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International Regulations for Bioequivalence Approval of Locally Acting Orally Inhaled Drug Products

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ABSTRACT

Bioequivalence (BE) is established between the brand drug and the generic drug to allow the linking of preclinical and clinical testing conducted on the reference listed drug. Regulatory agencies around the globe have come up with the guidance for locally acting orally inhaled drug products (OIDPs) for bioequivalence approaches. The prime intent of the present article is to compare approaches of different international regulatory authorities such as Health Canada, European Medicines Agency and the US Food and Drug Administration that have published guidance related to locally acting OIDPs. Moreover, the Central Drugs Standard Control Organisation, India, has published guidelines for bioavailability and bioequivalence studies. BE recommendations from global regulatory agencies were based on comparison for different parameters, namely inhaler device, formulation, reference product's selection, *in-vitro* as well as *in-vivo* studies (pharmacokinetics, pharmacodynamics, and clinical studies). In the case of *in-vivo* studies, details about study design, dose choices, inclusion/ exclusion criteria of the subject, study period, endpoint study, and equivalence acceptance criteria were discussed in the present review article.

[1]1. INTRODUCTION

OIDPs are a class of products that includes MDI, DPI, and nebulization products. Most inhalation products are designed as locally acting in the lungs, and their drug delivery does not entirely or necessarily directly count on the systemic circulation. Moreover, the majority of inhalation products are complex dosage forms that combine the device, adding complexity and formulation in their BE establishment [1].

Demonstrating BE for locally-acting OIDPs is challenging since the usual PK approach used for systemically acting drugs do not apply directly to OIDPs, which deliver drugs to the site of action [1]. Moreover, BE study is required to exhibit whether a generic product can be interchangeable with the brand innovator product [2]. TE can be reached when the generic product is bioequivalent to the brand product. BE plays an important role in supporting post-approval changes in drug applications as well as during the drug product development phase. To determine to BE for systemically acting drug products, the use of PK studies is common. Through systemic circulation, these drugs reach their sites of action. However, these approaches are not always considered sufficient to establish BE as their intended actions, and drug deliveries are at the local sites and do not depend on the systemic circulation, and for the same reason, alternative approaches are considered for the establishment of BE [3].

2. INTERNATIONAL GUIDELINES ON BIOEQUIVALENCE OF OIDPs

Generic medicine development requires the demonstration of bioequivalence with a reference product. BE studies typically proceed from the characterization of a reference product and the

[1] *Abbreviations:* ANDA, Abbreviated New Drug Application; APSD, Aerodynamic Particle Size Distribution; AUC, Area Under Curve; BE, Bioequivalence; CDSCO, Central Drug Standard Control Organization; CI, Confidence Interval; C_{max}, Maximum Concentration; COPD, Chronic Obstructive Pulmonary Disease; DPI, Dry Powder Inhaler; EMA, European Medicine Agency; FPM, Fine Particle Mass; FP-SX, Fluticasone Propionate Salmeterol Xinafoate; GSD, Geometric Standard Deviation; HC, Health Canada; HPA, Hypothalamic Pituitary Adrenal Axis; ICS, Inhaled Corticosteroids; LABA, Long Acting Beta 2 Agonist; MDI, Metered Dose Inhaler; MMAD, Mass Median Aerodynamic Diameter; OIDP, Orally Inhaled Drug Product; PBE, Population Bioequivalence; PD, Pharmacodynamic; PK, Pharmacokinetic; Q1, Qualitative; Q2, Quantitative; RLD, Reference Listed Drug; SABA, Short Acting Beta 2 Agonist; SAC, Single Actuation Content; T to R, Test to Reference; TE, Therapeutic Equivalence; USFDA, United States Food and Drug Administration.

design of a pharmaceutically equivalent and bioequivalent product. Most of the OIDPs is used for the treatment of asthma and COPD. Currently, only limited international agencies have published and implemented regulatory guidelines on BE standards. Demonstrating BE in locally-acting drugs is challenging because OIDP behavior is a series of interactions between the patient, device, as well as formulation [4]. In the present review, BE guidelines for OIDPs were compared between four global regulatory organizations such as the USFDA, HC, EMA, and CDSCO guidelines for bioavailability and bioequivalence studies. The draft guidance published by different regulatory agencies is summarized in Table 1.

Table 1. International regulatory draft guidance for BE studies of OIDPs published by different regions.

