Review

Bioequivalence of Orally Inhaled Drug Products : Focus on Current Regulatory Perspectives

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Abstract

Asthma/chronic obstructive pulmonary disease (COPD) medication market is a fast growing market, especially in the emerging markets where drugs have not been launched due to high costs. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Orally inhaled products (OIPs) should continue to remain an attractive clinical proposition. At the same time, establishing bioequivalence of an inhaled therapeutic can be a challenging proposition. The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug. 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. There is no one-size-fits-all programme. This review article mainly focused on current regulatory perspectives on bioequivalence of topically acting, orally inhaled drug products.

Keywords

bioequivalence, guidance, orally inhaled drug products, US, EU

Introduction

Generic medicines are those where patent protection has expired, and which may be produced by manufacturers other than the innovator (patent-holding) company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug[1].

Approval of Generics in the EU

In 2008, regulators in the EU (European Union) made it clear that abbreviated dossiers for inhaled products did not meet the definitions for generics and thus had to be approved as hybrids[2,3].

Generics are defined by community directive 2001/83 article 10.1/10.2, while hybrids are defined by article 10.3, which reads: "In case where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-a-vis reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided"[3,4].

In sense, the purpose of the 2009 guideline update was

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therefore to introduce "appropriate pre-clinical tests or clinical trials". This was done by proposing a stepwise approach to the development. Approvals can be based on *in vitro* testing, pharmacokinetic testing, or by pharmacodynamic testing[3].

Approval of Generics in the US

Generics are defined by section 505(j) titled "Abbreviated New Drug Applications" (ANDAs) of the Food, Drug and Cosmetic Act[5].

The applicant must provide documentation to show that the abbreviated new drug:

i) has the same label (prescribing information),

ii) "(…..) that active ingredients of the new drug are the same as those of listed drug (…..),

iii) shares the listed drug's route of administration, dosage form, and strength;

iv) is bioequivalent to the listed dug and can be expected to have the same therapeutic effect.

The definition of bioequivalence is not completely clear; title 21 of the Code of Federal Regulations title 21 section 320.23 (21CFR320.23) defines: "Two drugs will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose[3,6].

Whereas section 320.1 (21CFR320.1) reads:[3,7]

"Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study.

For drugs that act locally are not supposed to be absorbed into the systemic circulation in order to exert its effect the two definitions can be considered slightly discrepant absorption and availability at the site of action is not necessarily one and the same thing.

With the Draft Guidances by US FDA, the FDA has introduced requirements that entail elements from both definitions; applicants must provide proof of similarity in terms of local delivery via a pharmacodynamic study and must also investigate absorption. In addition, the draft imposes requirements on both the inhalation devices and the *in vitro* performance of the new drug. The new drug must come in a device that is similar in size and shape to the brand's inhaler. It must have a dose counter and must have comparable resistance.

The regulatory requirement for the approval of systematically acting generics is more or less harmonized in the International Conference on Harmonization (ICH) region. However, the guidelines for orally inhaled drugs products are different for the United States Food and Drug Administration (US FDA) and the Committee for Human Medicinal Products (CHMP)/European Union (EU), because the regulatory science has not been developed sufficiently for locally acting products. In the principal, clinical or pharmacodynamic studies are necessary to demonstrate therapeutic equivalence or locally acting products, because, on the other hand, the drug dose not reaches the site of action via systemic circulation. Therefore, pharmacokinetic studies have been considered traditionally as unable to reflect the drug concentration at the site of action. On the other hand, *in vitro* tests have not been validated as a surrogate of therapeutic equivalence, despite recent developments[8].

Consequently, the development of generic locally acting products is very expensive, unless a waiver of these in vivo studies can be obtained[8].

The development of OIPs has been complicated additionally by the lack of guidelines from the US FDA for orally inhaled drugs. In contrast, the CHMP requirements for orally inhaled drugs products have change recently[8].

Comparative pathways for establishing bioequivalence in oral and inhaled medicines

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. 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[9].

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[9].

Establishing the bioequivalence of inhaled drugs is a multistep process. 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[9] (**Fig. 1**).

