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Review

Rethinking bioequivalence and equivalence requirements of orally inhaled drug products

Dina Al-Numani [a], *Philippe Colucci* [a], *Murray P. Ducharme* [a,b,*]

[a] *Learn and Confirm Inc., St-Laurent, QC, Canada*

[b] *Faculté de Pharmacie, University of Montreal, Montreal, QC, Canada*

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ABSTRACT

Orally inhaled drug products (OIPs), such as corticosteroids and bronchodilators, are at the forefront of asthma and chronic obstructive pulmonary disease treatments, two diseases that afflict worldwide populations. Introducing generics of these products is essential, as the pricing of these medications remain a barrier to adequate patient care. Currently, there is no consensus between regulatory bodies as to the bioequivalence and equivalence requirements of OIPs that are intended for local action in the lungs. This manuscript critically reviews these requirements and presents future directions for clinicians, scientists, and regulators to consider to optimize the development and approval of OIPs.

1. Introduction

Drug delivery directly to the lung of patients with airflow obstructions allows the delivery of relatively small doses of drug directly to the airway achieving high local concentrations, while minimizing systemic adverse drug effects [1]. Inhalers are most commonly prescribed in the treatment of asthma and chronic obstructive pulmonary disease (COPD) [2].

Asthma has a prevalence ranging from 1 to 18% and affects approximately 300 million individuals worldwide [3]. Inhaled corticosteroids (ICS), such as fluticasone, are one of the cornerstones in the treatment of moderate to severe asthma [4]. They play a critical role in the long-term control of asthma through their anti-inflammatory effects. They have been shown to reduce asthma symptoms [5], improve quality of life [5], improve lung function [5], decrease airway hyper responsiveness [6], control airway inflammation [7], reduce the frequency and severity of exacerbations and reduce asthma-related mortality [8].

Inhaled bronchodilators are also used in the treatment of asthma [4] and are central in the treatment of patients with COPD [9]. COPD has a prevalence ranging from 7.8 to 19.7% world-wide, with a range of 3 to 11% among never smokers [10]. The relaxation of airway smooth muscles that lead to bronchodilation can be achieved by inhibiting acetylcholine signaling via muscarinic M_3 receptors expressed on airway smooth muscle. This can be performed with a muscarinic antagonist (e.g., tiotropium) or by stimulating beta-2 adrenoceptors with a beta-2 agonist (e.g., salmeterol) [9].

* *Corresponding author.* Learn and Confirm Inc., 3630 Bois Franc, St-Laurent, QC H4R 3K9, Canada. Tel.: +1 514 373 5346; fax: +1 514 373 5346.
E-mail address: murray.ducharme@learnandconfirm.ca (M.P. Ducharme).

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In light of the critical role of ICS and inhaled bronchodilators in the treatment of asthma and COPD, it is not surprising that there is considerable interest in developing new combinations of existing products, follow-ons and/or generic products of existing ICS and inhaled bronchodilators. The use of generic drugs in general is on the rise, accounting for 51% of prescriptions in 2002 and 67% in 2007 in the US [11]. Recent estimates indicate generic drugs account for approximately 80% of all retail prescriptions dispensed in the US [12], and 66% in Canada [13]. These growing trends, coupled with the urgent need to relieve the economic burden of prescription drugs on patients and healthcare providers, force us to reconsider how the drug development of generic ICS and inhaled bronchodilators can be improved to bring such products to market in a safe and timely manner. This puts additional pressure on innovative companies to bring new products on the market as their existing ones become preys to generic competition. With new products costing an average of one to two billion dollars [14], companies are not only developing new products entirely but have also repositioned old products by introducing new and improved devices (e.g., Diskus® line of products) or combination products (e.g., Advair®).

The aim of this manuscript is to review current regulatory recommendations for highly regulated regions (e.g., Health Canada (HC), US Food and Drug Administration (FDA), European Medicines Agency (EMA)) for the development of follow-on and/or generic inhaler products, critically examine assumptions and principles that underlie some of these recommendations, focusing on pharmacological principles, and suggest other approaches that may be considered in the future.

2. General bioequivalence requirements for OIPs: local vs systemic action

Clinical regulatory requirements to fulfill in order to obtain an approval for a generic or follow-on drug product typically depend first on the relationship between the systemic circulation and the assumed site of activity of the active pharmaceutical ingredient (API). For drug products reaching first the systemic circulation and then distributing to the theoretical site(s) of activity via the systemic circulation, pharmacokinetic (PK) studies indicating equivalence in terms of systemic exposure (e.g., typically C_{max} and AUC) between a follow-on/generic formulation and a reference one will ensure that their safety and efficacy will be similar because a similar systemic exposure will result in similar exposures at the theoretical site(s) of activity. For these products, a generic version would be demonstrated to be bioequivalent to a reference product using one or more PK equivalence studies. A theoretical example of such a product would be a potential generic inhaled insulin product, as insulin will reach its sites of activity via the systemic circulation.