International regulatory agency	**BE guidelines**	**Date posted/effective**
USFDA	i. Draft Bioequivalence Recommendations for Specific Product: Fluticasone Propionate/Salmeterol Xinafoate Dry Powder Inhaler (FP-SXDPI) [5].	September 2013
	ii. Draft Bioequivalence Recommendations for Specific Product: Nebulized Budesonide Inhalation Suspension [6].	September 2012
	iii. Draft Bioequivalence Recommendations for Specific Product: Albuterol Sulphate Metered-Dose Inhaler [7].	July 2013
	iv. Bioavailability and bioequivalence studies on Nasal aerosols and Nasal sprays for Local action [8].	April 2003
HC	i. Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Second Entry Short-Acting Beta 2 Agonist Metered-Dose Inhaler (MDI) [9].	February 1999
	ii. Submission requirements for subsequent market entry inhaled corticosteroid products for use in the treatment of asthma [10].	The draft guidance, August 2007

EMA	i.	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 Use in the Treatment of Asthma in Children and Adolescents [11].	January 2009
CDSCO	i.	Government of India, Ministry of Health and Family Welfare. CDSCO. Guidelines for bioavailability and bioequivalence studies [12].	June 2005

3. COMPARISON OF BE GUIDELINES

The focus of the present review is to compare regulatory approaches across different international organizations for establishing BE of generic OIDPs in correspondence to their reference drugs. A few jurisdictions, along with their relating regulatory agencies that have published related BE guidance on OIDPs, are covered. BE approaches from different regulatory authorities were compared for their similarities and differences and were categorized as follows [3].

- BE approaches of different international regions
- Reference product selection
- BE relating formulation and device considerations
- *In-vitro* bioequivalence studies
- *In-vivo* bioequivalence studies
    - PK studies
    - PD studies
    - Clinical studies

4. REGULATORY ADVANCES TO ESTABLISH BE ON OIDPs

Recent guidance on BE recommendations for OIDPs includes guidelines individually published by USFDA, HC, and EMA.

USFDA uses the term BE for both systemically and locally acting drugs. USFDA defines BE as "the lack of a significant difference in the rate and extent to which the active ingredient in a pharmaceutical equivalent becomes available at the site of drug action at the same molar dose when administered under similar conditions in an appropriately designed study". Under the US, BE context Clinical studies and PD are included, which symptomizes the drug at its site of action, and PK studies are included to depict the drug availability at the target site [13]. However, a note should be made that there will be a difference in the BE definition between USFDA and EMA.

EMA defines BE as "Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in-vivo* performance, i.e., the similarity in terms of safety and efficacy" [14].

Health Canada defines BE studies as "the test product can be expected to have the same therapeutic effects and safety profile as the reference product when administered to patients under the conditions specified in the labeling". HC states BE can be demonstrated through comparative PD studies and by comparison of pharmaceutical properties. A complete comparative clinical testing supports the therapeutic equivalence amongst the test and reference products [15].

CDSCO defines BE as "Bioequivalence of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose" [16].

USFDA has issued BE guidance for specific inhalation products, which include Albuterol MDI, nebulized Budesonide inhalation suspension, and FP-SX DPI products. USFDA's BE approach for OIDPs is based on the combined weight of evidence (Figure 1). It uses PK, PD, and in-vitro studies data to exhibit equivalence in localized delivery at the site Device similarities and formulation aspects are also considered [17].

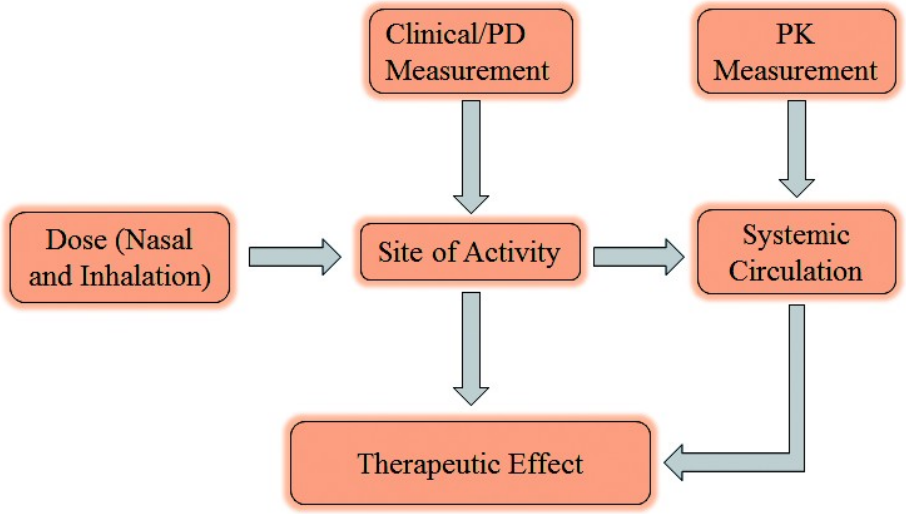

Figure 1. USFDA's approach to establish BE for OIDPs.

