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To cite this article: Irvin Mayers & Mohit Bhutani (2018) Considerations in establishing bioequivalence of inhaled compounds, Expert Opinion on Drug Delivery, 15:2, 153-162, DOI: 10.1080/17425247.2018.1381084

To link to this article: https://doi.org/10.1080/17425247.2018.1381084

Accepted author version posted online: 18 Sep 2017.
Published online: 21 Sep 2017.

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Considerations in establishing bioequivalence of inhaled compounds

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ABSTRACT

Introduction: Generic inhalers are often perceived as inferior to their branded counterparts; however, they are safe and effective if they can meet the regulatory requirements. The approach to assess bioequivalence (BE) in oral dosage form products is not sufficient to address the complexities of inhalational products (e.g., patient-device interface); hence, more considerations are needed and caution should be applied in determining BE of inhaled compounds.

Areas covered: This review outlines the evaluation process for generic inhalers, explores the regulatory approaches in BE assessment, and highlights the considerations and challenges in the current in vitro and in vivo approaches (lung deposition, pharmacokinetic, pharmacodynamic/clinical studies, and patient-device interface) for establishing BE of inhaled compounds.

Expert opinion: The ultimate goals in this field are to establish uniformity in the regulatory approaches to speed the drug submission process in different regions, clear physicians’ misconception of generic inhalers, and have meaningful clinical endpoints such as improvement in patient quality of life when compared to placebo and brand name drugs. As inhalational drugs become more common for other indications such as antibiotics, the technologies developed for inhaled compounds in the treatment of chronic pulmonary diseases may be extrapolated to these other agents.

1. Introduction

Generic drugs are often perceived as inferior to their branded counterparts; however, generic and brand name drugs have identical active ingredients. In Canada, generic drugs must demonstrate equivalence by meeting Health Canada’s standards for bioequivalence (BE) [1]. Bioequivalent drug formulations have the same bioavailability; therefore, new clinical studies are not required. All generic manufacturers must meet standards for good manufacturing practices; these include quality standards for ingredients, assays, manufacturing processes, and facilities. Moreover, Health Canada sets more stringent criteria for highly toxic drugs or those with narrow therapeutic range (e.g. antirejection drugs).

Unlike innovative new drugs, marketing authorization for a generic product can be obtained by an abbreviated new drug submission. There are regulatory approaches to ensure that the generic product is pharmaceutically equivalent and bioequivalent to the Canadian reference product (CRP), which is usually the branded product marketed by the innovator of the drug, using a series of comparative studies (e.g. bioavailability, pharmacodynamics [PD], or clinical studies) [1].

The approach to assess BE in oral dosage-form products (e.g. area under the curve [AUC] [2]) is not sufficient to address the complexities of inhalational products because AUC for inhaled products does not accurately reflect the product’s biological activity. Moreover, systemic assessments that are used for oral dosage-form products may not be applicable to compounds with localized targets such as inhalational products that are used to treat bronchoconstriction and/or localized inflammation in the airways [3,4]. As such, the use of a specific target end point (e.g. eosinophils or nitric oxide) is suggested over the use of secondary target measurements such as forced expiratory volume in 1 s (FEV1) when evaluating anti-inflammatory inhaled medications. In addition, the patient-device interface should be assessed for inhalational products, which adds complexity to the evaluation process.

A Canadian draft guidance for BE considerations for inhaled corticosteroids (ICS) suggested that the primary end point in a proposed study should be a marker of eosinophilic airway inflammation [5]. While this Canadian guidance document is intended for ICS, it can be used to frame the general guidance for BE assessment of inhaled compounds in chronic respiratory diseases such as chronic obstructive pulmonary diseases (COPD), which is currently lacking.

The purpose of this review is (i) to clear the misconception that generic inhalational products are inferior to their branded counterparts by describing the process of BE evaluation, and (ii) to emphasize the challenges in establishing BE of inhaled compounds by reviewing the in vitro and in vivo approaches and highlighting the considerations in each approach.

2. Generic inhalational products - what is BE?

According to Health Canada, pharmaceutically equivalent is defined as, when compared with another drug, a new drug containing identical amounts of the identical medicinal
In the evaluation approaches, aerosol behaviour should be studied, for bioequivalent drugs to be accepted, 90% confidence interval of the area under the curve must fall within 80% of the branded drug. Clinical trials should be of adequate duration (e.g., long-term studies), which include evaluations of both safety and effectiveness for each compound. There are still challenges in establishing BE of inhaled compounds; however, inhalational products require other comparative analyses.