On the other hand, a drug product for which its API is delivered from a formulation at its intended site(s) of activity before reaching the systemic circulation is typically called a "locally acting" product. For these products equivalence in terms of systemic exposure may not ensure "local" exposure equivalence and therefore a PK equivalence study may not suffice to ensure similar efficacy and safety. Examples of "locally" acting products within the lungs include inhalers for COPD and asthma, such as albuterol, budesonide, ipratropium, tiotropium, fluticasone and salmeterol.

3. Current regulatory requirements for generic submissions of "locally acting" inhaled products

3.1. *North American requirements (FDA and HC)*

Although clear guidelines exist in the U.S. with respect to the conduct of bioequivalence (BE) studies of OIPs [15], presently there is no general guideline on how to establish BE of OIPs.

In the US, the FDA has issued a general guidance documenting the CMC requirements [16], and three individual product BE guidances: one for budesonide suspension inhaler [17], one for albuterol sulfate metered dose inhaler [18], and one for the fluticasone propionate/salmeterol xinafoate dry powder inhaler [19].

Despite the absence of an FDA guidance document on the BE of OIP in general, scientific and regulatory considerations for demonstrating BE between dry powder inhalers (DPI) have been proposed [20], and recently reviewed [21]. The FDA has developed an aggregate weight-of-evidence approach which utilizes *in vitro* studies, PK equivalence studies, and pharmacodynamic (PD) or clinical endpoint (CE) studies (also called Therapeutic Equivalence (TE) studies), to establish BE of inhalation products [21]. Equivalence in all categories of interest is required [22]. As such, a generic formulation of a reference inhaler product needs to demonstrate that 1) its device will be judged to be equivalent in a patient's hand, 2) that its *in vitro* characteristics and performance in terms of emitted dose and aerodynamic particle size distribution is equivalent, 3) that its systemic PK exposure is equivalent, and finally that 4) its clinical efficacy is equivalent.

At the present moment, the requirements for HC are very similar to those of the US FDA. HC also demands that equivalence be demonstrated in terms of device, *in vitro* characteristics and performance, systemic PK exposure, and clinical efficacy. In Canada, the requirements are specified in three guidances, one specifying the requirements for second entry short-acting beta-2 agonist metered dose inhalers [23], one focusing on the *in vitro* requirements for nasal and inhalation products [24], and finally a draft guidance specifying what studies would be needed to prove similar clinical safety and efficacy [25]. This last guidance was however recently pulled from the HC website, possibly an indication that a new updated version is forthcoming. One difference with the FDA is that HC is less prescriptive in terms of study design for the clinical equivalence study and sponsors can theoretically use different designs as long as they can prove to the agency that it will ensure equivalent efficacy between the generic and reference inhaled products [25].

3.2. *European requirements (EMA)*

Many guidelines exist to describe what the requirements are for EU submissions. The guideline CPMP/EWP/4151/00 Rev.1

covers the overall requirements and specifies the needed clinical studies [26], while the guideline EMEA/CHP/QWP/49313/2005 Corr. specifies what the *in vitro* requirements are [27].

The EMA guidelines allow the theoretical approval on the basis of *in vitro* data only provided that results are all favorable. If an applicant cannot demonstrate complete *in vitro* similarity, or if the applicant's product is deemed too different from the reference product, then PK studies to establish equivalent safety and efficacy are suggested. Equivalence in terms of efficacy is typically recommended to be established via a PK systemic exposure equivalence study where charcoal is administered to block GI absorption so that only the exposure of the API absorbed via the lung is compared. Equivalence in terms of safety is done via a PK systemic exposure equivalence study but where charcoal is not administered, so that the total systemic exposure of the generic versus the reference product are compared, not just what is absorbed via the lung. Should PK studies fail or should they be considered to not address the specific *in vitro* failures of the test product, clinical studies are then needed to establish equivalent safety and efficacy. One important difference versus FDA or HC is that in Europe, OIPs are not approved as generic submissions but as hybrids, and they are not automatically substituted. Substitution is determined nationally. Very few international approvals appeared to have been granted since the issuing of the general guidance. The publicly available assessment reports suggest that not all regulators adhere strictly to all parts of the guideline.

It can be appreciated that the device and *in vitro* requirements are generally aligned between these three regulatory jurisdictions, but they differ substantially in how similar clinical safety and efficacy must be demonstrated. The general requirements are summarized and contrasted in Table 1.

We can see that the requirements for HC and US submissions are relatively similar, while they are very different in the EU. For this latter one, definite proof of device and *in vitro* similarity can theoretically suffice for a "hybrid" submission, although it appears in practice that EU regulators are feeling more comfortable if sponsors do a minimum of two Phase I PK studies, with and without charcoal concomitant administration. A "practical" requirements table can be constructed (see Table 2) using the example of the Advair Diskus® product.