EMA commends a step-by-step approach to establish therapeutic equivalence between the reference and test drugs [18].

Stage 1- *in-vitro* equivalence test;

Stage 2- comparison of systemic exposure with lung deposition;

Stage 3- clinical studies and PD for demonstrating BE.

The demonstration of stage 1 and stage 2 prevents the requirement of further BE studies. EMA guidance has given a diagram of the stepwise BE approach (Figure 2).

HC has adopted an approach similar to that of USFDA. It describes focus to establish BE for bronchodilators and inhaled corticosteroids [9].

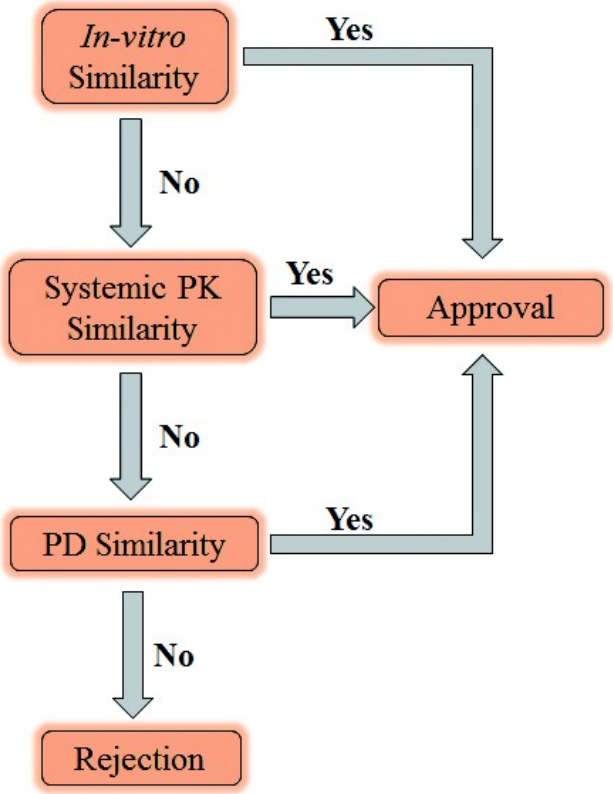

Figure 2. EMA's stepwise BE approach.

4.1 Reference product selection

USFDA and HC suggest that the reference product should be decided from the list of innovator products marketed in its own country. USFDA has the publication of Orange Book, wherein the specific Reference Listed Drug can be found [19].

EMA suggests the use of authorized innovator products as a reference product according to product availability. The reference product selection for each country is given in Table 2.

Table 2. Selection of reference products for OIDPs [20].

Parameter	USFDA	EMA	HC
Reference drug	The USA marketed	Authorized	Canadian

product selection.	reference products.	innovator product.	reference product.

4.2 Formulation and Device Related Guidance to Bioequivalence

USFDA, EMA, and HC, each has its own recommended guidance concerning drug substance, device design, formulation, and physicochemical properties of different OIDPs. OIDPs are unification products with co-development of formulation and device. The physicochemical properties (Table 3) influence the deposition of the drug in particularly targeted regions of the lungs and further affect clinical efficacy. Drug-related properties (Table 3) found to affect the adhesion and detachment of drug-carrier adhesive mixtures and thereby helps in the estimation of the device performance. Medical devices (Table 3) are tested for mechanism and operating traits along with which the dimensions of the device and relating factors are also a point of discussion. All these key factors influence the aerodynamic performance of the drugs [21].

Table 3. Comparison of the recommendations by USFDA, EMA, and HC for drug substance, formulation, and device of OIDPs.

