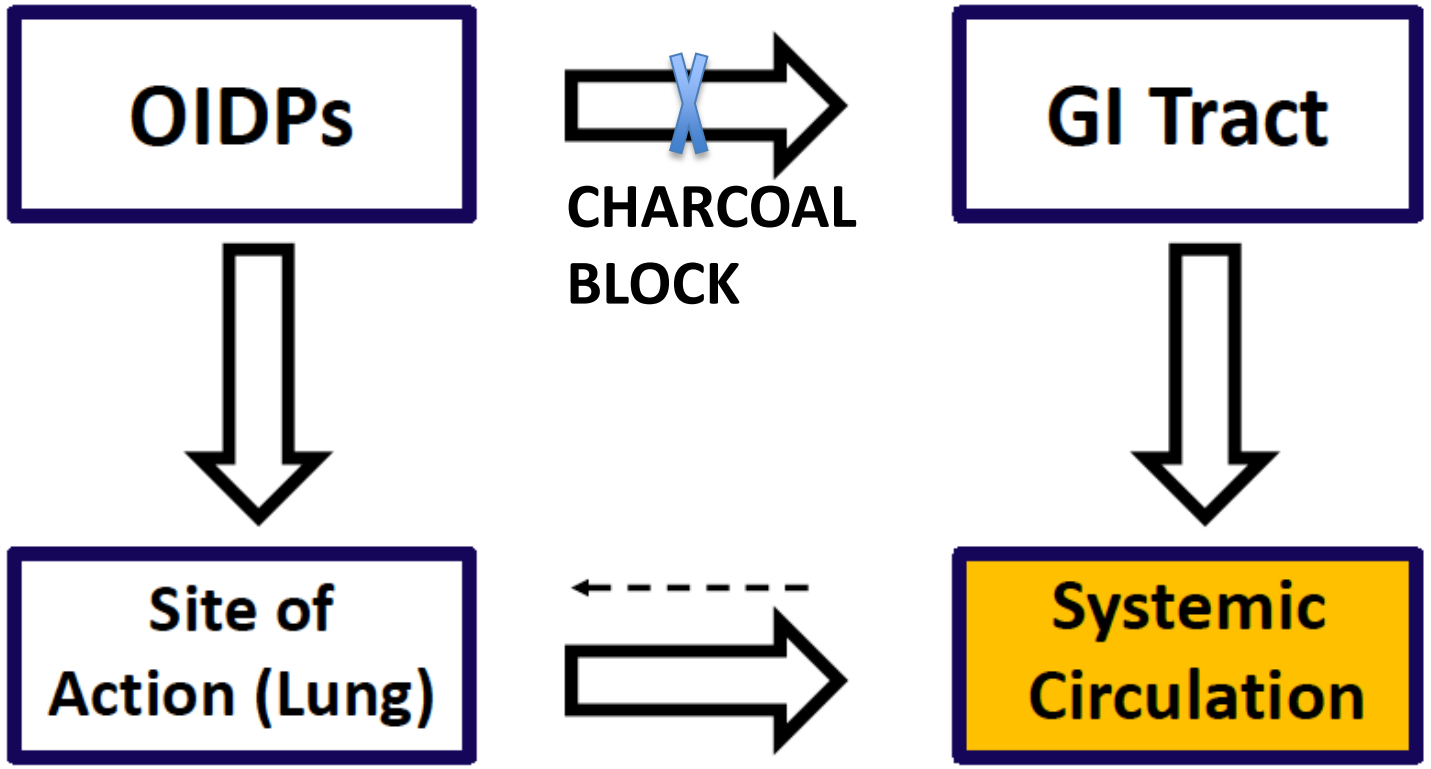
FDA Approach
Generic Advair™

- Clinical endpoint study
  - Trial design
    - RCT, multiple-dose, placebo-controlled, parallel group
    - 2 week run-in period followed by a 4-week treatment period of the placebo, T or R product
    - Fluticasone/salmeterol 100/50, twice daily
    - Males and non-pregnant females with asthma
  - Co-primary endpoints
    - (i) ($AUC_{0\text{-}12h}$ serial FEV_1-time on the 1st day of the treatment
    - (ii) FEV_1 pre-dose last day of a 4-week treatment.
      - Compared with baseline values
  - Equivalence based on T/R ratio for the primary endpoints.
    - The 90% CIs for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

FDA Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate Sept 2013

CAN A WELL DESIGNED PK STUDY REPLACE CLINICAL THERAPEUTIC EQUIVALENCE STUDY?

