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Establishing bioequivalence for inhaled drugs; weighing the evidence

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Introduction: During drug development and product life-cycle management, it may be necessary to establish bioequivalence between two pharmaceutical products. Methodologies to determine bioequivalence are well established for oral, systemically acting formulations. However, for inhaled drugs, there is currently no universally adopted methodology, and regulatory guidance in this area has been subject to debate.

Areas covered: This paper covers the current status of regulatory guidance on establishing the bioequivalence of topically acting, orally inhaled drugs, the value and limitations of *in vitro* and *in vivo* bioequivalence testing, and the practical issues associated with various approaches. The reader will gain an understanding of the issues pertaining to bioequivalence testing of orally inhaled drugs, and the current status of regulatory approaches to establishing bioequivalence in different regions.

Expert opinion: Establishing bioequivalence of inhaled drug products involves a multistep process; however, methodologies for each step have yet to be fully validated. Our lack of understanding about the relationship between *in vitro, in vivo* and clinical data suggests that in most cases, unless there is a high degree of pharmaceutical equivalence between the test and reference products, consideration of a combination of preclinical and clinical data may be preferable to abridged approaches relying on *in vitro* data alone.

Keywords: bioequivalence, *in vitro*, inhaled medicines, pharmacodynamics, pharmacokinetics

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1. Introduction

During the lifetime of a drug product, a manufacturer may wish to modify their initial registered formulation and/or inhaler device. For example, this can result from changes to the manufacturing process, modification of an existing device or switching to an alternative inhaler device. In addition, new products may also be developed as alternatives to innovator products. Under these latter circumstances, where products may not be pharmaceutically equivalent, the robust demonstration of product equivalence is essential to ensure patients continue to benefit from products with the same safety and efficacy profile.

In the case of oral, solid dose forms, patients who receive alternative but bioequivalent formulations are unlikely to perceive any difference between the treatments. The packaging and the colour of the tablet may differ, but the patient's interaction with the product will remain essentially unchanged and will not impact the safe and effective use of the product. In contrast, for orally inhaled drugs, a patient's experience may be different, particularly in terms of the patient's interaction with the inhaler. Even when an alternative device meets all the required *in vitro* bioequivalence criteria, the patient interface with the device and its optimal use could be altered by changes in external design features, instructions for use, airflow resistance and something as simple as the feel in the mouth or throat during inhalation.

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Article highlights.

- Establishing the bioequivalence of inhaled drugs is a multistep process with little experimental evidence to validate the use of data from one of the various *in vivo* and *in vitro* methods over those from another.
- This lack of clarity is one factor contributing to the absence of a consistent approach across regulatory authorities to establishing bioequivalence.
- *In vitro* assessments of emitted doses are not universally predictive of pharmacokinetic and pharmacodynamic outcomes in clinical studies, pharmacokinetic data do not always correlate well with *in vitro* or clinical efficacy data, and pharmacodynamic data lack the precision of pharmacokinetic data when used to determine bioequivalence.
- It is clear that more data and better models are required to describe the relationship between *in vitro* and *in vivo* observations.
- A weight-of-evidence approach to new formulations that can be applied on a case-by-case basis rather than a rigid regulatory approach may be more acceptable. This approach places greater responsibility on drug development scientists to determine the level of evidence necessary to establish bioequivalence.
- Our lack of understanding about the relationship between *in vitro*, *in vivo* and clinical data suggests that, in most cases, unless there is a high degree of pharmaceutical equivalence between the test and reference products, consideration of a combination of preclinical and clinical data may be preferable to abridged approaches relying on *in vitro* data alone.
- There are several unresolved issues preventing the agreement of general guidelines on the best approach to establishing bioequivalence for all classes of inhaled drug products. A way forward could involve the development of product- or drug class-specific guidelines allowing some of the outstanding issues to be circumvented.

This box summarises key points contained in the article.

The use of pharmacokinetic data obtained in healthy volunteers is established as the primary means of providing clinical data that support claims of bioequivalence for systemically acting drugs when administered orally or parentally. The theoretical basis for this is the assumption that the drug concentration in the systemic circulation is in equilibrium with the concentration at its site of action. Where this is a valid assumption, bioequivalence testing can rely on three steps, comprising: i) qualitative and quantitative sameness of the active pharmaceutical ingredient and excipients, ii) *in vitro* dissolution testing and iii) a human pharmacokinetic study (**Figure 1**). However, this simplistic approach is not as appropriate for inhaled drugs, as a drug's concentration in the systemic circulation does not necessarily reflect the drug's concentration at its (topical) site(s) of action in the lung. Uncertainty about the relationship between the dose delivered to the site of action in the lung, topical efficacy and systemic drug concentrations serves as an obstacle to relying solely on pharmacokinetic data to assess the bioequivalence of topically acting orally inhaled drugs. Therefore, other sources of data must be considered and establishing bioequivalence may take as many as five steps where data may be required comprising: i) qualitative and quantitative sameness of the active pharmaceutical ingredient and excipients, ii) device similarity to ensure the product performance and the patient device interaction is unchanged, iii) *in vitro* device performance testing including emitted fine particle mass (FPM) dose and particle-size profiling, iv) *in vivo* product performance including lung deposition and systemic pharmacokinetic data and v) confirmation of equivalent topical efficacy (**Figure 1**).