Current Regulatory Guidelines/Guidances for Orally Inhaled Products

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

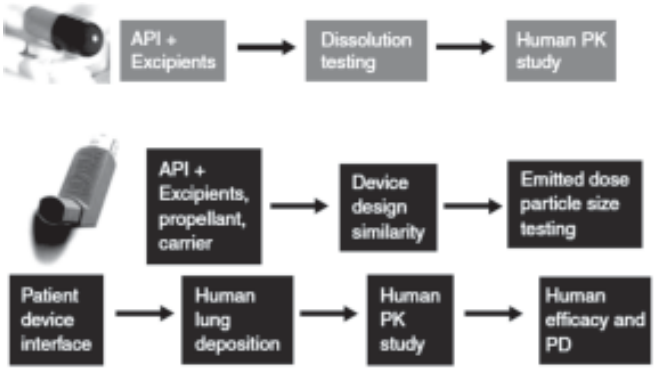

Fig. 1
Comparative pathways for establishing bioequivalence in oral and inhaled medicines

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 status of current Guidelines/Guidances for *in vitro/in vivo* be of orally inhaled products[8,10] are presented in **Table 1**.

EMEA Regulatory Framework

In 2005, European regulators decided to update the guidelines pertaining to the approval of orally inhaled products (OIPs), mainly due to concerns over assay sensitivity. The guidance was published in 2009 and came into force the same year[11].

Table 1
Status of Current Guidelines/Guidances for *In Vitro/In Vivo* BE of Orally Inhaled Products

Country	Guideline/Guidance	Status
EMEA	Guideline on the requirements for clinical documentation for Orally Inhaled Products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for treatment of asthma in children and adolescents.	Guideline, January, 2009
Canada	Guidance to establish equivalence or relative potency of safety and efficacy of a second entry short-acting $Beta_2$ agonists metered dose inhaler. Submission requirements for subsequent market entry inhaled corticosteroid products for use in the treatment of asthma.	Guideline, February, 1999 Draft guidance, August, 20074
USA	Informal only for inhalation products – presentations given at regulatory and scientific conferences. FDA seeking proposals.	

The European Union stepwise approach used for the development and assessment of second-entry orally inhaled products. This approach is similar to the approach used for systemically acting products. In some cases, *in vitro* data can be used to show equivalence without performing in vivo studies (e.g., solutions for nebulization in the case of inhalation products, and oral solutions or Biopharmaceutics Classification System–based biowaivers in the case of systemically acting drugs). If equivalence cannot be shown in the first step, the Applicant can show equivalence in a second step by means of conventional pharmacokinetic bioequivalence studies to assess directly systemic exposure and lung deposition indirectly. The dose absorbed from the lungs should be distinguished from the dose absorbed from the gastrointestinal tract. Then the fraction of dose absorbed (area under the curve) represents the dose that reached the site of action and the peak exposure gives information on the pattern of deposition within the lungs. This information is more discriminative than any pharmacodynamic or clinical endpoint, because these have flat dose–response curves. If equivalence is not shown with pharmacokinetic data, the Applicant can decide to show equivalence by means of pharmacodynamic or clinical trials, but assay sensitivity must be demonstrated within the study and relative potency should be estimated[3,8,11].

A generic product must demonstrate its therapeutic equivalence, i.e., efficacy and safety profile of the test and reference products are sufficiently comparable so that a clinically relevant difference between the products can be reliably be excluded (EMEA). EMA guideline provides the possibility to consider approving a generic version of an inhaler product based on stringent *in vitro* assessment. Alternatively, comparative lung deposition tests between T and R products are required. EMA: "Orally inhaled products are definitely not 'generics' but 'hybrids'" and that "simple bridging to bioequivalence model is mostly not sufficient." For this reason there are no therapeutically interchangeable inhalation products approved[12].

Stepwise approach in EMA Guideline

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 **Fig. 2**[9, 11].

In vitro Bioequivalence

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[9, 11]. A summary of the criteria from the guideline