Parameters	**USFDA**	**EMA**	**HC** [11]
Physicochemical properties of the drug product	Not specified	Not specified	**For aqueous product**: • Description • Osmolarity • Viscosity • Surface tension • pH • Specific gravity • Buffering capacity **For DPI:** • The particle size

			distribution of the carrier (if present) • Bulk and tapped density • Particle morphology and surface properties • Melting point • Porosity • Hygroscopicity • Moisture content **For MDI:** • Viscosity • Surface tension • Specific gravity • Vapor pressure • Freezing point • Refractive index **Acceptance criteria:** +/- 10% difference. [10]
API	For nebulized Budesonide inhalation suspension: • The same polymorphic form of the drug substance. • The same crystal habit of the drug substance [6]. For Albuterol sulfate MDI and FP-SX DPI: not specified [7].	The same form of the active substance, i.e., same ester, salt, solvate, or hydrate. For active substance in suspension or powder form: • Differences in polymorphic form and/ or crystalline structure should not influence the dissolution characteristics, the product performance, or the aerosol particle behavior [20].	Not specified
Inactive ingredients	For Albuterol MDI and nebulized Budesonide inhalation suspension: • Q1 the same, and	• For nebulization solution with the same qualitative and quantitative	• Q1 the same, and Q2 the same within a difference of +/- 10%.

	Q2 the same within a difference of +/- 5% from RLD [7]. For FP-SX DPI: • If Q2 is different from RLD, the justification to be provided along with pharmaceutical development data, relating *in-vitro* testing of multiple drug-to-excipient ratios that include combinations below and above the ratios used in the Test and Reference products [5].	composition as the RLD, the clinical study may be waived. • Any Q1 and/or Q2 differences in excipients should not influence the performance of the product, aerosol particle behavior, and/ or be likely to affect the inhalation behavior of the patient. • Any Q1 and/or Q2 differences in excipients should not change the safety profile of the product. • When new propellants/ excipients are used, then clinical efficacy, safety profile, toxicology, local tolerability studies are recommended [20].	
Device	A working model and engineering drawings of the product should be submitted to the Office of Generic Drugs before ANDA submission. For Albuterol MDI: • The size and shape of the device must be similar to the RLD device. • If the RLD product has a dose counter, then the test product should also have one [7]. For FP-SX DPI, the test product device should have the following	• Similar inhaled volume through the device is within a difference of +/-15%. • Similar resistance to airflow is within a difference of +/-15%. • Similar handling of the reference and test product inhalation devices must be the same [20].	Recommends qualitative and quantitative analysis of: • Physical attributes • Operating characteristics of the delivery devices [10].

	characteristics: • Similar size and shape to the RLD product device. • Comparable device resistance to the RLD product and with dose counter. • Pre-metered multi-dose format, with 60 doses. • External operating procedures are consisting of 4 steps as per RLD labeling [5].	

4.2.1. DRUG SUBSTANCE

OIDPs are complex dosage forms, which are a formulation integrated with a device. Hence the performance of the OIDPs depends on the interactivity of the formulation and the delivery device [22]. As per USFDA guidance, the drug substance under evaluation should be the same in the reference and test products. It recommended guidance on FP-SX DPI and Albuterol sulphate MDI do not necessarily specify any physical forms for the drug substance [5,7]. Moreover, in the case of US Budesonide inhalation suspension, it is advised that the same crystal habit and polymorphic form of the drug substance should be present for an *in-vitro* BE study in the test drug formulation [6].

However, EMA suggests that the same form of active substances such as ester, salts, solvates, or hydrates should exist in the test drug. EMA also accepts dissimilar polymorphic or crystalline forms of drug substance unless they do not affect the performance of the product [23].

HC guidelines do not have any specific recommendations for drug substance relating to physical forms or crystalline habits [9].

4.2.2. INACTIVE INGREDIENTS

USFDA recommends qualitative (Q1) and quantitative (Q2) sameness of the inactive ingredients to that of the reference products [1].

However, EMA has rules for sameness of Q1 and Q2 related only to pure *in-vitro* approvals. They permit Q1 and/or Q2 differences in inactive ingredients, given that they do not affect safety profile, product performance, etc. EMA recommends conducting safety and clinical studies additionally to toxicological and preclinical programs and instructs the applicant to evaluate localized tolerability as well as to inquire about the sign of augmented bronchial irritability, if any [20].

HC recommends Q1 and Q2 be similar to reference products, but the two jurisdictions USA and HC have different definitions for Q2 sameness [9].

