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Health Canada's Regulatory Approaches to Demonstrating Equivalence of Subsequent Entry Orally Inhaled Products

Clinical Perspective

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Background

1. **Currently, there is no consensus among regulatory agencies on the equivalence approaches with regards to the approval of Subsequent Entry (SE) Orally Inhaled Products (OIPs).**
2. **Health Canada (HC), under the expert advice of the Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT), has been working on providing potential Sponsors with relevant regulatory guidance related to the design and conduct of clinical endpoint studies since the early 1990s.**
3. **HC has the following clinical guidance documents for SE OIPs:**
   - **HC guidance on subsequent entry short-acting beta$_2$ agonist MDIs (1999)**
   - **HC draft guidance document on subsequent entry inhaled corticosteroids (ICS) for the treatment of asthma (2011) – update pending**
4. **Currently, HC does not have clinical guidance documents on long-acting bronchodilators or combination products, and has been providing consistent advice based on previous SAC-RAT Records of Proceedings.**

Outline

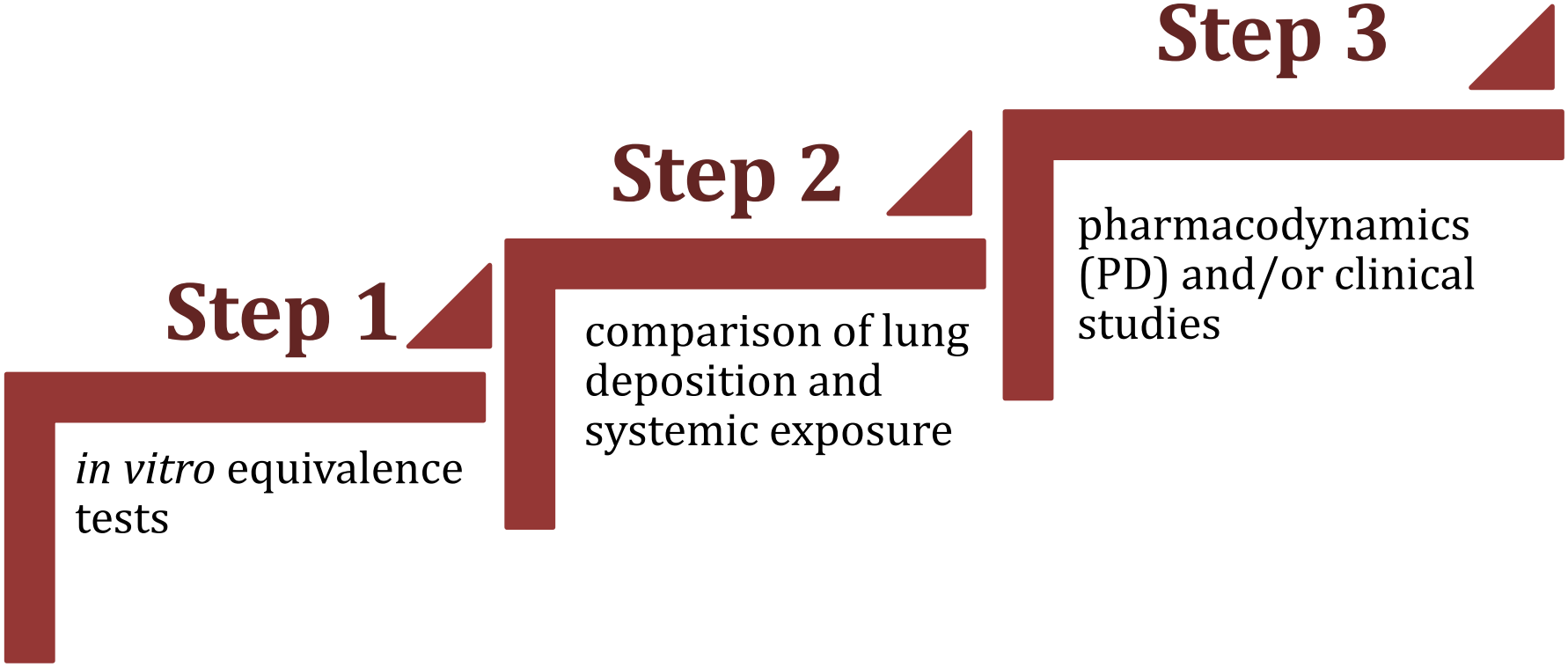
- **Brief overview of the current regulatory approaches for SE OIPs used by EMA, FDA, and HC**
- **Overview of HC's approaches to the clinical endpoint study requirements for SE OIPs [Abbreviated New Drug Submission (ANDS)]:**
  - **Short-acting beta$_2$ agonist MDIs**
  - **Inhaled corticosteroids (ICS) for the treatment of asthma**
  - **Long-acting Bronchodilators**