Health Canada, US Food and Drug Administration (FDA), and European Medicines Agency (EMA) all have different evaluation processes for establishing BE of inhalational products [7]. Overall, Health Canada and FDA endorse in vitro studies as the starting approach, while EMA accepts an in vitro-only approach. All three agencies aim to make safe, effective, and less costly medications available to their respective populations, but it is concerning that there is a great degree of diversity in their approaches to the same products.

2.1. Health Canada

The Canadian Food and Drug Regulations has strict guidance that address physical equality (e.g. particle size), which is necessary when considering inhalated products because physical properties of the medicinal ingredients could potentially cause differences in the safety and efficacy profiles [6,8]. Presently, Health Canada does not have guidance for long-acting generic inhaled compounds in the treatment of COPD. The guidance to determine equivalence of subsequent entry short-acting beta agonist (SABA) stated that reliance solely on in vitro data is not suitable due to unestablished correlations between in vitro and in vivo data [9]. Further to this guidance, the Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT) strongly recommended a 1-year safety study to support registration of a subsequent entry SABA [10]. In its guidance document relating to the pharmaceutical quality of inhalation and nasal products, SAC-RAT recommended that physical properties, such as particle size and extractables and leachables, be tested for these products [11].

Figure 1. For bioequivalent drugs to be accepted, 90% confidence interval of the area under the curve must fall within 80%–125% of the branded drug.
In 2011, the draft guidance for treatment of asthma using ICS delivered via metered dose inhalers (MDIs) and dry powder inhalers (DPIs) recommended the measurement of primary endpoints that reflect the action and effect of ICS (i.e. inflammatory outcome) [5]. Both generic and CRP should have 50% reduction in eosinophils when compared with placebo. The guidance strongly recommends the incorporation of secondary end points, such as FEV$_1$, and an asthma control questionnaire. Generic and CRP should have a mean FEV$_1$ that is greater than placebo by at least 10%. The 90% CI of the relative means must be within 80–125% in order to demonstrate equivalence.

Current evidence in COPD research indicates that changes in drug-device combinations, different dose and formulations, along with specificities of study design, can have a significant effect on measurable outcomes and associated BE [12]. The asthma-ICS draft guidance indicates that safety considerations for subsequent entry ICS products should be addressed via appropriate pharmacokinetic (PK) study and comparable in vitro characteristics [5]. In vitro characteristics include similar active and inactive ingredients (i.e. propellant mix), and similar performance characteristics such as particle size distribution and velocity of the aerosol plume. PK studies should be a single-dose study at the upper limit of the dosing range, and AUC, C$_{\text{max}}$, observed time at which C$_{\text{max}}$ is reached (t$_{\text{max}}$), half-life, and terminal elimination rate constant should be determined. PD study should be conducted in healthy adult volunteers over asthmatic patients in order to preclude the potentially confounding effects of past or current steroid therapy, and variability in the degree of airway inflammation and obstructive impairment, which could act to reduce the power of the analysis. A study duration of at least 3 weeks is needed if parallel study design is used because time is needed to reach the therapeutic plateau. The dosage of CRP should be below the therapeutic plateau but still on the steep slope of the dose–response curve. Alternatively, a balanced crossover schedule of treatments with washouts between each dose is recommended.

The asthma-ICS guidance and the latest scientific literature provide a scientific framework for a protocol to exhibit BE of subsequent entry long-acting compounds in the treatment of COPD. In 2009, SAC-RAT released a general, preliminary guidance for subsequent entry long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and fixed-dose drug combinations [13]. This guidance is preliminary and requires further consultation, but it should be considered as a starting point for future guidance documents for LABAs.

The preliminary guidance stated that, for subsequent entry LABAs, the basic data requirements include PD/clinical study, PK study (for safety), and in vitro characterization of the particles and the delivery device [11]. For PD/clinical study, a minimum of 1 year is recommended in efficacy trial, and a 1-year safety study is not necessary for LABAs indicated for COPD unless the generic was submitted as a new drug submission. SAC-RAT recommends including patients with stable COPD requiring no intervention in the preceding 6 weeks and Stage 2–3 severity per the Global Initiative for Chronic Obstructive Lung Disease, as well as healthy volunteers/controls. A randomized three-arm crossover design (i.e. test [generic], reference, placebo) with a washout period of 72 h and an adequate run-in period is recommended. The PD study design should be the same as that outlined in the asthma-ICS draft guidance, with AUC of the FEV$_1$ as the primary efficacy end point. To establish therapeutic equivalence (TE), the 90% CI of test/reference ratio of mean change in the primary efficacy end point should be within 80–125%. SAC-RAT also recommends including FEV$_1$ data for claiming alteration of disease progression, COPD-specific quality of life (QoL) questionnaires for claiming reduction of COPD symptoms, 6-min walk test results for claiming improvement of exercise capacity, and well-defined moderate-to-severe COPD exacerbations for claiming reduction of COPD exacerbations. For PK study, QTc interval, heart rate, serum potassium, and glucose levels should be tested as additional safety parameters.