4. Current controversial aspects related to locally acting inhaled products

4.1. *The need for concomitant charcoal administration in PK equivalence studies*

One study design aspect that not all regulatory agencies agree with is the requirement by the EMA to perform two PK equivalence studies if all *in vitro* tests are not conclusive of equivalence; one study with and one study without charcoal. The PK study without charcoal is performed to prove "safety equivalence" as the total systemic exposure from both the lung and gut absorptions will be measured. The charcoal PK study is performed to prove "efficacy equivalence" and will only measure the "lung absorption exposure" as the absorption from the gut will be inhibited by the charcoal. The theory for the charcoal study is that the systemic exposure from this study serves as a surrogate for the local lung absorption and exposure. This however ignores the fact that efficacy can also be due to systemic free drug exposure resulting from the part of the inhaled dose that is swallowed and absorbed through the gut. Of course this will be virtually nil for low oral gut bioavailability and highly protein bound drugs like fluticasone (fluticasone has 1% oral gut bioavailability and is 99% plasma protein bound [28]), but it may be somewhat important for others such as albuterol or

Table 1 – General regulatory agency requirements for demonstrating bioequivalence of generic OIPs.

	US FDA	HC	EU	Notes
Submission type	"generic" submission: ANDA	"generic" submission: ANDS	"Hybrid" submission	No specific declaration of equivalence or interchangeability in Europe for these products
Device similarity	Device must be deemed to be "similar" to the one used by the US marketed reference product (URP)	Device must be deemed to be "similar" to the one used by the Canadian marketed reference product (CRP)	Device must be deemed to be "similar" to the one used by a European marketed reference product (ERP)	Similar requirements for all three jurisdictions
In vitro performance	Device must have similar *in vitro* performance versus the URP	Device must have similar *in vitro* performance versus the CRP	Device must have similar *in vitro* performance versus the ERP	Similar requirements for all three jurisdictions, but in the EU complete *in vitro* similarity can remove clinical requirements
Similar safety	Generic Test product must show similar systemic exposure in a PK study versus the URP	Generic Test product must show similar systemic exposure in a PK study versus the CRP	Generic Test product must show similar systemic exposure in a PK study versus the ERP	EU does not theoretically need any PK study if *in vitro* requirements are completely met
Similar efficacy	Generic Test product must show similar efficacy in a Therapeutic Equivalence (TE) study with Clinical Endpoint (CE) versus the CRP and must be superior to placebo	Generic Test product must show similar efficacy in a TE study with CE versus the CRP and must be superior to placebo	Generic Test product must show similar systemic exposure in a PK study versus the ERP when administered with activated charcoal to block systemic absorption	EU does not need theoretically any PK or TE study(ies) if *in vitro* requirements are completely met

Table 2 – Potential minimum study requirements for generic submission of Advair Diskus® DPI.

Advair Diskus® DPI
0.1/0.05, 0.25/0.05 or 0.5/0.05 of Fluticasone propionate (mg/inhalation)/salmeterol xinafoate (mg base/inhalation)

	US FDA	HC	EU
Device similarity	To the US marketed reference product (URP), for example in terms of: – Dose counter – Device resistance – Number of doses – Size and shape – "Closed" device	Similar requirements as for the USA but using the Canadian marketed reference product (CRP)	Similar requirements as for the USA but using the European marketed reference product (ERP)
In vitro performance	Must have similar *in vitro* performance versus the URP: – Equivalent emitted dose at 3 flow rates and beginning, middle and end lifestages – Equivalent aerodynamic particle size distribution at 3 flow rates and beginning and end lifestages	Must have similar *in vitro* performance versus the CRP – Requirements similar to US ones	Must have similar *in vitro* performance versus the ERP – Requirements similar to US plus: Dose linearity across all strengths
Similar clinical safety	Three Relative Bioavailability PK studies showing equivalence in terms of exposure for: – High strength URP vs Test – Mid strength URP vs Test – Low strength URP vs Test	Two to three Relative Bioavailability PK studies showing equivalence in terms of exposure for: – High strength CRP vs Test – Mid strength CRP vs Test (should be able to be waived) – Low strength CRP vs Test	No studies needed theoretically if all *in vitro* comparability tests are successful In practice, a PK study with charcoal on the low dose, and one without charcoal on the high dose are preferred despite passing all *in vitro* tests
Similar clinical efficacy	One TE study with CE showing equivalence of URP with Test, and superiority vs. placebo of both Test and URP Three way parallel study design comparing Placebo, Test and URP using CE after single and 4 weeks of dosing in ~1000 patients with mild to moderate asthma	One TE study with CE showing equivalence of CRP with Test, and superiority vs. placebo of both Test and CRP HC is slightly more flexible in their specific design requirements than the US, but the US requirements should be acceptable theoretically with the CRP. HC may accept TE studies done with either URP or ERP if equivalence to the CRP can be demonstrated.	No studies needed if all *in vitro* comparability tests are successful, or if *in vitro* fails the dose linearity for example but PK studies (some with and some without charcoal) indicate similarity across all strengths

levalbuterol, drugs that are very little plasma protein bound (8%) and that have high oral gut bioavailability (50%) [29,30].