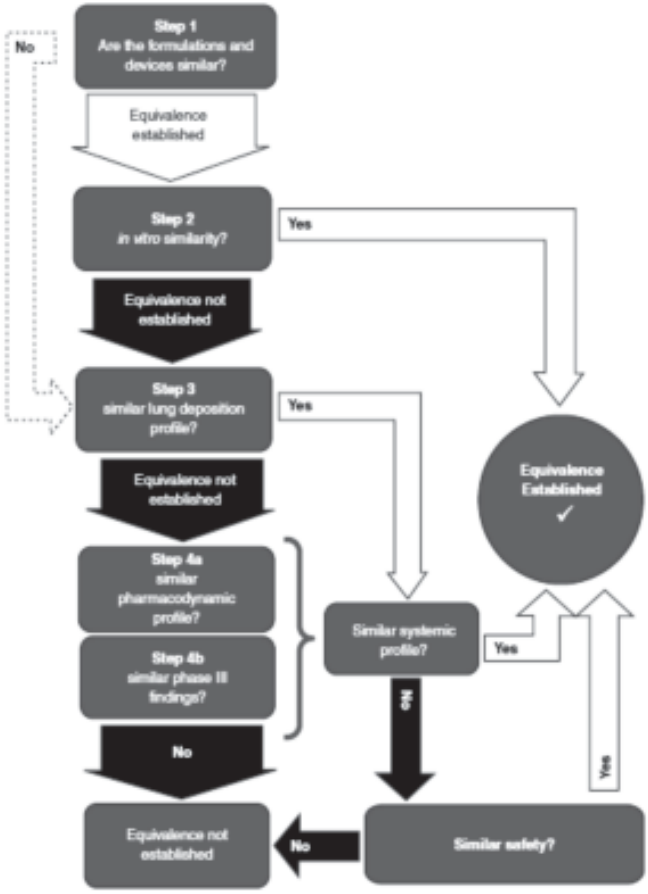

Fig. 2
Schematic of the stepwise approach for establishing bioequivalence advocated by the European Medicines Agency

Table 2
EMEA *In vitro* Bioequivalence

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., pressurized MDI, non-pressurized 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 behavior
- Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g., delivered dose uniformity, etc.), aerosol particle behavior (e.g., hygroscopic effect, plume dynamic and geometry) and/or be likely to affect the inhalation behavior 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%)

MDI: Metered dose inhaler; DPI: Dry powder inhaler

is presented in **Table 2**. The interpretation of this aspect of the guidance has been the subject of continuing debate.

Pharmacokinetic Bioequivalence[9, 11]

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.

A summary of the key regulatory requirements for pharmacokinetic studies with orally inhaled products are presented in **Table 3**.

Pharmacodynamic Bioequivalence[9, 11]

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 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 (PC_{20} FEV1)[9, 11].

The stepwise approach of the CHMP (Committee for Medicinal Products) allows the approval of all inhalation products in the European Union based only on *in vitro* data if certain conditions are fulfilled. This approach is expected to be applicable not only for solutions for nebulization, but also for pMDIs in the solution or suspension and suspensions for nebulization, because the differences in dissolution of the suspensions at the site action are assessed based on the particle size distribution and crystallographic comparison. For DPIs, demonstration of similarity based on *in vitro* data only seems unlikely[9].

In vitro data comparisons are also essential to demonstrate that the evidence of equivalence obtained with one or more strengths can be extrapolated to other strengths of the product series and to demonstrate that the flow-rate dependency is similar between test and reference product

Table 3
EMEA Pharmacokinetic Bioequivalence

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 pressurized 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

in the order to accept pharmacokinetic studies in healthy volunteers[9].

Health Canada guidance[9,13]

Health Canada released proposals on the assessment of bioequivalence for inhaled corticosteroids, 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 characterize systemic exposure profiles in terms of area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}).

US Regulatory Framework

Inhalation products are combination product – drug and device and fall under 21 CFR 3.2, 503(g)(1) regulations and are reviewed in FDA by CDER and CDRH. A generic product should provide evidence on the quality of the test product with reference to existing safety and efficacy data of RLD. (i.e., to PE + BE to RLD). The dosage form/ device should comply with the pharmacopeia standards (USP or EP). Regulatory pathways have been developed for drug / device combination approval. When TE cannot be established by a BE (i.e., lung deposition PK study), a PD/clinical effect study - the lung function parameter (FEV1) or PD marker from biological fluid - should be considered. The study should include two dose levels of at least one of the products and show that the outcome from the two dose levels differed significantly - This is a challenge. Discussions are ongoing to find a meaningful ways to establish BE and TE. Establishing PD equivalence also requires sufficient sensitivity and relative potency to be within 90% CI of BE limits. The FDA approach for demonstrating BE (Bioequivalence) of DPI's (Dry Powder

Table 4
USFDA – DPIs

Key scientific considerations of Generic DPIs[12,14]

- Comparative *in vitro* studies
- Comparative pharmacokinetic studies
- Comparative pharmacodynamic studies (requiring dose response studies) or clinical endpoint studies
- Device and formulation design (Many DPI designs are patent protected)