2.2. US Food and Drug Administration

At present, the FDA adopts a stepwise approach to establish BE of generic inhalers. It uses the weight of evidence approach, meaning that each drug application should incorporate qualitative and quantitative formulation similarities within acceptable margins, data from PK studies for the assessment of equivalent systemic exposure, and data from studies for the evaluation of equivalent local delivery [14,15].

The draft guidance released by the FDA in 2003 for the design of bioavailability and BE studies for nasal aerosols and nasal sprays for local action gave key considerations to drug particle size and distribution patterns, which are dependent on the drug substance, formulation, and device characteristics; similar biophysical considerations would be applicable to inhaled compounds [16]. In recent years, instead of releasing a general guidance document for determining BE between test and reference for all LABAs and LAMAs, the FDA released draft guidance that are tailored for individual inhaled compounds and their combinations; draft guidance are available for fluticasone/salmeterol [17], indacaterol maleate [18], ipratropium bromide [19], aclidinium bromide [20], beclomethasone dipropionate [21], ciclesonide [22], formoterol fumarate/mometasone furoate [23], budesonide/formoterol fumarate dihydrate [24], albuterol sulfate [25], and levalbuterol tartrate [26]. All of these draft guidance recommend a combined in vitro and in vivo approach for establishing BE of the test and reference inhalers. Generally, in vitro analysis should include a measurement for single actuation content and aerodynamic particle size distribution, with specific requirements for the device design and formulation. A PK study with crossover design in healthy volunteers is recommended, and equivalence is based on AUC and C$_{\text{max}}$ for the inhaled compound. PD/clinical study should have a parallel or crossover design with washout periods, and it should be conducted in COPD or asthmatic patients. Overall, FEV$_1$ is recommended as the primary end point, but there are specific endpoints for albuterol sulfate, and levalbuterol tartrate.

In vivo tests in humans measuring concentration-time profiles are the most thorough approach in terms of accuracy, sensitivity, and reproducibility for determining BE. However,
for drugs that are not intended to be absorbed into the systemic circulation, such as inhaled compounds, BE should be assessed by measurements intended to reflect bioavailability at the site of action. The FDA recognizes that the assessment of BE for locally acting products has presented a unique scientific challenge, and that the means by which certain tests are carried out can have a significant effect on outcomes. PK studies cannot easily address the extent of pulmonary deposition and the ratio of central to peripheral lung deposition. As such, lung deposition study is suggested to accompany PK results. In addition, trials of appropriate statistical power for preselected endpoints should be conducted to establish TE and determine the clinical effect of the compound.

2.3. European medicines agency

The EMA has considered the underlying scientific challenges associated with inhalational products. Current guidelines outline that BE between two inhaled products cannot be determined, but appropriate evaluation may lead to comparable TE. The guidance document by the EMA considers a stepwise in vitro and in vivo approach for determining equivalence. Approval of a generic inhaler based solely on in vitro testing is possible if the following criteria are met: identical dosage form, aerosol particle behavior, identical delivered dose (±15%), inhaled volume through the device to be ±15% of reference device, same resistance of the inhalation device to airflow (±15% of reference device), and similar handling of the inhalation devices to release the required amount of active ingredient [27].

If a generic inhaler fails in vitro assessment, TE can be established through in vivo pulmonary deposition using imaging studies or PK evaluation, with technical considerations acknowledged by the EMA, and PK similarity (i.e. upper limit of 90% CIs for the test/reference ratio is 125%) is desirable [7]. If lung deposition is not sufficient, clinical equivalence can be established through demonstrating both equivalent efficacy and safety. Alternative approaches to PD safety analysis can be considered, such as assessing the biochemistry, hematology, and electrocardiogram (ECG) activity at maximal effect (fasting state) [7]. Safety effects are generally not seen with approved and lower doses of SABAs and LABAs; thus, doses greater than the maximal approved dose may need to be assessed to observe known class effects. Vital signs, ECG, serum potassium, and blood glucose should also be evaluated. Specific to LAMAs, local adverse events (e.g. dry mouth) should be considered.

2.4. Summary of regulatory approaches

The brief review of regulatory approaches described above is summarized in Table 1, and it highlights the complexity of determining BE or TE between test and reference products and the inconsistency between different regulatory agencies regarding interpretation of similar scientific challenges. Drug-device design and patient-device interfaces may add more complexity to these evaluation approaches. In order to further establish BE standards for locally acting inhaled products, more work is needed to develop well-defined protocols with established end points for comparative clinical studies, develop and validate in vitro–in vivo correlations, and construct statistically justified criteria for declaring BE [28].