The challenge faced in establishing the bioequivalence of inhaled therapies was first highlighted following the Montreal Protocol on the use of chlorofluorocarbons (CFCs) as propellants in metered dose inhalers (MDIs) [1]. It was noted that, despite the patent for the β_2-receptor agonist salbutamol (or albuterol as it is named in some countries) having expired in 1989, the first generic MDI preparation of salbutamol was not approved by the US FDA until late 1995 [2]. The main reason for the 6-year time period between patent expiry and generic approval was the lack of an acceptable and valid method for establishing *in vivo* bioequivalence of the generic salbutamol inhaler. Among the various methodological approaches, the FDA did not consider the use of urine and plasma pharmacokinetic data alone [3-5] or lung deposition data from gamma scintigraphy methods to be reliable as a means of confirming the relative quantity of drug delivered to the site of action in the lung. The consequence of the FDA's concern over industry responding promptly to the requirements for the Montreal Protocol was the publishing of their specific guidelines for establishing bioequivalence [6,7]. Regulatory agencies have since had time to consider the importance of the issues raised by this problem but have yet to agree a globally accepted approach on establishing the bioequivalence for inhaled drugs. Regulatory agencies have consulted with various interested parties over the type of data they felt would be necessary to determine the bioequivalence of inhaled drugs. Some guidance has been provided either in draft or final forms. In 2007, the European Medicines Agency (EMA) released a consultation document describing a proposed approach for the determination of bioequivalence [8]. At the end of the consultation period, a stepwise method outlining the requirements for clinical documentation for orally inhaled products was published in which consideration was then given to the use of *in vitro* data where predefined criteria for pharmaceutical equivalence have to be met [9]. Other agencies have placed emphasis on the collection of different types of data, for example, Health Canada focused more on pharmacodynamic end points for topical efficacy in their draft guidance published in 2007 [10].

Determination of bioequivalence of inhaled drugs remains an active area of debate and further discussions were held at the Product Quality Research Institute Workshop in 2009 [11], at the Respiratory Drug Delivery Conference 2010 [12,13] and at the International Society for Aerosols in

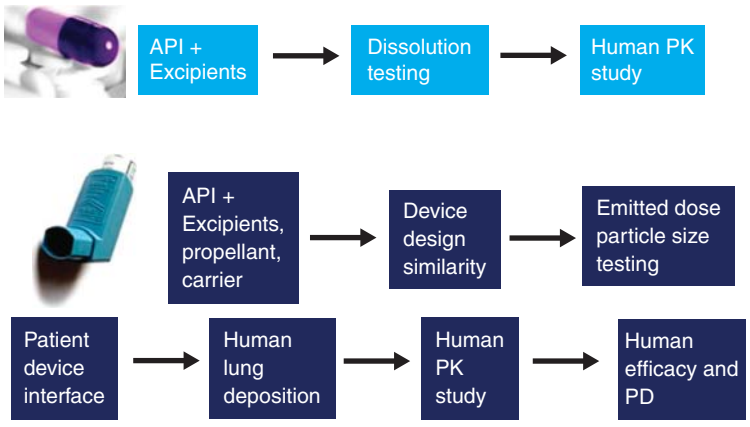

Figure 1. Comparative pathways for establishing bioequivalence in oral and inhaled medicines.

Medicine and International Pharmaceutical Aerosol Consortium on Regulation and Science conference in October 2010 [14]. Although several years of consultation have occurred, the FDA has yet to publish any general guidance on demonstrating the bioequivalence of orally inhaled products. In contrast to other regulatory agencies, the FDA currently recommends a 'weight-of-evidence' approach [15] and are also sponsoring studies looking at the potential utility of surrogate markers of efficacy.

2. Current status of regulatory guidance

Thus far, the only published final guidance has been from the EMA, Health Canada has only published draft guidance for the purposes of consultation, the FDA has yet to publish any general guidelines and, in other regions of the world, guidelines are also being considered. The EMA guidance has not only been taken up in Europe but has also been adopted by other regions such as Australia. After consulting on the revision of its guidance concerning the development of orally inhaled drugs in 2007, the EMA adopted its revised guideline in 2009 [9]. The revised guidance can be considered in conjunction with the draft EMA regulatory guideline on bioequivalence [16]. The EMA advocates a step-wise approach to the investigation of bioequivalence between test and reference products: step 1 involves *in vitro* comparison of formulations (only acceptable if criteria for formulation and device equivalence have been met); step 2 comprises the comparison of formulations using lung deposition models (pharmacokinetics and scintigraphy); and step 3 involves the use of pharmacodynamic and clinical efficacy data. Importantly, the demonstration of bioequivalence at step 1 or step 2 precludes the need for further comparisons. A schematic of this approach is shown in **Figure 2**.

The guideline also addresses the problem of different requirements depending on the type of inhalation device under investigation [9]. For dry powder inhalers (DPIs), consideration of device resistance is required and sufficient *in vitro* data must be included in the submitted dossier to describe the flow deposition characteristics of the products within the range of clinically relevant pressure drops/flow limits. For pressurised MDIs, the possible impact of any new propellant or excipient on clinical efficacy or safety should be studied and appropriate data should be provided to support the use of a named spacer device. *In vitro* characterisation of the drug product should be conducted prior to any therapeutic bioequivalence studies for all inhaler types.