4.2.3 MEDICAL DEVICE CONSIDERATIONS

For inhalation devices and formulation integrated products, all three regions have different requirements. The US recommends the generic product device should be the same in terms of mechanism, handling procedures, etc. when compared to the reference device. Special mention is given in recommendations of BE for FP-SX DPI and Albuterol MDI to confirm the interchangeability of the reference and generic product, as well as the reference, and the test device should be identical in size and shape [5,7,20].

EMA recommends that device-related parameters should be compared with the reference device, and the acceptance criteria are within the difference of +/- 15%. EMA also states, the required amount of the drug substance released while device handling should be similar [11].

HC has no specific acceptance criteria for device comparison. It demands the quantitative and qualitative analysis results of device-related physical attributes and their operating characteristics [9]. All the formulation, device, and drug-related recommendations are listed in Table 3.

4.2.4. *IN-VITRO* STUDIES

Important approaches for assessment of BE is to test the *in-vitro* performance. *In-vitro* methods are rigid and highly sensitive. Some tests are relevant to all nasal aerosols and nasal sprays, irrespective they are formulated as solution or suspension products. These tests are as follows:

a) SAC test throughout container life

b) Laser Diffraction for Droplet Size Distribution

c) Cascade Impactor for Particle Size Distribution

d) Spray Pattern

e) Plume Geometry

f) Priming and Repriming

USFDA has a special mention for *in-vitro* testing. USFDA recommends drug particle size distribution and comparative mean nebulization time tests in the ampoule for nebulized budesonide inhalation suspension. Unlike EMA and HC, FDA endorses plume geometry, spray pattern, priming, and repriming tests for Albuterol MDI [7].

4.2.5. DELIVERED DOSE

It is the amount of drug substance per dose available to the user. USFDA guidance recommended for Albuterol MDI, and FP-SX DPI admits the SAC test at the beginning (B), middle (M), and end (E) life stages. Individual SAC determination is founded on one

actuation of the product. SAC test recommendation for DPI is three flow rates per Reference product labeling, and for MDI, it is one flow rate as per reference product labeling. For DPI, one of the flow rates was selected from the labeled flow rates of the device, whereas the other two flow rates equal to +/- 50% of the labeled flow rate was selected. The equivalence is determined using PBE statistical approach as a recommended tool for data analysis. The detailed PBE analysis procedure is published in the FDA's drug-specific bioequivalence recommendation for nebulized Budesonide inhalation suspension [6,20].

However, EMA has recommended the similar targeted dose delivery between the reference and test product within an acceptable range of +/- 15% difference.

HC recommends giving grounds on the variance between the dose delivered and the potential influence on the efficacy and safety of the drug product. Moreover, potential overdose and underdose of the test product must also be studied. Although a specific statistical method is not stated in HC guidance, the testing data must be analyzed using a statistical approach [9,20].

4.2.6. PARTICLE SIZE DISTRIBUTION UPON AEROSOLIZATION

In-vitro particle size distribution using a cascade impactor is a standard approach used to characterize the APSD performance of the OIDPs. In this technique, separation is done based on an aerodynamic diameter of the emitted aerosol particles into a series of size ranges. The ideal size required for lung deposition is within the range of 1-5 μm, and it is usually described as FPM. GSD and MMAD are the key parameters used in the determination of the aerodynamic behavior of the aerosols from OIDPs [24].

USFDA has different recommendations for all three types of OIDPs, i.e., for MDIs, DPIs, and nebulized products. The APSD is tested at one flow rate for MDIs, whereas at three flow rates for DPI. During the life stages, doses are tested at the beginning for MDI and the end for DPI [8,25]. The APSD test for nebulized products is conducted as per the reference product

labeling with the use of the same nebulizer as specified in the RLD label. Moreover, the aqueous droplet size distribution using the laser diffraction method is also recommended for nebulized Budesonide suspension. On individual stages, MMAD, GSD, FPM, data needs to be submitted for evaluation [6,8].

EMA has defined more specific recommendations for the APSD test and analysis procedures. For the APSD test, there are no fixed acceptance criteria set. However, the maximum acceptable *in-vitro* difference must be justifiable. The test is conducted at a certain range of flow rates concerning a particular patient population, and further, the flow rate dependence is compared. Investigation for the minimum (e.g., 10 %), and maximum (e.g., 90 %) attainable flow rate in that particular patient population is studied, and further comparison is made for the stages representing the fine particle mass and also the impactor stages that are pertinent to *in-vivo* safety and efficacy of the product. A minimum of four groups of stages that justify the deposition sites in the lung must be given in a case where group data is to be analyzed [10,24].