In addition, it can be argued that the difference in systemic exposure due to the lung versus gut can easily be obtained using population PK modeling from the full exposure study performed without charcoal, and therefore the charcoal study could be avoided altogether because it is relatively easy to discriminate, using a population approach, the drug absorbed via the lung versus the gut [29]. For products with a low gut bioavailability such as fluticasone (<1%) [28], the systemic exposure anyways represents only the lung exposure as exposure due to gut absorption is negligible. For these products the charcoal study would provide essentially the same results as the study given without charcoal. For drugs where exposure due to gut absorption is expected to be significant (e.g., exposure due to gut absorption accounting for let's say more than 20% of total exposure) such as albuterol [31], then the plasma concentration–time profile will typically show very clearly the dual absorption peaks with the first peak appearing shortly after administration reflecting lung absorption and a second peak appearing later reflecting gut absorption. Population PK modeling can be performed to characterize the exposure associated with the lung and gut absorption separately, and determine if these different exposures are equivalent between products. The use of this population approach was previously reported by Auclair et al. [29]. While it is reasonable for EMA to ask that PK equivalence be shown for lung absorption only (with charcoal) as well as lung and gut absorption (without charcoal), this could all be calculated from a single study without having to administer charcoal.

4.2. *The need for dose–response for TE studies to be robustly discriminative*

TE studies with CE are currently required by the US FDA and HC for a generic submission of OIPs. Based on the step-wise

approach, the EU would require such studies only when the *in vitro* and/or PK studies do not show equivalence. A vital element of a TE study with CE is the demonstration of a dose–response relationship, in order to confirm that a lack of difference in the CE is truly because the test and reference generate a similar level of effect, and not because the study lacks sensitivity in detecting a difference. This has been a major challenge, especially for products such as ICS, and is discussed further below.

An ideal biomarker for a TE study must possess several characteristics. It must be clinically relevant, i.e., there must be a link between the biomarker and the pharmacological mechanism of the drug. It must also be objective, reproducible with a reversible effect that is dependent on the dose [32,33]. As such, this would make it possible to establish a clear dose–response relationship and apply the dose-scale approach that is favored by the FDA [34]. A biomarker that is ideal for one drug may not be ideal for another, as its relevance depends upon the drug's mechanism of action, and in some cases, there may be no ideal biomarker at all. For example, forced expiratory volume in 1 second (FEV_1) is a biomarker used to assess the response to beta-2 agonists [18], and it is an ideal biomarker as it is reversible and related to systemic drug concentrations, thus it exhibits a clear dose–response relationship. This biomarker has been used now for approximately 20 years for submissions of inhaled short-acting beta-2 agonists. FDA recently published an individual BE guidance for the beta-2 agonist albuterol that confirms its usage [18].

FEV_1 may not be a good choice of a biomarker for ICS, however, as it does not necessarily capture the dual mechanism of action of these drugs. The response to ICS occurs in two waves: the first response occurring on Day 1 after the start of therapy and a latent response occurring 7 to 10 days later. One of the major mechanisms behind the anti-inflammatory effect of ICS in the treatment of asthma is via inhibition of the effects of pro-inflammatory cytokines following binding with glucocorticoid receptors [35]. By contrast, endocrine and metabolic effects of corticosteroids are mediated through DNA binding [35]. An ideal biomarker would be able to capture the spectrum of responses to ICS and maybe not just the early or late bronchodilatory response that is seen with FEV_1. Regardless of this, fluticasone and the combination product fluticasone/salmeterol have been approved by many diverse regulatory agencies including the US FDA based on FEV_1 measures. Because of this, the FDA has published an individual BE guidance for the combination product fluticasone/salmeterol and is asking generic sponsors to prove TE using FEV_1 measures after single dose administration and after 4 weeks of continued dosing [19].

Despite FDA issuing a BE guidance for the fluticasone/salmeterol inhaler combination product, there is still a need for a better biomarker for ICS response than FEV_1 [36,37]. One potential biomarker that used to be suggested for many years by the FDA was exhaled nitric oxide (ENO). Although this biomarker was hoped to reflect the secondary (latent) mechanism of action of ICS, its response is influenced by many factors, such as collection techniques, disease states, and other patient factors (food, drink, smoking) [38]. Even though there is still some interest in using this biomarker for ICS [39], it is not necessarily recommended anymore by regulatory agencies as studies have revealed the absence of a dose–response relationship between ENO and fluticasone administered at the marketed dosing regimens. The lowest labeled dose (88 mcg twice daily (BID)) was associated with responses on or near the plateau of the dose–response curve and responses did not return to baseline levels after the 14-day washout period [40]. Others have shown that ENO on its own cannot provide useful therapeutic information regarding response to ICS [41] or that it could be useful as an adjunct to guide therapy [42].

HC was recommending the use of sputum eosinophils for many years [25], believing that due to the presence of primed eosinophils in airways that contribute to inflammatory processes in asthmatics [37], this biomarker could characterize the anti-inflammatory activity of ICS. No consensus appears to exist though on the correlation between sputum eosinophils and ICS response. Some researchers have found a positive relationship between the two [43–49], while others have shown little or poor correlation [50,51]. It is not clear if HC is still as optimistic regarding this biomarker for ICS as in the past, as the guidance document that contained it has been withdrawn from HC's website.