Provided that requirements for formulation and device similarity are met, the EMA guideline allows the applicant to submit an 'abridged' application that contains only comparative *in vitro* data to substantiate a claim of therapeutic bioequivalence with a reference product. If the *in vitro* data satisfy specific criteria, no additional data from clinical pharmacokinetic or efficacy studies need be provided. A summary of the criteria from the guideline is presented in **Box 1**. The interpretation of this aspect of the guidance has been the subject of continuing debate [14,17] (see **Table 1** and Section 4).

If the *in vitro* data alone do not support a claim of bioequivalence, the next step in terms of the EMA guidelines is to conduct a pharmacokinetic study. The recommended design for pharmacokinetic assessment of orally inhaled drugs by the EMA is a four-period, crossover study where test and reference drugs are each administered in the presence and absence of a charcoal block (except where very low oral bioavailability precludes the need for the assessment of gastrointestinal drug absorption). This appears to be a scientifically sound approach as inhaled administration includes a swallowed fraction that will make some unknown contribution to systemic pharmacokinetic profiles. However, the methodology may need to be specifically validated for each drug product. Although the EMA guideline states that pharmacokinetic studies should be conducted in the intended patient population, bioequivalence studies are often conducted in healthy subjects. The choice of subjects is frequently based on the greater and less variable systemic exposure data often

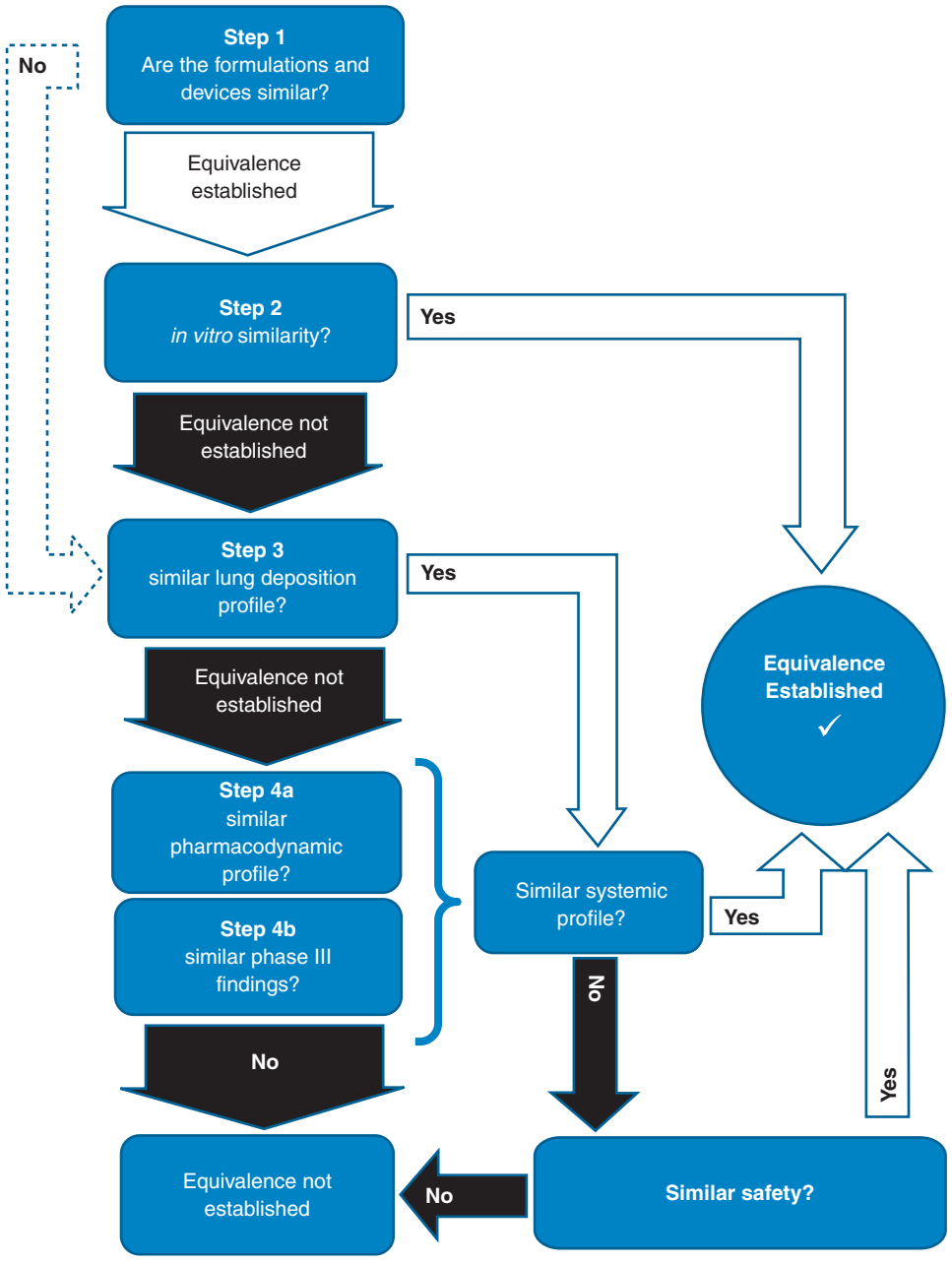

Figure 2. Schematic of the stepwise approach for establishing bioequivalence advocated by the European Medicines Agency.

seen in healthy volunteers compared with patients with lung disease [18], but having data in patients is invaluable in understanding the product performance in the target population. A summary of the key regulatory requirements for pharmacokinetic studies with orally inhaled products are presented in **Box 2**. At present, the question remains as to whether pharmacokinetic data are predictive of topical efficacy either directly or via pharmacodynamic end points, or more fundamentally, whether the drug concentration measured in plasma is a marker for topical efficacy at the site of action in the lung.