In the case of HC, details for the APSD procedure were not did not provided, but it recommends a statistical comparison.

4.2.7. DOSE UNIFORMITY

Different regions have specified current recommendations for the content uniformity test only related to the nebulization inhalation products. USFDA recommends this test for nebulized Budesonide inhalation suspension. However, HC recommends it only for inhalation single dose nebulization products [20]. The comparison of *in-vitro* test criteria is summarized in Table 4.

Table 4. Comparison of the regulatory recommendations for *in-vitro* tests of OIDP equivalence.

Parameters	**USFDA**	**EMA**	**HC**

Delivered dose	• Nebulized budesonide inhalation suspension: Test: mean delivered dose Equivalence criteria: population bioequivalence (PBE) [7]. • FP-SX DPI and albuterol MDI: Test: single actuation content at the beginning (B), middle (M), and end (E) life stages using three flow rates Equivalence criteria: PBE [5].	The targeted, delivered dose should be similar (within ±15% difference) [11].	Statistical comparison.
Particle/ droplet size distribution profiles	• Nebulized budesonide inhalation suspension: Tests: 1. Comparative drug particle and agglomerate particle size distribution in nebulized aerosol at the specified flow rate per RLD labeling. 2. Aqueous droplet size distribution by a laser diffraction method Equivalence criterion: PBE [6]. • FP-SX DPI and albuterol MDI: Test: APSD at the B and E life stages at three flow rates for DPI and one flow rate for MDI [5].	• Data should be obtained within a range of clinically relevant flow rates.	Statistical comparison.
Other factors	Nebulized budesonide inhalation suspension: • Comparative mean nebulization time. • Comparative drug particle and agglomerate particle size distribution in the suspension. • Comparative unit dose content of the drug in the ampoules [6]. Albuterol MDI: • Spray pattern at B life stage at two distances [7].	Not specified.	For nebulization inhalation product-content uniformity is suggested.

5. *IN-VIVO* BIOEQUIVALENCE STUDIES

In-vivo BE for OIDPs is estimated by three basic methods:

- Pharmacokinetic studies

- Pharmacodynamic studies
- Clinical studies

The human PK study for locally acting OIDPs is carried out either to estimate the systemic exposure of the inhaled active substances or to evaluate the systemic safety of the test drugs concerning the reference drug. PK studies gave indirect evidence in support of local delivery to the targeted site of action. Human PD study is conducted in the case where the blood concentration of an active substance is too low to be quantified in PK studies. Moreover, PD and clinical studies are frequently used to study the equivalence in terms of clinical effect for locally acting OIDPs [4].

USFDA recommends *in-vivo* studies along with *in-vitro* BE studies for FP-SX DPI and Albuterol MDI. However, EMA insists on conducting *in-vivo* studies to provide evidence to support equivalence in case if the product does not fulfill the criteria for equivalence. HC states that if *in-vitro* and *in-vivo* correlations are not established, dependence only on *in-vitro* data is insufficient for MDI test products, and hence, the *in-vivo* studies are advised to establish the equivalence [4,20].

6. DETAILED *IN-VIVO* STUDIES

6.1. Systemic Exposure evaluation by human PK studies

Systemic exposure of the active substance is estimated in the blood. US suggested the use of PK study for comparing the systemic exposure of the reference and test products. EMA states two motives for the PK studies for OIDPs [4]:

i. To investigate total systemic safety exposure of lungs and GI tract.

ii. To estimate pulmonary deposition with the exclusion of the active moiety absorption from the gastrointestinal tract.

However, in HC, PK study is done to examine the safety of generically marketed ICS in comparison to a reference product.

In the case of study design, not much information is available from any of the mentioned jurisdictions. USFDA's BE recommendations for Albuterol MDI and FP-SX DPI suggests a single dose, crossover PK study under fasting condition. HC has given a single dose study design.

However, the dose selection for PK studies is different among various regions. US recommends considering a minimum number of inhalations of the reference and test products that must be sufficient to distinguish a PK profile. Moreover, a sensitive analytical method must be used for this characterization. EMA indicates that a single dose is used. HC recommends a single, highest labeled adult dose.

Concerning the study subject, USFDA states that healthy males and healthy non-pregnant females are ideal for the study, whereas EMA points out the need to included adults from the intended population for undergoing PK studies.