3. How to establish equivalence – in vitro studies

In vitro studies can be used to predict the in vivo behavior of inhalational products such as lung deposition. Typically, in vitro studies characterize the physical properties of the inhaled compound, which include, for example, particle size (median and distribution), solubility, shape, density, rugosity, charge, crystallinity, and velocity of the aerosol plume [11]. Particularly, the FDA recommends that in vitro analysis includes a measurement for single actuation content and for aerodynamic particle size distribution [17–26]. The properties to be tested vary and depend on the mode of inhalation.

Establishing BE for generics purely on the basis of in vitro results is insufficient because there are different mechanisms involved in in vitro sampling and in vivo deposition for

Table 1. Requirements for bioequivalence from Health Canada, FDA, and EMA.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada</td>
<td>Must meet all of the following:</td>
</tr>
<tr>
<td>FDA</td>
<td>● In vitro similarity</td>
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<tr>
<td></td>
<td>○ Similar active ingredients</td>
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<tr>
<td></td>
<td>○ Similar performance characteristics (e.g. particle size distribution,</td>
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<td></td>
<td>velocity of aerosol plume)</td>
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<tr>
<td></td>
<td>○ Systemic PK similarity</td>
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<tr>
<td></td>
<td>○ Single-dose study at the upper limit of the dosing range</td>
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<tr>
<td></td>
<td>○ Similar AUC, Cmax, Tmax half-life, and terminal elimination rate constant</td>
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<tr>
<td></td>
<td>○ Lung deposition study</td>
</tr>
<tr>
<td></td>
<td>○ PD or clinical similarity</td>
</tr>
<tr>
<td></td>
<td>○ Mean FEV1 greater than placebo by at least 10%; 90% CI of test/reference</td>
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<td></td>
<td>ratio of the mean change should be within 80–125%</td>
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<tr>
<td></td>
<td>○ Inflammatory outcome – 50% reduction in eosinophils compared to placebo</td>
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<tr>
<td></td>
<td>○ Efficacy trial of at least 1 year, with AUC of FEV1 as the primary</td>
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<td></td>
<td>end point</td>
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<tr>
<td></td>
<td>○ 1-year safety study</td>
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<td></td>
<td>○ COPD-specific QoL questionnaires</td>
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<td></td>
<td>○ 6-minute walk test</td>
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<td></td>
<td>○ Reduction of COPD exacerbations</td>
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<tr>
<td>EMA</td>
<td>Must meet one of the following:</td>
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<tr>
<td></td>
<td>● In vitro similarity</td>
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<tr>
<td></td>
<td>○ Identical dosage form</td>
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<tr>
<td></td>
<td>○ Identical aerosol particle behavior</td>
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<td></td>
<td>○ Identical delivered dose (±15%)</td>
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<td></td>
<td>○ Inhaled volume through the device (to enable enough active ingredient into</td>
</tr>
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<td></td>
<td>the lungs) to be ±15% of reference</td>
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<tr>
<td></td>
<td>○ Same resistance of the inhalation device to airflow (±15% of reference)</td>
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<tr>
<td></td>
<td>○ Similar handling of the inhalation devices between test and reference for</td>
</tr>
<tr>
<td></td>
<td>releasing the required amount of active ingredient</td>
</tr>
<tr>
<td></td>
<td>● Systemic PK similarity</td>
</tr>
<tr>
<td></td>
<td>○ Similar AUC, Cmax</td>
</tr>
<tr>
<td></td>
<td>○ Upper limit of 90% CIs for test/reference ratio is 125%</td>
</tr>
<tr>
<td></td>
<td>○ Lung deposition study</td>
</tr>
<tr>
<td></td>
<td>○ PD or clinical similarity</td>
</tr>
<tr>
<td></td>
<td>○ Equivalent efficacy and safety</td>
</tr>
<tr>
<td></td>
<td>○ Alternatives to PD safety analysis: biochemistry, hematology,</td>
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<tr>
<td></td>
<td>electrocardiogram activity at maximal effect</td>
</tr>
</tbody>
</table>

AUC: area under the curve; CI: confidence interval; Cmax: maximum observed concentration; COPD: chronic obstructive pulmonary disease; EMA: European Medicines Agency; FDA: Food and Drug Administration; FEV1: forced expiratory volume in 1 s; PD: pharmacodynamic; PK: pharmacokinetic; Tmax: observed time at which Cmax is reached.
inhalational products. First, *in vitro* sampling involves principles of impaction based on sequential stages, each of which has increasing linear velocity at a constant volumetric flow rate. In the principles of inertial impaction, large aerosol particles are deposited on the walls of airway conduit and the impaction tends to occur where the airway direction changes; in contrast, small particles have less inertia and are more likely to be carried around corners and continue in the path of the airflow. In the airways of the lungs, linear velocity largely decreases toward the periphery due to increasing cross-sectional area at any given flow rate, and variable cyclic airflow velocities are involved, which give rise to a different mechanism for *in vivo* deposition compared to *in vitro* sampling [28] (Figure 2).