Pharmacodynamic assessment of test and reference products is the next step when bioequivalence has not been demonstrated with *in vitro* or pharmacokinetic data. The EMA provides guidance on appropriate pharmacodynamic methods to determine therapeutic bioequivalence. For bronchodilator and anti-inflammatory compounds, two types of studies appear to be acceptable to the EMA: studies of bronchodilatation/improved airway function and studies of bronchoprotection. The primary outcome variables are forced expiratory volume in 1 s (FEV1), such as the measurement of bronchodilatation over at least 80% of the duration of

Box 1. Regulatory criteria leading to the acceptance of *in vitro* data alone as proof of bioequivalence to a reference medicinal product (European Medicines Agency 2009).

The product contains the same active substance (i.e., same salt, ester, hydrate or solvate, etc.)
The pharmaceutical dosage form is identical (e.g., pressurised MDI, nonpressurised MDI, DPI, etc.)
The active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behaviour
Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g., delivered dose uniformity, etc.), aerosol particle behaviour (e.g., hygroscopic effect, plume dynamic and geometry) and/or be likely to affect the inhalation behaviour of the patient (e.g., particle-size distribution affecting mouth/throat feel or 'cold Freon' effect)
Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product
The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within ±15%)
Handling of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar
The inhalation device has the same resistance to airflow (within ±15%)
The target delivered dose should be similar (within ±15%)

DPI: Dry powder inhaler; MDI: Metered dose inhaler.

action after a single inhalation (FEV1 AUC), change in FEV1 at appropriate time points or the provocative concentration (or dose) that produces a 20% fall in FEV1 (PC20 FEV1). High variability in pharmacodynamic end points reported within the literature questions the reliability and repeatability of measures of orally inhaled drugs in a clinical study population through this type of study. At least two doses on the steep part of the dose–response curve need to be studied. The demonstration of equivalence in anti-inflammatory efficacy is difficult as it requires the demonstration of a dose–response relationship where a flat dose–response curve is often seen.

Health Canada released proposals on the assessment of bioequivalence for inhaled corticosteroids [10], but these are less detailed than the EMA guideline. In the Health Canada guideline, in addition to comparative *in vitro* product testing, second entry medicines must be assessed for bioequivalence in terms of clinical efficacy criteria. The recommended co-primary end points are sputum eosinophil count and FEV1. The draft guideline also states that sponsors should characterise systemic exposure profiles in terms of area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}). In contrast to the EMA and Health Canada, applications to the FDA are viewed on a case-by-case weight of evidence basis (**Box 3**). Although specific guidelines have not been published, it is assumed that comparisons between test and reference will need to provide data on all aspects of product performance. Hence, although the emphasis on *in vivo* and *in vitro* may differ in each case, the principles underlying the interpretation of the data and hurdles for approval are likely to be similar for the FDA and EMA.

3. Interpreting *in vitro* equivalence data

Characterising the *in vitro* particle-size distribution of inhaled therapies using cascade impaction has become a standard quality control approach to describing the aerodynamic particle-size distribution (APSD) performance of these products. This technique relies on separating the emitted aerosol into a series of size ranges based on their aerodynamic diameter. In the case of the Andersen Cascade Impactor operated at 28 l/min, the larger (> 9 μm) particles are trapped in the induction port with the subsequent stages covering the aerodynamic particle-size range from 9 (stage 0) to 0.4 μm (stage 7). The relevant size range for lung deposition is typically expected to be in the range of 1 – 5 μm and, for MDIs, grouping of data for stages 3 – 5 is frequently described as the FPM. There is an implied assumption that the particle-size profile, particularly the FPM of an inhaled therapy, is predictive of the *in vivo* lung deposition profile. Although this is not universally true, larger particles tend to be deposited in the mouth, throat and upper airways and smaller particles are likely to achieve greater lung penetration.

The ability to correlate clinical lung deposition and penetration with *in vitro* physical characteristics of an inhaled drug product is compelling as it would greatly simplify product evaluation. However, this assumption is more supported by theoretical than by empirical data. There is also a lack of data to support the definition of acceptable thresholds for demonstrating similarity between particle-size profiles. In this regard, the current EMA guidance to a large extent leaves the applicant to justify the testing of a product and the level of acceptance.

Many of the deficiencies encountered when attempts to correlate *in vitro* results with lung deposition data are inherent to the currently available methodologies. For example, differences in relative humidity can mean that the delivered particle-size distribution for a product can differ due to hygroscopicity or evaporation effects.

Cascade impactors generally use a metal induction port that does not replicate deposition that is observed in the oropharyngeal region of the respiratory tract. Furthermore,

Table 1. Relationships between pharmacokinetic data and *in vitro* particle-size profiles and clinical efficacy findings.