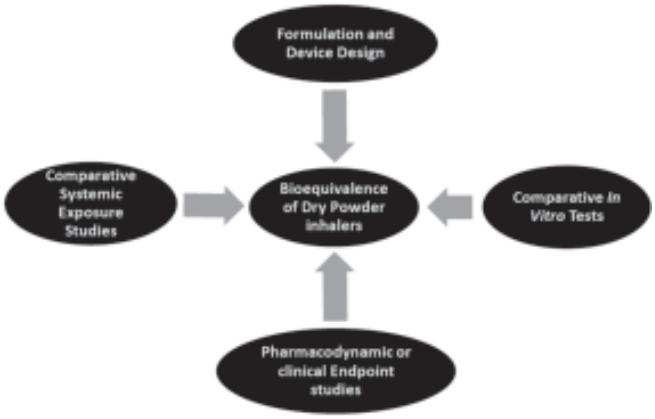

Fig. 3
The FDA approach for demonstrating BE of DPI's
Weight of Evidence Approach

Inhalers) Weight of Evidence Approach is presented in **Fig. 3**[12]. The key scientific considerations of generic DPIs are presented in **Table 4**[9].

In contrast to the EMA and Health Canada, applications to the FDA are viewed on a case-by-case weight of evidence basis. Key components of the aggregate weight of evidence approach described by the FDA[9,15] are described in **Table 5**.

The Agency (USFDA) currently uses a "Weight of Evidence" approach to include: (1) Qualitative (Q1) and Quantitative (Q2) sameness of formulation, (2) acceptable comparative *in vitro* performance, (3) equivalent systemic exposure, and (4) equivalent delivery to the local site of action (lung). Among these four components, the latter three require comparative studies to support BE between the generic and reference products[16].

It is likely that the 'weight of evidence' approach taken by the FDA will lead to the development of specific guidance facilitating abbreviated application submission. However, the balance between *in vitro* and clinical performance characterization may well depend on the specific drug product in development and the body of evidence on the safety and efficacy of the innovator[17].

Current US FDA Draft Guidance on generic dry powder inhalers containing Fluticasone propionate and Salmeterol xinafoate[3,18]

In 2013, the US FDA published a draft guidance document for the development of generic dry powder inhalers containing fluticasone propionate and salmeterol xinafoate. Getting US regulatory approval for a generic dry powder inhaler containing fluticasone propionate and salmeterol xinafoate will be very difficult due to the testing burden if the requirements given by the draft guidance are

Table 5
Weight of evidence approach by the US FDA

Key components of the aggregate weight of evidence approach described by the FDA

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

all implemented. It will involve a total of 50 tests (36 in vitro, 12 pharmacokinetic, 2 pharmacodynamic), which must all evaluate towards equivalence. This means each of the 50 individual tests must be highly powered in order to get an acceptable level of overall success[3,18].

The US Draft guideline introduces the need for a total of 50 tests, all of which must shoe equivalence:

- 36 *in vitro* tests (2 active ingredients tested at three flow rates, with endpoints for all three strengths);
- 12 pharmacokinetic tests (two active ingredients that must each pass equivalence testing for two endpoints for all three strengths);
- 2 pharmacodynamic tests (two endpoints for one strength).

In the absence of a relaxation of the requirements introduced by the FDA in their draft guidance, getting a generic dry powder inhaler approved in the US will be extremely difficult because of the testing burden[3,18].

Currently, USFDA released draft guidance on Budesonide (Sep 2012), Albuterol (April 2013) and most recently Fluticasone + Salmeterol combination (Sep 2013). But based on comparative data, there are various unresolved issues with regards to lower strength, higher strength, variations in confidence interval (CI), and variations in clinical endpoints as well as *in-vitro* studies. Based on budesonide guidance, the agency has no recommendations regarding the clinical bioequivalence study design, however remaining both are recommended the same. Based on above current guidances, there are various challenges in performing studies for generic approval[18-20].

Differences between EU and US

Increasing health care costs results in political pressure to increase availability of quality generic products. Different regulators present their opinions on weighing risk/benefit ratios and the need for clinical confirmation.[21] The differences between EU and US is presented in **Fig. 4**.

In the EU, if *in vitro* similarity cannot be demonstrated, applicants have two other opportunities to demonstrate therapeutic equivalence. While EMA allows for approval based on one of three criteria (or a combination), the FDA requires all three to be proven[21].