Second, the *in vitro* predictive method would at best model the physical properties of the airways because impactors and their inlets have fixed dimensions with rectangular air ducts, whereas airways of the lungs are flexible with variable diameters and lengths, and possibly changing angles of bifurcation upon inhalation [29]. Despite the above concerns, inertial impaction has been used as the standard method for determining the aerodynamic particle size distribution of pharmaceutical aerosols for approximately 50 years [30].

Finally, it is difficult for *in vitro* models to address all variables involved in aerosol generation. *In vitro* models are generally static and will not allow for considerations such as patient-device interface and the inherent variability associated with the disease, which is accounted for in robust clinical trial programs of the reference product.

Given these differences in sampling and deposition, *in vivo* studies and clinical tests are needed for establishing BE of inhaled compounds.

4. How to establish equivalence – *in vivo* studies
4.1. Lung deposition studies
Lung deposition studies are often used as a means to understand the *in vivo* performance of generic inhalers/formulations in relation to the established products. These studies are suggested to complement PK assessments because they allow quantification of whole and regional lung deposition as well as extra-thoracic deposition [31]. PK studies, which evaluate systemic exposure, and conventional pulmonary function tests such as FEV1 do not provide information about regional drug deposition [32]. Moreover, data from lung deposition studies positively correlate with clinical efficacy of inhaled drugs [33].

Efficient drug targeting to airway regions is influenced by factors such as aerosolized particle size distribution and density, efficiency of aerosolization technology, timing of the aerosolization during inspiration, inhalation flow rate-time profile, inhalation volume, and geometrical configuration of airways [32,34,35]. Generally, particles with size <5 μm can be distributed deep into the lung with good clinical response [35]. One study reported that there is a high degree of variability in respiratory tract deposition of 3-μm particles in patients with different respiratory symptoms due to differences in flow rates [36]. Particles with size <2.5 μm are mainly deposited into the capillary-rich alveoli where they may exert no PD effect and are rapidly absorbed [33,35]. The finest particles with size <1 μm are mostly exhaled if they are not aggregated and/or not migrating to the lung walls [35].

Lung deposition studies commonly use radionuclide or radiolabel imaging, which allows for noninvasive quantification of whole and regional lung deposition. Care should be exercised with the use of radionuclide labeling in lung deposition studies, which includes correction for differences in breathing patterns and tissue attenuation, development of radiolabelling methods and lab-to-lab variation, validation testing for demonstrating that the addition of radiolabel has not changed the chemical and physical properties of the drug, and changes in particle size distributions over the shelf life of the product, which may affect deposition [37].

Most lung deposition studies to date have used 2D (e.g. gamma scintigraphy) and 3D imaging methods, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) [35,38,39]. Briefly, gamma scintigraphy uses the radionuclide ²⁹⁹ᵐTechnetium (⁹⁹ᵐTc)
and it is the most commonly used method in lung deposition analysis [35,40]. SPECT allows full 3D reconstruction of the lungs and it generally uses $^{99m}$Tc as the radiolabel [40]. PET uses a positron-emitting radionuclide such as $^{11}$C, which can be incorporated in the molecule’s structure without changing its chemical properties, allowing for highly accurate measurements of deposition and clearance; however, this method is limited by short half-lives of the positron emitters and cost [35,40,41]. There are currently devices with a combined PET/CT feature which allows for accurate incorporation of PET images with anatomical data [35].

Recently, magnetic resonance imaging (MRI) has been considered in lung deposition analysis. MRI uses nuclear magnetic resonance and thus, no radiolabel is required. However, contrast agents are usually added to aerosol formulation for measurements, which limits most of these studies in animals [35]. There are also novel simulation methods such as functional respiratory imaging (FRI), which is based on computerized tomography analysis and computational fluid dynamics. FRI simulates outcomes such as ventilation, lung deposition, and perfusion of airway blood vessels in a patient-specific manner. The enhanced sensitivity with FRI allows it to detect clinically relevant changes on a regional level and provide regional information in terms of deep lung deposition (distal and peripheral airways) and bronchodilation [32].