Example	*In vitro*	Pharmacokinetics	Efficacy	Design
Budesonide Turbuhaler® vs Budesonide Flexhaler®[1,2]	Good match	Equivalent (no charcoal block)	Not equivalent	Open-label, randomised, active-control, crossover, single dose; n = 37 Double-blind, randomised, placebo-controlled, parallel group, 12-week; n = 621 Double-blind, randomised, placebo-controlled, parallel group, 12-week; n = 516
Budesonide Turbuhaler® vs Budesonide Easyhaler®[3,4]	Small differences	Equivalent (charcoal block)	Equivalent	Open-label, randomised, active-control, crossover, single dose; n = 33 Double-blind, randomised, active control, parallel group, 12-week; n = 161
BDP Innovator CFC MDI vs BDP Generic CFC MDI[5]	Good match	Equivalent (no charcoal block)	Equivalent	Double-blind, randomised, crossover, single dose; n = 51
FP/Salmeterol Innovator pMDI vs FP/Salmeterol Generic pMDI[6]	Similar	Equivalent for FP; not equivalent for salmeterol	ND	Open, randomised, crossover, single dose (charcoal block); n = 31 Double-blind, randomised, crossover, single dose; n = 31
FP Diskus vs FP Diskhaler®[7–9]	Small differences	Not equivalent in healthy. Close match in asthmatics (no charcoal block)	Equivalent	Double-blind, randomised, placebo-controlled, crossover, 4-day dosing; n = 21 Double-blind, randomised, active-control, crossover, single dose; n = 12 Double-blind, randomised, active-control, crossover, single dose; n = 12 Open-label, nonrandomised, uncontrolled, 7.5 day; n = 24 Double-blind, randomised, active-control, crossover, 6-week; n = 232 Double-blind, randomised, active-control, crossover, 12-week; n = 212
FP HFA MDI vs FP CFC MDI[10]	Good match	Not equivalent at all doses (no charcoal block)	Equivalent	Open-label, randomised, active-control, crossover, single dose; n = 23
Salm/FP Diskus® vs Salm/FP RPID®[11]	Good match	Not equivalent (no charcoal block)	Equivalent	Double-blind, randomised, active control, crossover, 14 day; n = 22
Beclometasone DP CFC MDI vs Beclometasone DP HFA MDI[5]	Big differences	Not equivalent (no charcoal block)	Not equivalent	Double-blind, randomised, crossover, single dose; n = 51
Flunisolide CFC MDI vs Flunisolide HFA MDI[12]	Big differences	Not equivalent (no charcoal block)	Not equivalent	Open-label, randomised, active-control, parallel group, 13.5 days; n = 31

[1]Persson 2008; [2]Kerwin 2008; [3]Lähelmä 2004; [4]Tukiainen 2002; [5]Daley-Yates 1999; [6]Clearie 2010; [7]Falcoz 2000; [8]Mackie 2000; [9]Kunka 2000; [10]Daley-Yates 2009; [11]Noltinga 2001.

Box 2. Key regulatory requirements for pharmacokinetic studies of orally inhaled drugs in the European Medicines Agency guideline.

The demonstration of bioequivalence for orally inhaled drugs requires that standard criteria be fulfilled, that is, 90% confidence intervals for the log-transformed test/reference C_{max} and $AUC_{(0-t)}$ ratios should lie within 80 – 125% Tighter limits for AUC and possibly C_{max} may be appropriate for drugs with a narrow therapeutic index. Widened limits for C_{max} may be acceptable for highly variable products

Bioequivalence should be confirmed for partial AUC as a measure of early exposure where a rapid onset of effect is important

Both pulmonary deposition and total systemic exposure should be assessed, unless drug absorption via the oral route is very low such that pulmonary and systemic bioavailabilities are essentially the same

Total systemic exposure may be acceptable as a surrogate of systemic safety

Dose selection should be based on pharmacokinetic linearity/nonlinearity

Both urinary or plasma pharmacokinetic studies are acceptable in adults, whereas in children only the latter are advocated.

Where urinary pharmacokinetic studies are undertaken, plasma C_{max} should be estimated, if feasible, alongside the urinary data

Pharmacokinetic data for parent compounds/pro-drugs should be presented alongside that of active metabolites, assuming pharmacokinetics of the former are linear and plasma concentrations easily measurable, as C_{max} for parent compounds is more sensitive to detect differences between products

For pressurised metered dose inhalers, pharmacokinetic data comparing test and reference products in conjunction with spacers should be provided unless comparative *in vitro* spacer data satisfy stringent criteria for bioequivalence

For dry powder inhalers, the relevance of differences in intrinsic device resistance should be considered with respect to children

$AUC_{(0-t)}$: Area under the plasma concentration–time curve from time zero to infinity; C_{max}: Maximum plasma concentration.

Box 3. Key components of the aggregate weight of evidence approach described by the FDA [15].

Similarity of formulation
Similarity of device design
Comparative *in vitro* tests
Comparative systematic exposure studies
Pharmacodynamic or clinical end point studies

in vivo the oropharyngeal cross section can vary with device type, device resistance, tongue position and patient effort [19]. Attempts to design induction ports that better reflect and/or mimic physiological reality have included changing the dimensions and angles in the port, using 'sticky' surfaces to reflect those present *in vivo* and using casts from cadavers [20-22]. Magnetic resonance imaging data have also been used to determine the retention effect of the oropharyngeal airspace during the administration of drug aerosols as well as to generate mouth–throat models that can be used with patient relevant flow profiles to evaluate emitted APSD [23,24].