Brief overview of the current regulatory approaches for SE OIPs used by EMA, FDA, and HC

Two main regulatory approaches for SE OIPs

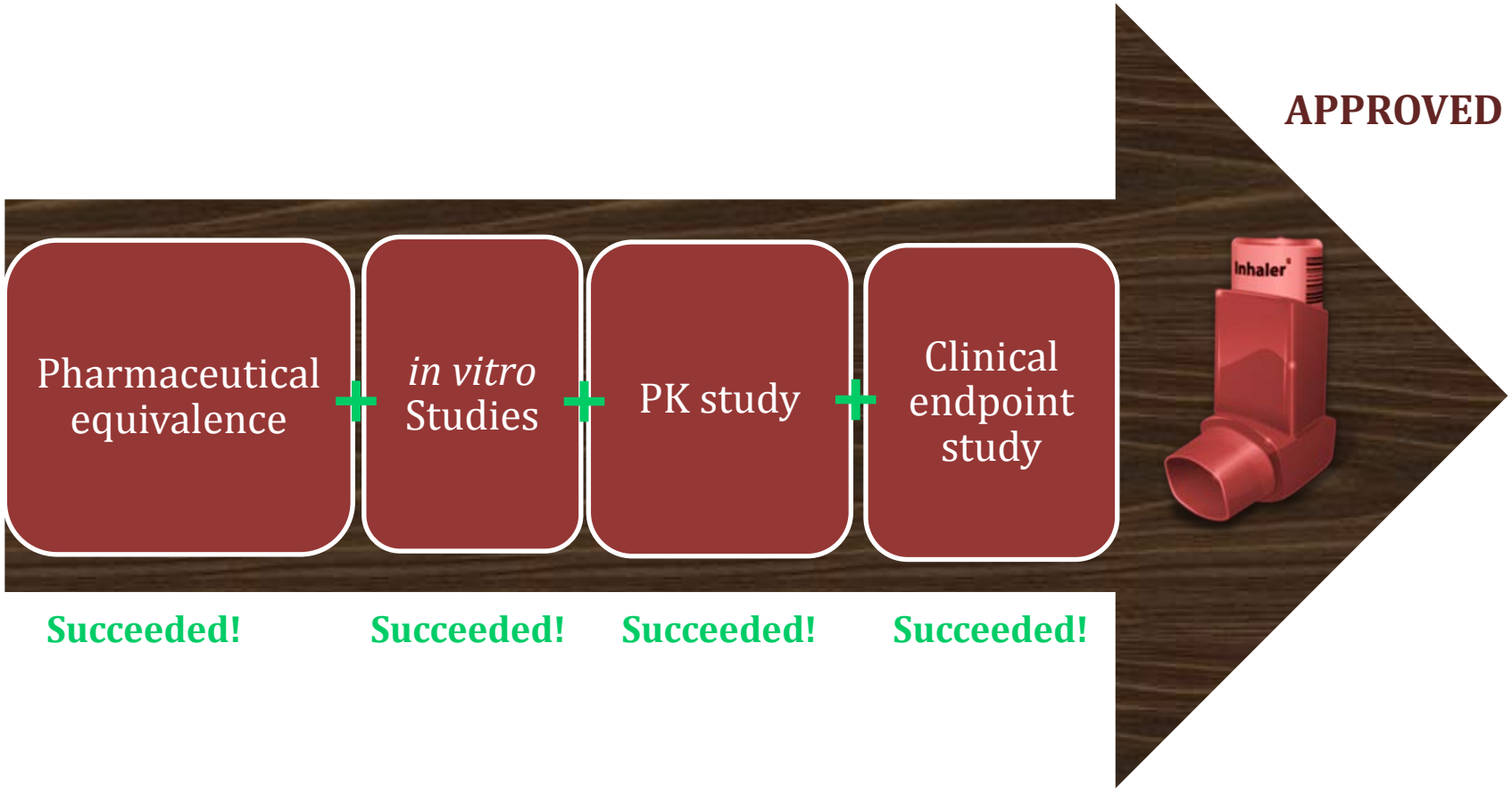
- Stepwise Approach (EMA)
- Aggregated Weight-of-Evidence Approach (FDA and HC)

Stepwise Approach (EMA)



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 USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS 2009

Aggregated Weight–of–Evidence Approach (FDA and HC)



Health Canada's Perspective

General requirements for an ANDS for OIP

1. **Quantitatively and qualitatively the same (Q&Q)**
   - ❑ *In vitro* requirements
   - ❑ "Sameness" of device and conditions of use
2. **PK studies with different strengths**
3. **Clinical endpoint study**

"Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Subsequent Entry Short-Acting Beta$_2$-Agonist Metered Dose Inhaler (MDI)"

Health Canada, 1999

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/inhalers/guidance-establish-equivalence-relative-potency-safety-efficacy-second-entry-short-acting-beta2-agonist-metered-dose-inhaler.html

Short-Acting Beta$_2$ Agonist MDIs

- **Proposed study design: a 4 sequence, 4 period, 4 treatment crossover design.**
  - **Treatment 1:** Subsequent Entry Product - 1 puff of 100 mcg
  - **Treatment 2:** Subsequent Entry Product - 2 puffs of 100 mcg (total of 200 mcg)
  - **Treatment 3:** Reference Product - 1 puff of 100 mcg
  - **Treatment 4:** Reference Product - 2 puffs of 100 mcg (total of 200 mcg)
- **Analysis of variance (ANOVA)**

Short-Acting Beta$_2$ Agonist MDIs

- **Bronchodilator Study Protocol**
  - The 90% confidence intervals for relative potency for maximum FEV1 and AUC must be contained entirely within 80-125%.)
- **Bronchoprotection Protocol**
  - The 90% confidence interval for the relative potency for test to reference PC20 must be contained entirely within 80-125%.

"Data Requirements for Safety and Effectiveness of Subsequent Entry Inhaled Corticosteroid Products for Use in the Treatment of Asthma"

Draft; Health Canada, 2011

HC held a meeting with the SAC-RAT in 2018 to discuss finalizing the guidance – finalizing guidance is referenced in conclusions

Proposed Study Design

- **Double blinded, randomized, repeated dose, study in mild steroid naïve asthmatic patients**
- **Parallel group design**
  - **Test (T):** Subsequent Entry Product
  - **Reference (R):** Canadian Reference Product
  - **Placebo (P):** Formulation Placebo

Proposed Study Design

- **Sample Size:** Sponsor's responsibility
  - Reasonably powered to demonstrate therapeutic equivalence
- **Study Duration:** minimum 4 weeks
  - Run-in period of 2 weeks
- **Choice of Dose:**
  - Lowest ***marketed*** strength of the Canadian Reference Product (if dose proportionality has been shown)

Proposed Primary Endpoint

- **Trough Forced Expiratory Volume in 1 second (FEV1):** FEV1 measured in the morning prior to the dosing of inhaled medications on the last day of treatment
- Alternative endpoints: airway inflammatory markers (e.g. sputum eosinophils)

Proposed Clinical Efficacy Criteria

To ensure study sensitivity:

- **Test (T) and reference (R) statistically superior to placebo ($p<0.05$)**
- **Clinically meaningful increase from baseline for FEV1 for both T and R**

Proposed Therapeutic Equivalence Criterion

90% CI of T/R:

- within 80-125% (log-transformed)
- within ±20% (non-log transformed)

Long-Acting Bronchodilator Clinical Endpoint Studies

- LABA
- LAMA

Based on: *Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT) Record of Proceedings November 13, 2009*

LABA or LAMA Clinical Endpoint Studies

- Randomized, single-dose, blinded (where possible), placebo-controlled, parallel group or crossover design at minimum consisting of a 2-week run-in period followed by a one-day treatment period of the placebo, T, or R product
- Inclusion/Exclusion criteria are product specific and are based upon the original design of the pivotal study of the Reference product

LABA or LAMA Clinical Endpoint Studies

- **AUC FEV1 (baseline adjusted) from serial spirometry (product specific: 12h or 24 h)**
  - **T and R statistically superior to placebo ($p < 0.05$)**
  - **The 90% confidence intervals for the T/R ratio for the study endpoint should fall within 80.00 - 125.00%.**
- **Tmax (time to effect)**
- **Shape of the curve (as assessed by the peak and trough) should be similar**

Conclusions

- **HC has a consistent regulatory approach for the approval of SE OIPs (Short acting bronchodilators, such as SABAs, ICS, LAMA, and LABA products)**
- **HC's regulatory requirements for clinical endpoint studies for OIPs are generally consistent with the EMA and FDA (e.g. primary endpoint, study duration, inclusion criteria)**
- **HC has a 1999 clinical guidance document on SE SABA MDIs, which provides guidance to Sponsors**
- **HC has a draft guidance for SE ICS products for the treatment of asthma, which is in the process of being finalised;**
- **HC has no clinical guidance documents on SE long-acting bronchodilators and has been providing advice to Sponsors based on previous SAC-RAT Records of Proceedings**

Thank you!

Questions?