Although biomarkers such as FEV_1 are generally accepted to evaluate response to bronchodilators (short-acting and long-acting beta-2 adrenoreceptor agonists) [18,26], it can be argued that their utility for ICS response should be limited, because similarly to ENO, the smallest marketed dosing regimen of fluticasone, for example, results in a response that is already at the top of the dose–response curve for FEV_1.

Unfortunately no biomarker has been found or proposed to date that would enable a dose–response to be seen across the marketed doses of fluticasone inhalers or other ICS. Ideally and assuming that an adequate biomarker could be found, therapeutic equivalence would have to be demonstrated by proving that a dose–response relationship exists, otherwise the study may not be discriminative at all if the doses studied are already at the top of the response curve. The study should ideally include a placebo and assess a low dose of the drug (the lowest dose as recommended in the product labeling), as well as a high dose (generally 2 to 4 times higher than the low dose). For the study to be valid, theoretically the response to the low dose of the drug must be superior to the placebo, and the response to the high dose of the drug must be greater than the response of the low dose. It is critical to be able to clearly distinguish between responses to varying drug doses, otherwise it may be impossible to distinguish reliably between drug formulations.

With the accumulated experience we now have concerning the relationship between dose and response of PD parameters such as FEV_1 and ENO, simulations were made to understand the importance of the existence or not of a dose–response on the resulting power and alpha error of TE studies with CE [52]. Using NONMEM®, thousands of TE studies each with a 5-way crossover design (placebo, low dose test, low dose reference, high dose test, high dose reference) were simulated. Different scenarios (i.e., equivalent or non-equivalent product, varying test to reference ratios) were simulated. Each scenario included 1000 simulated TE studies, and each study had a sample size of 136 subjects completing the 5 way crossover. Equivalence was assessed using the dose-scale approach (Fig. 1), in which the equivalence is calculated on the dose scale, and not on the response scale which is non-linear.

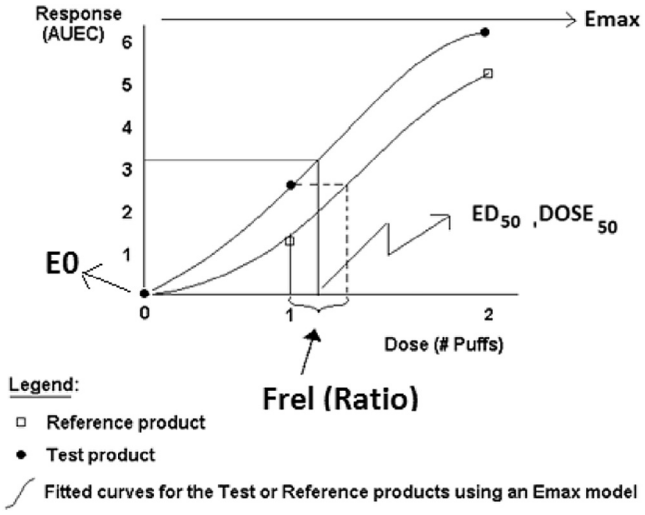

Fig. 1 – Graphical representation of the dose scale approach to assess TE.

Simulations were performed when a dose–response truly exists (e.g., the dose at which 50% (ED_{50}) of the maximum effect (E_{max}) is equivalent to the lowest dose marketed) and when a dose–response does not exist, as in the case for ICS with FEV_1, as the ED_{50} is much lower than the lowest marketed dose. Results of the scenario where the dose–response is present are highlighted in Table 3. It can be seen that in the case where ED_{50} occurs at approximately the low dose, such a TE design has adequate power (>80%) to conclude equivalence with the dose scale approach when indeed the products are bioequivalent. When products are not bioequivalent, the alpha error is slightly increased, 1 to 13.5% for a true test to reference ratio of 60 to 70%, but overall the products are shown to not be equivalent.

Results of the scenario where the dose–response is not present are highlighted in Table 4. This would be the case for example for fluticasone using FEV_1 or ENO as the CE using the dose-scale, as the maximum effect is approximately seen with the lowest dose marketed. Results show that any TE study in this scenario using the dose-scale approach would have very little power (<20%) to conclude equivalence even when the products are truly equivalent. Results show that it would be almost impossible to prove equivalence and the method would not really distinguish between a bioequivalent product and a non-bioequivalent one, as the alpha error rates for non-bioequivalent products are virtually the same as the statistical power for bioequivalent products.

Table 3 – Statistical power and alpha error of TE studies when a dose–response does exist and when the dose scale method is used to prove equivalence.

	True ratio of test to reference	Power	Alpha error
Equivalent	95%	>80%	
	90%	>80%	
Non-equivalent	70%		13%
	60%		1%

Table 4 – Statistical Power and Alpha error of TE studies when a dose–response does not exist and when the dose scale method is used to prove equivalence.

	True ratio of test to reference	Power	Alpha error
Equivalent	95%	<20%	
	90%	<20%	
Non-equivalent	70%		13%
	60%		14%

These results show the importance of an existing dose–response at the doses studied in a TE study with CE when the dose scale method is used. If the studied doses are at the top of the response curve, then the dose scale method unfortunately does not work and will almost never show equivalence between a test and a reference formulation.