Deposition within the cascade impactor occurs through impaction that differs from the *in vivo* situation where deposition occurs through impaction, sedimentation and diffusion, the extent of which is dependent on particle size and the inhalation manoeuvre of the patient. The cascade impaction test is conducted at a fixed flow rate so as to allow the aerosol to be characterised into predefined size ranges, this differs from the *in vivo* situation where the inhalation profile is dynamic with varying flow and acceleration rate.

In an MDI, drug delivery is ballistic in nature being driven by the propellant present in the formulation, this means that the patient has to carefully coordinate their inhalation manoeuvre with actuation of the device; any differences between MDIs that may impact this coordination would not be detected by the cascade impaction test. In the case of the DPI, aerosolisation is driven by the patient's inhalation manoeuvre. This means that, when comparing DPIs, the resistance of the device itself must be considered as few devices have the same airflow resistance [25], thus affecting the flow rates achieved by patients.

As DPI performance is often a function of flow rate, which can differ from device to device [26], it is necessary to compare *in vitro* product performance across a range of flow rates. Several different approaches have been adopted to address these issues. Flow rate dependency can be studied using a range of fixed flow rates such as 30, 60 and 90 l/min; however, this approach results in different pressure drops across the device for devices of differing resistivity [27]. An alternative approach is to compare devices using the same pressure drop [typically 4 kPa (European Pharmacopedia)], but this means that the devices operate at different flow rates. Therefore, the stage cutoffs for the two test conditions will differ. Consequently, attributes such as fine particle dose (< 5 µm) can only be derived by interpolation, and comparison of full cascade profiles is not straightforward. Using the same pressure drop with different flow rates may still not allow the comparison of devices from the perspective of comparing devices with the same patient inspiratory effort [28]. Cascade impactors are limited in the range of flow rates at which they can operate to ensure that stage cutoffs are in the appropriate size range [29]. This means that the flow rates at which they are operated may not be the same as those actually achieved by some patient populations using the device in clinical practice.

In addition to a fixed flow rate, cascade impactors also use fixed high acceleration rates and airflow profiles that do not

reflect patient profiles [30]. This is relevant when comparing DPIs, as the performance of a device may be influenced by the acceleration rate used in testing [31]. In contrast, others have concluded that constant flow rates could be used providing that the rates selected reflected those expected *in vivo* [32].

The differences discussed might explain some discrepancies between clinical observations and *in vitro* data. For example, a comparison of two DPIs raised concerns about the predictability of *in vitro* FPM data [33]: the reservoir powder inhalation device (RPID) and Diskus® (GlaxoSmithKline, Ware, UK) inhalers administered the same lactose blend of salmeterol and fluticasone propionate. The performances of the inhalers were comparable over a range of flow rates. *In vitro* FPM data were similar for the two devices, but pharmacokinetic data showed that the devices could not be considered bioequivalent in terms of fluticasone propionate AUC [RPID:Diskus estimated ratio: 2.00; 90% confidence interval (CI): 1.56 – 2.55] and salmeterol C_{max} (ratio: 1.92; 90% CI: 1.64 – 2.25). However, data showed the two inhalers to be bioequivalent in terms of mean morning peak expiratory flow in a clinical efficacy study. There was clearly a lack of association both between *in vitro* FPM and *in vivo* pharmacokinetic data and between the pharmacokinetic data and clinical efficacy data. The key point to takeaway from this observation is that the difference in pharmacokinetic profile between the two inhalers could not be predicted from the *in vitro* data alone.

4. Interpretation of clinical bioequivalence studies

There are relatively few well-documented examples of inhaled product bioequivalence assessments that contain data from *in vitro* profiling, pharmacokinetics, lung deposition and clinical efficacy findings. Some of the best documented examples were summarised recently [34]. These studies included comparisons of generic and innovator products and studies assessing the effect of changes made to propellant or inhaler type. In most examples, *in vitro*, pharmacokinetic and clinical efficacy data were not in agreement. In general, *in vitro* data did not predict correctly the findings of pharmacokinetic and/or clinical efficacy studies (**Table 1**), and the pharmacodynamic data were less discriminating than pharmacokinetic assessments. Of the examples shown in **Table 1**, three are studies where bioequivalence was concluded from pharmacokinetic data. However, it would appear that, when other data are considered more closely, these conclusions may be unreliable. For example, a comparison of budesonide administered using either a Flexhaler™ (AstraZeneca, Soldertalje, Sweden) (budesonide 180 µg) or a Turbuhaler® (AstraZeneca, Soldertalje, Sweden) (budesonide 200 µg) features two products designed to have similar *in vitro* performance. Pharmacokinetic analysis demonstrated bioequivalence within the confidence limits of 0.8 – 1.25 for AUC (treatment comparison: 0.96; 90% CI: 0.91 – 1.02) and C_{max} (treatment comparison: 1.00; 90% CI: 0.92 – 1.09) [35]. A subsequent clinical efficacy study, although not designed to test equivalence, showed that lung function responses were lower for the Flexhaler formulation than Turbuhaler [36]. In the second example, budesonide administered by Easyhaler and Turbuhaler showed bioequivalence in terms of AUC (Easyhaler:Turbuhaler ratio: 1.02; 90% CI: 0.96 – 1.09) and C_{max} (ratio: 0.94; 90% CI: 0.86 – 1.03) [34]. However, the *in vitro* performance of these devices is likely to be different [37]. As charcoal block methodology was used in the study, only lung deposition was assessed, with no assessment of total systemic exposure. Another study presented total systemic exposure data, but with insufficient data to allow an assessment of bioequivalence in terms of systemic safety as only limited sampling was conducted around C_{max} and the Easyhaler showed greater variability than the Turbuhaler [38]. Therefore, it would be unwise to conclude true bioequivalence without additional and robust systemic pharmacokinetic data. A third comparison investigated the administration of beclometasone dipropionate using innovator and generic MDIs. Reviewing the pharmacokinetic data obtained at the 250-µg strength product, bioequivalence was concluded for pharmacokinetic, *in vitro* and clinical studies. However, when data obtained at different dose levels were reviewed, clear indications of nonbioequivalence emerged: differences were observed in the FPM and pharmacokinetics data at other doses and, therefore, it was concluded that bioequivalence could not be assumed for the high and low doses [39].