Overall, 2D scintigraphy provides a simple index of regional lung deposition with limited information on the anatomical site of deposition because 2D images of the lung represent the compression of a complex 3D architecture, consisting of a mixture of large and small conducting airways and alveoli, into two dimensions [31]. 3D imaging methods provide more information on regional lung deposition than 2D imaging (e.g. distribution in different planes) but they are more technically challenging than 2D scintigraphy.

An example of lung deposition study is the evaluation of Respimat® Soft Mist™ Inhaler (a propellant-free inhaler) and the Handihaler® for inhaled tiotropium. Respimat® Soft Mist™ Inhaler is an alternative to the Handihaler® for the delivery of inhaled tiotropium (a long-acting anticholinergic bronchodilator). Scintigraphic studies showed that there was greater lung deposition with the Respimat® platform when compared with a pressurized MDI (pMDI); and the mechanism of drug delivery of the Handihaler® suggests a lesser degree of lung deposition compared to the Respimat® platform [42]. Using the EMA’s equivalence algorithm, equivalence was not established between the Respimat® and Handihaler® devices based on deposition data.

When assessing BE using lung deposition studies, the difficulties of establishing dose–response relationships for inhaled asthma and COPD drugs should be considered. Clinical response to a bronchodilator reaches a plateau (ICS have relatively flat dose–response curves), and further drug deposition in the airways does not further augment the response [43]. Deposition studies are generally conducted using optimal inhalation techniques in order to maximize lung deposition, whereas inhalation techniques are not as well controlled in clinical studies (consider breathing patterns) [44]. Also, deposition studies have often been carried out in healthy volunteers, in whom aerosol deposition and its variability differ from patients with lung disease.

Given the benefits of lung deposition studies, they should be considered an important factor in assessing and establishing BE of inhalation compounds.

### 4.2 PK studies

Two inhaled products would be expected to show equivalence if the same dose is deposited in the lung with delivery to the same central and peripheral parts of the lung, and the drug enters the same pulmonary cells at the same rate with the same receptor kinetics.

PK analyses utilize measurements from serum (plasma) or urine [40]. For inhaled drugs, the sampling site for PK studies is a compartment that is downstream of the site of action (lung); thus, results from PK studies may not adequately reflect the therapeutic effect resulting from drug–receptor interaction within the lung. PK studies can estimate differences in total systemic delivery of inhaled products via AUC; however, two formulations could lead to a similar AUC calculation over a dosing interval even if the central and peripheral deposition is different [40]. Relative changes in $C_{\text{max}}$ or partial AUCs may provide a measure of different rates of absorption from different areas of the lung.

Previously, PK studies demonstrated that hydrofluoroalkane formulations of beclomethasone dipropionate had greater pulmonary deposition than the chlorofluorocarbon product, which agreed with the superior efficacy shown in PD studies [45]. In another study, two DPI-based combinations of fluticasone propionate and salmeterol showed significant differences in PK profiles, but clinical studies evaluating the pulmonary effects did not suggest any differences [46,47]. In addition, the study that compared Respimat® and Handihaler® for the delivery of tiotropium showed that BE was not established because the 90% CI was below the pre-specified acceptance interval of 80–125% [48]. Despite the lower systemic exposure of tiotropium with Respimat®, both devices demonstrated similar bronchodilator efficacy in clinical studies.

PK studies need to be designed carefully to account for regional absorption and potential differences in absorption rates. Systemic delivery via GI and pulmonary routes can be separated by blocking GI absorption with the administration of oral charcoal during lag time of the absorption phase [40]. While not sufficient on its own, an appropriately designed comparative PK study provides great insight into the clinical safety of a generic inhaler. Plasma levels are usually more closely related to side effects or adverse events of inhaled drugs, which are mainly systemic effects occurring downstream of the central compartment; thus, these effects can be evaluated through comparative PK studies. In addition to absorption, attention should also be given to excretion of the drug as it can affect systemic absorption (e.g. renal clearance).

Pulmonary residence time is another consideration in PK studies that is applicable to some formulations. Pulmonary residence time affects the degree of pulmonary selectivity and it should be similar amongst bioequivalent formulations because thin alveolar membranes and significant pulmonary blood flow allow solubilized drugs to be quickly absorbed into the systemic circulation. Depending on the chemical properties of the inhaled compound, $C_{\text{max}}$ and possibly $t_{\text{max}}$ may
decrease with decreasing absorption rate; therefore, PK studies may provide insights into potential differences in pulmonary residence time [49]. In addition, these studies should be carried out during PK steady state to reduce the effects of initial plasma fluctuations.