4.3. *When using the dose-scale approach should one study the high dose effect only for the reference or also for the generic product?*

As presented earlier, the dose scale approach is a good method to assess TE in a study with CE when a dose–response truly exists at the dosing regimens studied. We have seen in Table 3 that with this method, and in an appropriately powered study, the power to prove equivalence is as expected when the test and reference products are equivalent, while when not equivalent the discriminatory power is also adequate although resulting in a slightly higher alpha error than what we typically see with PK equivalence studies. Therefore this method should be used when TE studies with CE are performed versus the alternative of creating ratios and confidence intervals on the response scale which is not robust due to the non-linearity of the response.

FDA's recommendations for a few products requiring the dose-scale approach are currently not always consistent. For albuterol inhalers, FDA is recommending a 4-way instead of a 5-way study [18]. These are obviously minimum recommendations as a sponsor could always study more, but this study design includes a placebo, low dose test, low dose reference, and high dose reference. What is missing is the high dose of the test. Although not absolutely needed, as the dose–response curve can be assessed with reference doses only and equivalence is assessed on the low dose, we aimed at discovering the impact of including or not this fifth arm in these studies. Ten-thousand TE studies with either 4- or 5-arm crossover designs including 136 patients each and for five different scenarios (three equivalent products and two non-equivalent products) were simulated using NONMEM®. Results are presented in Table 5 and indicate that the statistical power to prove equivalence is as expected with the 5-arm design (approximately 80%), while it becomes much lower (approximately 60%) when a 4-arm design is selected and the test is not administered as a high dose. In order for the 4-arm design to be associated with 80% power, the study would have to include almost double the

Table 5 – Power of TE studies using the dose-scale approach with 4-arm (placebo, low dose test, low and high dose reference) versus 5-arm (adding high dose of the test) designs.

	True ratio of test to reference	5-arm design		4-arm design	
		Power	Alpha error	Power	Alpha error
Equivalent	100%	79.8%		60.7%	
	95%	73%		57.4%	
	90%	67.7%		54.5%	
Non-equivalent	70%		24.3%		23.6%
	60%		6.4%		10.6%

number of patients. Doubling the number of patients in a 4-arm study is much more complicated and costly than adding an additional arm. Pharmaceutical companies should therefore perform these studies as 5-arm designs instead of what is minimally recommended.

4.4. *The need for TE studies once PK equivalence is demonstrated*

Once a test and reference products are shown to be equivalent based on comparative PK studies, we are presenting an argument herein that TE studies using CE are no longer necessary. The basis of this argument is that 1) TE studies are not as discriminative as PK studies; 2) the lungs should not be considered a "topical" organ per se, as it is one of the most highly perfused organ in the body because of its critical importance in oxygenating the body; and 3) a drug product can only act "locally" once it is in solution, not before, and once the API will appear in solution at the site of activity in the lung then its free drug concentrations should be immediately in equilibrium with the systemic circulation.

Daley-Yates and Parkins [53] summarized the *in vitro*, PK and PD studies of several inhaled products, and concluded that there was a lack of understanding between *in vitro*, PK and PD studies. The authors mentioned an example of a product that was found to be equivalent in terms of PK in one study [54], but not equivalent in terms of efficacy (using FEV_1) in another study (Kerwin et al. [55]). This comparison between two studies is completely misleading though, because the efficacy study they referred to (Kerwin et al. [55]) saw aligned differences between PK and efficacy (i.e., when PK was different the efficacy was different). All other examples presented in the review by Daley-Yates and Parkins [53] showed that when PK was equivalent, efficacy was always equivalent, but when PK was not equivalent, efficacy was sometimes equivalent and sometimes not equivalent. This suggests that comparisons made using PD data when equivalence is assessed on the response scale lacks specificity and with the tools we are using to date (e.g., no dose–response, proving equivalence with only one dose and with a biomarker that may not reflect the wide efficacy of the OIP) it may not allow for a meaningful product discrimination for the assessment of equivalence and therefore one could argue that the study does not serve any true scientific purpose. PK studies, on the other hand are much more sensitive and specific to detect differences between two products. The ultimate question is, are OIPs acting "locally" within the lungs with their systemic exposure unrelated to their theoretical exposure therein? Lawrence et al.'s paper from 1998 [56] is often quoted in this regard as offering evidence that much higher systemic exposure of fluticasone following oral versus inhalation dosing does not result in efficacy and therefore suggests that fluticasone acts locally within the lungs with no equilibrium with the systemic circulation. We will see that this conclusion is incorrect in the next paragraphs.