Pharmacokinetic data in various studies appear to suggest only partial bioequivalence when comparing inhaled products [40-42]. In a study that compared the pharmacokinetics of fluticasone propionate administered via the Diskus or Diskhaler® (GlaxoSmithKline, Ware, UK), data from patients with asthma differed markedly from that obtained from healthy subjects. *In vitro* analysis showed similarities between the Diskus and Diskhaler for FPM (17.0 and 16.9%, respectively), although a difference was observed for particles < 2 µm (2.0 and 3.4%, respectively) [43]. Data from healthy subjects demonstrated higher fluticasone propionate systemic exposures following Diskus inhaler administration and *in vitro* FPM differed between the two devices [44]. In patients with mild-to-moderate asthma, systemic exposure to fluticasone propionate was ~50% that in healthy subjects with little difference between the two devices within population groups [40]. These findings emphasised the need to carry out studies in the target patient population. In another example, the delivery profiles were compared for two different propellants, CFC and hydrofluoroalkane (HFA), following the administration of fluticasone propionate via two MDIs [41]. The inhalers had similar *in vitro* FPM. At the 250-µg dose, systemic exposure was similar for the two formulations in terms of AUC (HFA:CFC ratio: 0.88; 90% CI: 0.75 – 1.05) and C_{max} (ratio: 1.01; 90% CI: 0.86 – 1.18). However, at the 125-µg dose, there was a marked difference between the formulations, with systemic exposure approximately one-third lower for the HFA formulation than CFC in terms of AUC (ratio: 0.67; 90% CI: 0.57 – 0.79) and C_{max}

(ratio: 0.63; 90% CI: 0.75 – 1.05). It was clear that the pharmacokinetic profile for the 125-µg dose could not be extrapolated from the 250-µg dose, and therefore, the two formulations should not be considered bioequivalent at all doses. Another study showed similarity of an innovator and generic fluticasone propionate/salmeterol combination product in terms of overall fine particle dose (particles < 4.7 µm) for both the fluticasone propionate and salmeterol components [42]. On pharmacokinetic assessment, the salmeterol moiety of the generic product produced significantly greater systemic exposure than the innovator product, although bioequivalent systemic exposure was observed for fluticasone propionate. No major differences were observed in pharmacodynamic end points. As the authors noted, the results of this study highlighted the potential pitfalls of extrapolating *in vitro* data for fine particle dose to a clinical setting for *in vivo* pharmacokinetic and pharmacodynamic outcomes. Taken together, the findings of these three comparisons highlight the difficulty in cases where *in vitro* data alone are used to assess the bioequivalence of two inhaled drug products.

In three of the examples presented in **Table 1** [33,39,45], pharmacokinetic data did not establish bioequivalence in terms of AUC and C_{max}. In comparisons of MDIs delivering drugs with either CFC or HFA propellants, the *in vitro* FPM profiles, median mass aerodynamic diameter and systemic availability were sufficiently different to offer a low expectation that *in vivo* bioequivalence would be found, and this was confirmed [39,45]. An example in which an innovator MDI administering beclometasone dipropionate propelled by CFC was compared with a generic inhaler propelled by HFA indicated that pharmacokinetic data may be more discriminating than pharmacodynamic data [39]. In this instance, both *in vitro* and pharmacokinetic assessments showed differences between the two inhalers in terms of the emitted FPM dose and systemic exposure to the active metabolite. Serum cortisol AUC data showed little difference between the inhalers, so inappropriate conclusions of bioequivalence would have been made for the lower dose inhalers if the bioequivalence assessment had been based on serum cortisol AUC alone.

As stated earlier, the role of pharmacokinetic data in establishing the bioequivalence of topically acting inhaled drugs relies on an assumption that the systemic concentrations of an orally inhaled topically acting drug reflect those at the site of action. The validity of this assumption was assessed indirectly in a study originally designed to investigate whether the therapeutic benefits of inhaled fluticasone propionate are mediated through topical effects in the lungs rather than via systemic effects. The study compared the effect on morning FEV1 of inhaled (100 and 500 µg twice daily) and orally (20 mg once daily) administered fluticasone propionate and placebo after 6 weeks in 274 patients with asthma [46]. High oral doses of fluticasone propionate achieved steady-state plasma concentrations approximately twofold greater than those following inhaled fluticasone propionate. However, although both inhaled doses improved morning FEV1, oral dosing showed no significant improvement. This finding provides further compelling evidence that the systemic plasma concentrations and the concentrations at the site of action in the lung are not in equilibrium, and consequently, it must be considered that pharmacokinetic data are not a valid surrogate of topical efficacy. However, it is important to emphasise that pharmacokinetic data remain a valid surrogate of systemic safety.