4.3. PD studies/clinical trials

PD studies report on the clinical efficacy and safety of generic inhalational products. Large phase III clinical programs may not be needed to establish safety if lung deposition and PK studies have stringent evaluation criteria and if analysis shows comparable results to the reference product. However, the FDA encourages clinical studies in patients for inhalational drugs due to their complexity and associated delivery systems; discrepancies have been observed amongst in vitro studies, PK studies, and safety [50].

While healthy volunteers are usually deemed suitable for PK studies, in studies of inhaled drugs conducted in patients, pulmonary disease significantly influences the deposition of the drug due to factors such as narrowing of conducting airways, mucus, and plugs. This issue can be addressed by adopting a crossover design, which allows for increasing study power and reducing the number of patients needed in the study [51,52].

In determining the clinical efficacy of inhaled products, two key effects should be evaluated – bronchodilation and bronchoprotection. Bronchodilation may be assessed through FEV\textsubscript{1}, measurement before and after delivery of inhaled drug at steady-state conditions [51,52]. Time-dependent bronchodilation may be evaluated through repeated FEV\textsubscript{1} measurements and generation of the area under the FEV\textsubscript{1}-time curve. Bronchoprotection may be evaluated through bronchial challenge studies, in which a bronchoconstrictive agent is introduced at increasing dosage, and FEV\textsubscript{1} is repeatedly measured until a 20% decrease is observed compared to baseline, thus defining a provocative concentration; then, comparison of this value before and after delivery of inhaled drugs allows for comparison of their therapeutic effects [53].

While most compounds used in the treatment of COPD may exhibit bronchodilation and bronchoprotection effects, reference products are typically studied for other outcomes such as degree of daily symptoms, rate of exacerbations, need for hospitalization, and health-related QoL. Safety evaluation is important in establishing BE of inhaled compounds. For example, two different formulations of tiotropium (Respimat® compared with Handihaler®) were compared in a 3-year study in terms of time to all-cause mortality and time to first COPD exacerbation [54]. Results demonstrated that tiotropium delivered by Respimat® was non-inferior to tiotropium delivered by Handihaler® with respect to the risk of all-cause mortality and not superior to Handihaler® with respect to the risk of first exacerbation.

For considerations in PD studies, caution must be applied when extrapolating the effects of a generic inhaler to all outcomes associated with the reference product. Trials of appropriate length and sample size should be conducted in order to provide sufficient statistical power for accurate comparisons between a generic and reference inhalational product. Moreover, careful consideration should be given to dosage in the design of trials. It is desirable to test drugs on the steepest part of their dose-response curve because it is usually ‘S’-shaped; thus, evaluating BE on either plateau of the curve would be inaccurate. Evaluating two dose strengths of the test and reference drugs may improve accuracy. For statistical methods in evaluating BE of inhaled compounds (i.e. comparing dose–response curves), the Finney parallel regression analysis and the nonlinear Emax model can be used [55,56].

Given the complexities of determining equivalence between a test and a reference product, clinical studies are necessary to establish comparable efficacy and safety, especially if PK analysis is not feasible.

4.4. Patient-device interface

Treatment in the pulmonary area is heavily device-dependent and the device component of the drug-device combination adds complexity to BE assessments. There are two essential factors in achieving reproducibility – design of the device and the patient’s technique to correctly use the device.

4.4.1. Design of inhaler device

Inhaler devices have been designed based on patient physiology and the molecule’s physical characteristics. In terms of patient physiology, efficacy of the inhaled drug can be affected by the type of disease even if the same device was used. For example, in the study of Sharma et al., the C\textsubscript{max} of tiotropium administered by the Respimat® platform is 50% lower in patients with asthma compared to COPD [57]. For physical characteristics, the device and the drug are not easily separable in suspensions or in dry powder devices; thus, an extensive series of physical property measurements are required before any BE testing can be considered.

In the design of a device, patient needs are important considerations and these can be placed into three categories – use, interface, and perception. In terms of patient use, the fundamental functions of the device (i.e. dose metering, flow resistance, handling, and sequence) should be considered. Differences in airway flow rate between healthy and disease states should be accommodated in the design. It should be noted that suboptimal flow in patients with COPD does not allow complete inhalation from DPI, leading to poor clinical outcome [58]. For the patient–device interface, the functionalities (e.g. dose counter, graphical instructions for ease of use, intuitive operations, and locking mechanisms) should be considered. Patient perception may include patient preference measures but they are difficult to quantitate. While risk management analysis can be used to determine the required studies to address these concerns, little consensus has been reached in a regulatory framework to address them.