The lung epithelium differs in cell type and thickness, with diminishing thickness from the trachea to alveoli. Following absorption via the inhalation route, an API reaching the lung epithelium must first dissolve into a solution before it can act at the site of activity. Therefore, the exposure of the API at the site of activity in the lungs depends on the drug formulation characteristics, as well as physiologic ones [57]. The lungs are the most or one of the most perfused organs of the body and these should not be considered as a topical site of absorption like the skin [36] but rather an extension of the systemic exposure because of this high perfusion. This permits drug in a solution state at the site of activity in the lung to be almost instantaneously distributed to the systemic circulation. This explains why maximum concentrations are seen virtually immediately in a few seconds and minutes after inhalation for drugs that have high solubility within the lungs. For example, in a previous study we have found that the absorption half-life of levalbuterol via inhalation into the systemic circulation in dogs was less than 2 minutes, virtually as fast as administering the drug via the intravenous route (29). The observed "total" systemic concentrations after lung absorption therefore should directly reflect the "active" unbound drug concentrations within the lungs. Drugs absorbed by the gut (e.g., tablet formulation) are accessible to the lung but only "unbound" drug will be available to be in equilibrium with the site of activity in the lung. As mentioned earlier, many argue that only local exposure from the lung is involved in the efficacy of fluticasone when concentrations following inhalation versus oral administrations are compared [56]. This is an incorrect comparison because only "unbound" drug will equilibrate between the systemic circulation and the site of activity in the lungs, and therefore any comparison using total systemic concentrations (sum of fluticasone bound and unbound to plasma proteins) after gut absorption will overestimate the exposure reaching the lung and consequently overestimate the expected efficacy. This incorrect comparison can be shown with fluticasone as presented by Lawrence et al. [56].

Fluticasone has an oral bioavailability that is less than 1% and its plasma protein binding is reported to be 99% [28]. In the study reported by Lawrence et al. [56], no efficacy was

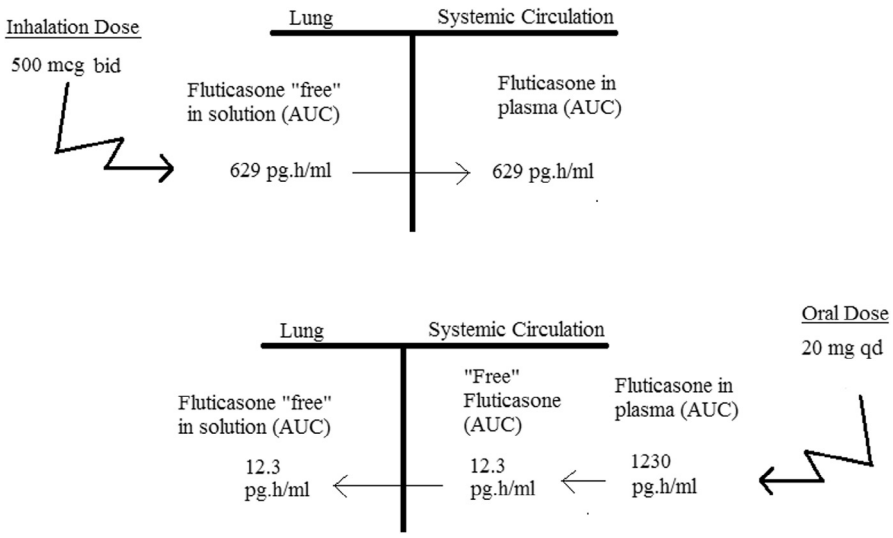

Fig. 2 – Fluticasone total AUC after oral and inhalation dosing cannot be compared directly; only free drug concentrations will equilibrate between the lungs and the systemic circulation.

observed with a 20 mg oral administration of fluticasone when compared to 100 and 500 mcg inhalation administrations. This was true even though systemic concentrations after oral administration were 2 to 3 times higher than after the 500 mcg inhalation administration. If we consider that total plasma concentrations after inhalation reflect the lung concentrations and that only unbound plasma concentration (less than 1% as protein binding is 99%) after oral administration reflects lung concentrations, then the lung fluticasone exposure from the oral administration was approximately 50 times lower than that for the 500 mcg inhalation administration. In order to have equivalent lung exposures with the 100 and 500 mcg inhalation dose, the oral dose would have needed to be as high as 200 to 1000 mg instead of 20 mg. The importance of considering free drug concentrations and not total drug concentrations is further presented in Fig. 2 for this particular fluticasone example.

Fig. 2 clearly indicates that because fluticasone is 99% protein bound, a systemic overall exposure (AUC) of 629 pg.h/ml after inhalation dosing suggests that the AUC of fluticasone in solution as free drug concentration at the site of activity in the lung was also 629 pg.h/ml because only free drug can go from the lung to the systemic circulation. On the other hand, administering a 20 mg oral dose may result in a systemic fluticasone AUC of 1230 pg.h/ml but only 1% of this is free drug concentration, so a free AUC of only 12.3 pg.h/ml. Therefore an exposure of only 12.3 pg.h/ml can reach the lungs in terms of AUC. It is because only free drug concentrations are active and equilibrate through membranes resulting in a tiny exposure of fluticasone in the lung (e.g., AUC of 12.3 pg.h/ml) that a 20 mg fluticasone oral dose was not efficacious in that study, not that fluticasone is not active from the systemic circulation as suggested [56]. Considering that the fluticasone AUC in the lung would only be 12.3 pg.h/ml with the 20 mg oral dose, it is not surprising that this dosing regimen was not efficacious as the resulting AUC at the site of activity would be 10 times lower than what would be achieved with the lowest fluticasone inhalation dosing regimen of 100 mcg BID.