Systemic PK study of Inhaled products provides safety information in terms of systemic exposure, but presently, PK studies alone are not accepted for establishing bioequivalence. Therefore, efforts are being made from all jurisdictions, pharmaceutical industries, etc. for the use of PK study in concurrence of *in-vitro* tests to establish BE of OIDPs.

The acceptance criteria for PK equivalence in all regions is 90% CI of the T to R ratio of AUC, which must be within the range of 80.00–125.00%. The PK-BE studies for USFDA, H, and EMA are summarized in Table 5.

Table 5. Comparison of pharmacokinetic bioequivalence study for OIDPs.

Sr. No.	Parameters	USFDA	EMA	HC
1.	Study design	• The PK study is	• For the purpose	Single-dose

		recommended in the choice of combination of *in-vivo* and *in-vitro* BE studies [8]. No details on study design. • FP-SX DPI and albuterol MDI: Fasting, single dose [5].	of a pulmonary deposition, the PK study has to be able to exclude absorption of the active moiety from the GI tract • For safety purposes, the PK study should include the measurement of that amount via the lung and GI tract [11].	study
2.	Dose	FP-SX DPI: minimum number of inhalations that is sufficient to characterize a PK profile [5].	Single-dose	Maximum labeled adult dose [10]
3.	Subjects	Normal healthy males and non-pregnant females, general population.	For safety purposes, the adult intended patient population [11].	No additional recommendations
4.	Equivalence acceptance criteria	90% CI for the C_{max} ratio is within 80.00–125.00%; a reference scaled approach can be considered for highly variable drugs [8].	T_{max} is also compared [11].	Relative mean of C_{max} (T/R) is within 80.0–12.5.0% for inhaled corticosteroids [10].

6.2. Systemic safety evaluation by human PD studies

USFDA considers conducting PD studies only when PK study is improbable. EMA and HC guidelines only give PD studies for systemic safety. EMA and HC have recommendations for cases where plasma or blood levels are very low to be distinguished in PK studies. Hence,

systemic exposure can be determined then by PD studies by assessing the effect of HPA. EMA classifies this study as per the age group. PD-BE equivalence studies for countries above are summarized in Table 6.

Table 6. Comparison of bioequivalence on pharmacodynamics studies for systemic safety.

Sr. No.	Parameters	USFDA	EMA	HC
1.	Dose	Not specified	Not specified	single- or multiple-dose study to compare T and R [10].
2.	Study details	Not specified	Adults: C_{max} during 24 h measurement. • Steady-state has to be reached • There are special considerations for children [11].	Serum cortisol is measured every two hours for a period of 24 hrs [10].
3.	Acceptance criteria	Not specified	Not specified	90% CIs of T/R SCO-24 AUC should be within 80–125% [10].

6.3. PD and Clinical BE studies

Clinical and PD studies provide direct evidence on bioequivalence in case of determination of efficacy. BE efficacy studies are mainly focused on ICS and bronchodilators. Bronchodilators include SABA and LABA. SABA is used as quick-relief inhalers, and LABA is used on a long-term basis, which has everyday use in case of asthma. All the international regions covered in this article recommend bronchodilation and bronchoprotection studies in the case of bronchodilators. Clinical efficacy studies for ICS and bronchodilators are given in Table 7.

USFDA recommendation on Albuterol MDI is a bronchodilator on which the guidance is based. HC has guidance on SABA MDI only. HC mentions two bronchodilation and bronchoprotective and PD measurement studies for locally acting SABA MDI.

Table 7. Comparisons of the bioequivalence recommendation for clinical efficacy studies for inhaled corticosteroids and bronchodilators.

Sr. No.	Parameters	USFDA	EMA	HC
1.	Clinical studies for inhaled corticosteroids	A confirmatory clinical study is measuring lung function [8].	Bronchodilation and bronchoprotection studies. Quantitative sputum eosinophil counts Exhaled nitric oxide (eNO) is also suggested [11].	Quantitative sputum eosinophil counts Exhaled nitric oxide (eNO) is also suggested [9].
2.	Clinical efficacy studies for bronchodilators	Bronchodilation and Bronchoprotective studies [8].	Bronchodilation and Bronchoprotective studies [11].	Bronchodilation and Bronchoprotective studies [9].