4.4.2. Device handling by patients

Incorrect inhaler usage and non-adherence to therapy have been recognized as major factors in uncontrolled asthma or exacerbation of COPD [59]. An observational study found that up to 76% of patients were reported to improperly use delivery devices [60]. Another study showed that upon switching devices, the reported rate of successful treatment decreased
from 34.3 to 19.7% [61]. In particular, when switching from branded to generic inhalers, if patients with asthma or COPD do not receive appropriate training to use the device, this can result in poor clinical outcomes, increased healthcare costs, and poor patient–physician/patient–pharmacist relationship [59,62]. It has been demonstrated that devices with lower velocity of the aerosol could allow for greater lung deposition when compared with conventional pMDIs, possibly due to better coordination for patients (i.e. better technique) [42]. In general, factors such as patient age, severity of airway obstruction, and degree of training have been associated with poor patient-device interfaces [63]. For example, a 53% increase in lung deposition was observed in patients who were trained on the Respimat® device [64].

Given these complexities, a true generic inhalational product cannot be evaluated independent of the device [65]. In fact, the patient-device interface is increasingly being considered in the design of clinical trial programs.

5. Conclusion
This review outlined the evaluation process for generic inhalational products and the current in vitro and in vivo approaches for establishing BE of inhaled compounds, and highlighted the considerations and challenges in these approaches. There are still multiple considerations and challenges in establishing BE between generic inhalers and their corresponding reference drug products. At present, PK studies are commonly used to determine BE for systemically acting drug products; however, such an approach is unlikely to be sufficient to establish BE of inhaled drugs because their intended actions and deliveries are at the local sites and consequently, they do not rely on systemic circulation. As such, lung deposition studies are recommended to accompany PK analyses. For inhaled medications, drug-device combination and device-patient interface are both critical considerations in the development of these products. The same active ingredient can be formulated in similar or different inhalational devices but their aerodynamic performance may vary, which may lead to dissimilar drug delivery to the airways. Thus, it is imperative that comparative clinical efficacy and safety be properly evaluated with a robust clinical trial program to ensure that patients achieve the desired clinical outcome with the generic inhaler. Furthermore, safety evaluation should be established via long-term clinical studies in patients with the disease state.

6. Expert opinion
Currently, Health Canada, the FDA, and the EMA have different sets of approaches for BE assessment. There should be a unified, general set of evaluation approaches as a starting point for establishing BE for all inhaled products. Once these basic requirements were met, it is recommended that the test compound be assessed through drug-specific and/or device-specific approaches. Ideally, a comprehensive document should be developed through a collaboration of several regulatory agencies to cover all important issues, which would ensure that future products meet the high standards and be adopted internationally and allow for a streamlined process to expedite market entry for generic inhalers.

In addition to formulation, device characteristics and patient-device interface are important factors that affect clinical response to orally inhaled drug products. However, clinically important differences in patient–device interactions have not been established; thus, clinical studies should consider adding this end point to the study design.

In the field of generic inhalational products, the ultimate goals are to establish uniformity in the evaluation approaches to speed the drug submission process in different regions, clear physicians’ misconception of generic inhalers, and have meaningful clinical endpoints such as improvement in patient QoL when compared to placebo and brand name drugs.

In the coming years, there will be increased pressure in the approval of generic inhalers to gain market entry, and regulatory process should not be the limiting reason. In the approach to evaluate BE, lung deposition studies will become the center of attention. The methodology to assess lung deposition of separate compounds in a combination inhaler will be of interest because currently, there are no such techniques available. It can be foreseen that lung deposition studies will be increasingly used for BE assessment, and with the advancement in medical imaging technology and computational capabilities, lung deposition analysis may be sufficient to establish BE once in vitro studies are completed. In addition, there will be combination inhalers with more than two compounds, which makes drug-device design and BE study designs more challenging.

As inhalational drugs become more common for other indications (e.g. antibiotics, mucolytics), the technologies developed for LABAs and ICS may be extrapolated to these other agents.

Funding
This paper was not funded.

Declaration of interest
I Mayers has received an honorarium from Boeringher Ingelheim for CME related to generic inhalers. Medical writing assistance was used in the development of this paper and was carried out by Jane Cheung (SAGE Medica Inc.). The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


• This summarizes the requirements for a second-entry product to be considered a generic. It includes important definitions and concepts related to generics.

**This guidance outlines an approach to establishing BE using changes in inflammatory markers rather than relying upon changes in lung function.**


**This manuscript describes the EMA’s approach to in vitro testing for a second-entry product.**


**This manuscript describes the limitations of utilizing PK studies only in evaluating inhaled second-entry products.**


**This guidance from the FDA outlines the multiple steps and the complexity for a second-entry product to be accepted as a generic for salmeterol/fluticasone inhaler.**


45. Harrison L, Novak CC, Needham MJ, et al. Comparative pulmonary function and pharmacokinetics of fluticasone propionate and...