For other ICS products that have higher gut bioavailability or low protein binding, systemic concentrations from gut absorption do present efficacy and this absorption from other sites should not be ignored. For example, oral albuterol has an oral bioavailability of 44 to 63% [30,58] and negligible plasma protein binding at approximately 8% [59]. Orally administered albuterol has been demonstrated to be efficacious in asthma patients [60] with improved morning and evening FEV_1 values comparable to inhaled salmeterol indicating that albuterol administered orally was able to have an effect on the lung.

The importance of protein binding on the efficacy of inhaled drugs has been recognized by Wu et al. where the authors showed that glucocorticoids with higher plasma and tissue binding showed a reduced efficacy in the lung [61].

5. Future directions

5.1. *Global harmonization and the pursuit of the global worldwide reference product*

We have seen that there is still more work to do for highly regulated regions like the USA, Europe, and Canada to present and enforce aligned regulations regarding OIPs. In this current global economy, it would be very advantageous and less confusing if regulatory bodies of highly regulated regions such as FDA, EMA, and HC would present aligned regulations. There is a lot of “gray” in scientific understanding (e.g., it is not “black or white”) and regulations do follow science, so it is not surprising that opinions between regulators vary based on this level of “gray”. It may be reasonable scientifically for EMA to suggest performing PK equivalence studies with charcoal and without charcoal, but then it may be reasonable for HC and FDA not to request it as well. The same can be said for TE studies. Regulators should grasp the opportunity to better align their regulations and guidances based on an understanding of what may be a common reasonable scientific position.

Even more limiting, though, is the fact that FDA, EMA, and HC have to ask generic pharmaceutical companies to assess BE of their test product versus a reference product that is available in their own respective market. So theoretically even though regulations and guidances would be perfectly aligned, generic pharmaceutical companies would still need to perform all studies versus the US reference product, versus an EU reference product, and again versus the Canadian reference product. This is obviously not financially viable nor desirable in regards to OIPs. Regulatory agencies do not share between themselves submitted pharmaceutical company dossiers, preventing them to assess if the reference product from one country is identical to the one in theirs. This has been the major impediment toward declaring a "global worldwide reference product" that generic pharmaceutical companies could use in their development. It is however very likely that most of the reference products marketed in highly regulated regions such as the USA, Europe, and Canada are in fact the identical products, making the topic even more frustrating to not just generic pharmaceutical companies themselves, but also to patients who need to pay more for their generic drugs because of greater development costs, and to regulatory agencies themselves who would save time and money if they could share between themselves the review of these submissions. We would propose that highly regulated regions such as the USA, Europe, and Canada agree to accept studies with either the US, EU, or Canadian reference products if all of the different product labels of these three reference products are quoting the exact same pivotal Phase III studies to establish their safety and efficacy. When this is the case, it then means that all of these marketed reference products had to be proven to be bioequivalent to the formulation used in the pivotal Phase III trials, and therefore they should by extension be bioequivalent between each other.

Harmonizing regulations and accepting more often studies performed with a "foreign" reference product, or declaring a "global worldwide reference product" in appropriate cases, would bring more clarity to pharmaceutical companies, patients, and health care professionals as to what is required, and encourage more companies to invest in the development of products.

5.2. *Drop of the requirement for TE studies if PK study is successful*

We have seen that the usefulness of TE studies is limited on its own because of its very low discriminatory power when equivalence is assessed on the response scale, or because of its impossibility at assessing equivalence with the dose-scale approach when the commercialized doses of the OIPs are already all associated with effects residing at the top of the response curve. TE studies for OIPs are prohibitively expensive. A single TE study that follows the FDA guidance for a generic formulation of Advair Diskus®, for example, may have to enroll thousands of patients at an overall cost listed in the 7 figures. If this study was absolutely necessary to establish clinical equivalence then it would be reasonable to perform. But understanding that this study is not really discriminative even if powered correctly, understanding that the systemic exposure PK equivalence study is on the other hand discriminative, and understanding that due to the high perfusion nature of the lung the systemic PK exposure should reflect the free drug PK exposure "in solution" at the site of efficacy in the lung, then the conclusion is that TE studies should not be necessary to establish BE once device, *in vitro*, and PK equivalence are all established.

6. Conclusion

While there are many factors to consider with OIPs for local action in comparison with orally administered drugs, it can be argued that PK equivalence studies could be used to establish BE between such products without necessitating TE studies with CE. Although some have argued that systemic drug concentrations that are used in PK equivalence assessments do not reflect drug levels or PK processes in the lungs, this is often incorrectly based on total drug instead of free drug concentrations. Because of the high-perfusion nature of the lungs, systemic exposure levels should be in equilibrium with and adequately inform on what would be the free active drug in solution at the site of activity in the lungs for OIPs.

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