7. INDIAN PERSPECTIVE FOR ESTABLISHING BE OF OIDPs: A GUIDANCE DOCUMENT FOR MEDICAL DEVICES

This reference document provides details of standards, regulatory, and other requirements to the importers, manufacturers, traders/distributors, healthcare professionals, clinical establishments related to the medical devices in India [26].

7.1. CDSCO guidelines for bioavailability and bioequivalence studies

DCGI has not defined the specific guidelines for evaluation of the safety and efficacy of orally inhaled products [27]. However, generic drug applications need to refer to the 'Guidelines for bioavailability and bioequivalence studies' issued by CDSCO [12]. In India, all trials are

regulated by guidelines/rules *viz.* Rule122A to Rule122E [28] and Schedules Y of Drugs and Cosmetic Act and Rules thereunder (Amended in 2005) [29], Good Clinical Practice guidelines issued by CDSCO [30] and Ethical guidelines for Biomedical Research on Human Subjects [31].

7.1.1. METHODS TO DEMONSTRATE BIOEQUIVALENCE

In India, PK-BE studies for OIDPs is not a well-established concept. The correlative study of lung deposition systemic levels is progressing science. When the test drug is an inhalation solution that comprises the same active in the same strength and necessarily with the same excipients in similar contents as the reference product, then BE between the test drug and the reference product is assumed as the self-evidence with no additional requirements of *in-vivo* studies. The device specifications may or may not be similar between the test and reference products. Additional *in-vitro* testing is essential to exhibit and compare the performance of the inhalation device between the reference and the test drug product [12].

As per bioavailability and bioequivalence guidelines for OIDPs intended for lung targeted action, BE based solely on PK studies is not suitable, and hence, comparative PD studies or clinical trials are needed to establish equivalence between the products. Till today there has been no importance of the locally acting OIDPs, which have been approved solely based on PK-BE studies. However, a correlation between the C_{max} and AUC_{0-t} and lung deposition were observed with advanced research. Hence, PK-BE studies are progressively accepted globally for being adequate to establish the equivalence of OIDPs [27,32]. The available pulmonary dose is cast back with an assessment of AUC_{0-t} and the deposition of the drug in the targeted region from the estimation of C_{max}. Therefore, with the necessary justification, an estimation of 'interchangeability' between the reference and test drug products using PK-BE studies may be a substitute for clinical trials [27].

7.1.2. DESIGN CONSIDERATIONS FOR PD STUDIES

For designing the PD trials, some of the recommendations like the response metric, therapeutic or pharmacological effect related to the safety and/or efficacy of the drug, quantitative measurements of responses, etc. are similar to other jurisdictions of the world [12,27].

However, that are some recommendations specific to India, as listed below:

- The acceptance range stated for PK-BE studies does not apply to PD studies.
- The test and reference drug should not produce maximum response throughout the entire study as it may prove impossible to discriminate between the formulations given in doses required to produce the maximum response.
- The necessity for investigation of a dose-response relationship.
- The criteria for the identification of responders and non-responders must be clearly stated within the protocol. The prior screening must be used to exclude non-responders from the study.
- If the PD studies are not decisive, then the clinical trials should be conducted.

8. CONCLUSION

Only a finite number of regions around the worldwide have published draft guidance related to the establishment of bioequivalence of generic orally inhaled drug products. Every guidance has resemblance and variance amongst each other. Recognizing these resemblance and variance regarding BE recommendations provides a better insight into different approval standards required by the jurisdictions around the world. By studying the guidelines of the countries above, it can be concluded that they have taken different paths to establish BE. USFDA and HC suggest an aggregated weight of evidence approach, EMA promotes a stepwise approach, whereas India does not have any published guidance specifically on OIDPs but provides pieces on information on bioequivalence study design.

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AUTHOR CONTRIBUTIONS

Atmaram P. Pawar and Kakasaheb R. Mahadik have conceptualized the idea for the article. Prajakta P. Patil has performed the literature search and data analysis. Vinod L. Gaikwad has drafted and critically revised the work.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any experiments on human participants and/or animals performed by any of the authors.

CONFLICT OF INTEREST

All authors (Vinod L. Gaikwad, Prajakta P. Patil, Atmaram P. Pawar, Kakasaheb R. Mahadik) declare that they have no any potential conflict of interest.

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FIGURE LEGENDS

Figure. 1. USFDA's approach to establish BE for OIDPs.

Figure 2. EMA's stepwise BE approach.