Limitations of PK Studies



The sampling site for PK studies (plasma) is a compartment that is downstream of the site of action (the lung)

Lee S. Scientific and Regulatory Considerations for Bioequivalence (BE) of Dry Powder Inhalers (DPIs). 2011 GPhA/FDA Fall Technical Conference October 4, 2011

Limitation of PK Study

- Plasma levels of orally inhaled products are not related to the positive clinical effects of the agent
  - Plasma levels are usually more closely related to side effects or adverse events
    - HPA suppression for ICS
    - Tachycardia for LABA

Pharmacokinetic Study

- The concentration-time curve is influenced by how much drug is deposited in lung and where it is deposited.
  - Assuming physical characteristics of Test and Reference products are similar
  - Deposition pattern in lung is mirrored by plasma-concentration time curve
- EMA has approved generic inhalers based upon PK and PD safety studies

Summary of Bioequivalence Criteria for DPI

Device and Formulation
- Similar size and shape
- Same basic operating principle
- Same number of doses
- Q1 and Q2

In Vitro Performance
- Equivalent emitted dose
  - 3 flow rates
  - B, M and E lifestages
- Equivalent APSD
  - 3 flow rates
  - B and E lifestages
- Comparable resistance

Equivalent Systemic Exposure
- Based on PK (AUC and Cmax) data
- For all strengths

Equivalent local delivery
- Based on PD endpoints showing dose-response
- Dose-scale method

Lee S. Scientific and Regulatory Considerations for Bioequivalence (BE) of Dry Powder Inhalers (DPIs). 2011 GPhA/FDA Fall Technical Conference October 4, 2011

FDA Approach
Generic Advair™

- The US draft guideline requires 50 tests
  - 36 in vitro tests
    - two active ingredients tested at three flow rates, with two endpoints for all three strengths
  - 12 pharmacokinetic tests
    - two active ingredients that must each pass equivalence testing for two endpoints for all three strengths
  - 2 pharmacodynamic tests
    - two endpoints for one strength.
- All tests must show equivalence

Fuglsang A. Pharm Med (2014) 28:169–173

What is Coming Soon

- FDA has had Abbreviated New Drug Applications (ANDA) for fluticasone propionate 100, 250, 500 mcg and salmeterol 50 mcg inhalation powder
- Canadian submissions are likely to increase in numbers
- EMA has approved 4 Fluticasone/Salmeterol generic products since 2011

- Why is this important?
  - Advair Diskus had U.S. sales of approximately $4.8 billion for the 12 months ending Dec. 31, 2015, according to IMS Health
  - Cost for Canadian drug plans and indiviudals is also significant for Reference product
  - There will be more submissions including other FDCs and monotherapy products for LAMA or LABA

Summary

- Inhaled medications offer multiple challenges
  - Simple PK testing may not be sufficient to ensure therapeutic equivalence
- EMA and FDA have recent guidances
  - Different approaches have resulted in generic approvals in Europe but not America
- Health Canada has guidance for SABA, SAMA and draft for ICS
- Health Canada does not have current guidance for combination inhalers or for long acting bronchodilators
- There are many companies with active pharmaceutical products with the same active ingredient(s) to those currently in Canadian and American markets

What Does “Generic” Mean to Patients

- Patients want less expensive medications
- Drug plans want less expensive generics
- Many patients and their physicians do not trust that generic medications are in practice the same as branded product