Looking to the future, imaging technologies have been proposed as a means to provide further information on lung deposition of inhaled drugs. Three methods are available: planar gamma scintigraphy, currently the most frequently used technique, single photon emission computed tomography and positron emission tomography (PET). The first two techniques involve passive radiolabelling of the aerosol particles or droplets and PET requires direct labelling of the drug molecule. At the RDD 2010 conference, a workshop session discussed this area in particular. The output describing these discussions has recently been published [47]. There are two main problems to overcome in adopting these techniques, first, the process of labelling the drug particles has the potential to alter the drug product such that it is no longer representative of a commercially manufactured batch of the test or reference product. Second, the drug particles may only be surfaced-labelled or the marker is too labile and hence does not give a true picture of lung deposition of the unadulterated product.

5. Integrating guidance with experience

Rigorous standards are needed to ensure that alternative bioequivalent products are truly interchangeable without compromising patient safety or efficacy. Guidance is beginning to emerge on what might be regarded as an acceptable level of proof. As these guidelines are new, or not finalised, it is likely that they will go through a process of evolution as more data become available. The step-wise approach proposed by the EMA places the burden on the regulatory authorities to develop a robust and appropriate framework by which sponsors can determine bioequivalence unequivocally. In Canada, focus has been placed on surrogate marker data for efficacy, hence the burden falls on the Sponsor identifying and conducting appropriate clinical studies. In the weight-of-evidence approach suggested by the FDA, the burden also falls on the Sponsor to deliver a well-conceived and executed bioequivalence programme that provides data to support claims of bioequivalence.

Clinical experience, including those studies presented in this review, shows that the determination of bioequivalence of topically acting, orally inhaled drugs is complex particularly where significant differences in formulation and/or device are present. In these cases, the evidence to support the reliance on a single source of data such as *in vitro* or pharmacokinetic data was lacking. In such examples, a complete package of *in vivo* and *in vitro* data is likely to be required to make a decision

on bioequivalence. For some comparisons, pharmacokinetic data have shown bioequivalence of two products, whereas other data have shown differences in terms of *in vitro* data or a lack of bioequivalence for clinical efficacy.

Overall, the published data highlight how contrasting findings between *in vitro*, pharmacokinetic and clinical efficacy studies imply that reliance solely on *in vitro* data may not provide a complete profile (including the justification of pharmaceutical equivalence) that permits the observer to conclude that sufficient bioequivalence between inhaled products has been established. The most widely used *in vitro* particle-size testing methodologies do not always predict *in vivo* performance despite its widespread and almost universal adoption for *in vitro* testing. The balance of evidence favouring this approach is theoretical rather than empirical. In the future, imaging technologies may assist in determining lung deposition patterns; however, two issues need to be resolved: first, whether there is sufficient methodological agreement between laboratories to allow direct comparison of imaging data and, second, acceptance by regulators that passive labelling, which changes the drug formulation, does not represent adulteration of the test sample.

Finally, it is clear that although pharmacokinetic data do not always correlate well with *in vitro*, efficacy or safety data, they are an important component in establishing the bioequivalence of topically acting inhaled products. As systemic pharmacokinetic data do not necessarily reflect drug concentrations at the site of action in the lung, their primary role should be to establish bioequivalence in terms of the systemic safety profile. In this role, pharmacokinetic data are likely to be superior to pharmacodynamic end points.

6. Expert opinion

Establishing the bioequivalence of inhaled drugs is a multistep process with little experimental evidence to validate the use of data from one of the various *in vivo* and *in vitro* methods over those from another. This lack of clarity is one factor contributing to the absence of a consistent approach across regulatory authorities to establishing bioequivalence. *In vitro* assessments of emitted doses are not universally predictive of pharmacokinetic and pharmacodynamic outcomes in clinical studies, pharmacokinetic data do not always correlate well with *in vitro* or clinical efficacy data, and pharmacodynamic data lack the precision of pharmacokinetic data when used to determine bioequivalence. It is clear that more data and better models are required to describe the relationship between *in vitro* and *in vivo* observations. A weight-of-evidence approach to new formulations that can be applied on a case-by-case basis rather than a rigid regulatory approach may be more acceptable. This approach places greater responsibility on drug development scientists to determine the level of evidence necessary to establish bioequivalence. Unless there is a high degree of pharmaceutical equivalence between the test and reference products, as might arise from minor changes to an existing product, confidence in the predictability of *in vitro* data is likely to be low. Our lack of understanding about the relationship between *in vitro*, *in vivo* and clinical data suggests that, in most cases, the consideration of a combination of preclinical and clinical data may be preferable to abridged approaches relying on *in vitro* data alone. There are several unresolved issues preventing the agreement of general guidelines on the best approach to establishing bioequivalence for all classes of inhaled drug products. A way forward could involve the development of product- or drug class-specific guidelines allowing some of the outstanding issues to be circumvented.

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Both authors are employees of GlaxoSmithKline, who develop and manufacture inhaled drug products.

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