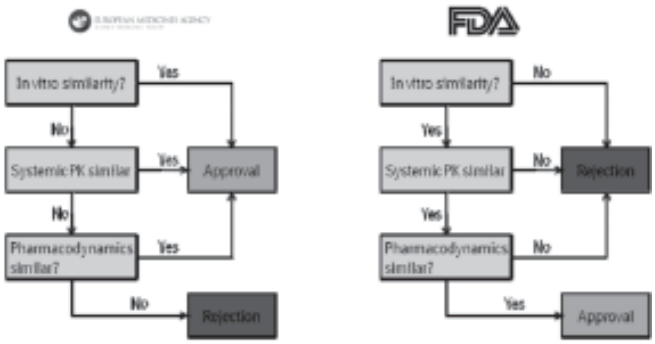

Fig. 4
Perspectives on Risk Management: Differences between EU and US

The differences in regulatory requirements between the EU (European Union), Canada, and the United States are summarized below:

The European regulatory perspective on demonstrating therapeutic equivalence of OIPs (Orally Inhaled Products) is described in a CHMP Guideline that was issued as final in early 2009 and came into force in August 2009. This guideline applies to products that are used to treat asthma and chronic obstructive pulmonary disease (COPD), and is relevant for a variety of OIP dosage forms, including pressurized and non-pressurized metered dose inhalers (MDIs), dry-powder inhalers (DPIs), and solutions and suspensions for nebulization. In Europe, locally acting products such as OIPs do not meet the strict definition of a ''generic medicinal product.'' Such products are commonly called ''hybrid medicinal products'' and their submission basis is described in article 10.3 of directive EC/2001/83.

The EMA (European Medicine Agency) 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[9,11, 22,23,24,25].

Health Canada issued a guidance for second entry short acting beta agonists (SABA) in 1999, which does not accept

''blood-level'' studies ''unless it can be shown that the analyte measured in the blood indicates what went through the lungs and its effect.'' The Health Canada 2007 draft guidance for subsequent market entry of inhaled corticosteroids (ICS) for asthma recommends determining the systemic exposure via PK (Pharmacokinetic) studies; it also provides for systemic exposure to be determined in a pharmacodynamic (PD) study by assessment of the effect on the hypothalamic–pituitary–adrenal axis (HPA) if the plasma levels are too low to enable reliable analytical measurement. No specific *in vitro* acceptance criteria for bioequivalence purposes are included in the 2007 draft guidance, although that guidance requires ''complete chemistry, manufacturing, and quality data'' as well as ''appropriate comparative data versus the Canadian reference product.'' Pharmaceutical quality requirements were published in a joint Canadian–European guideline[9,13,24,26,27].

The FDA Office of Generic Drugs (OGD) has previously issued interim draft Guidances for documentation of BE of pressurized metered dose inhalers (pMDIs) and locally acting aqueous nasal aerosols and sprays. In addition, FDA/OGD has provided insight into their expectations for demonstrating bioequivalence of OIPs through public meetings and publications. Although there is currently no formal FDA guidance in effect on demonstrating BE for OIPs, based on the available information, a ''Weight-of-Evidence'' approach is used by FDA. This approach incorporates qualitative (Q1) and quantitative (Q2) formulation sameness, device similarity (e.g., from the patient-use perspective), *in vitro* equivalence of the product performance, PK assessment of systemic exposure (safety), and PD assessment of local delivery or clinical end point studies (efficacy). 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[9,24,28,29].

Summary

Establishing BE through 'normal' procedure is difficult. There is a lack of consensus around the critical issues in BE assessment. Orally inhaled products should continue to remain an attractive clinical proposition. Although a potentially lucrative market, different formulations and device technologies can have a significant impact on the lung deposition characteristics of the drug and potentially on efficacy. At the same time, establishing bioequivalence of an inhaled therapeutic can be a challenging proposition. There is no one-size-fits-all programme. Companies need to be able to adapt as bioequivalence data in the programme evolves, and they must be able to incorporate additional *in vitro* or *in vivo* studies depending on the strength of the data package and agency feedback.

Confirming with draft US requirements will be very difficult for most, but not all, companies because numerous *in vivo* and *in vitro* tests must all proven equivalence. Approval in the US requires *in vitro* equivalence and pharmacokinetic equivalence and pharmacodynamic equivalence, whereas approval in the EU requires *in vitro* equivalence or pharmacokinetic equivalence or pharmacodynamic equivalence.

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