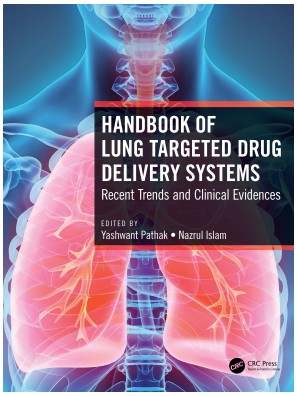

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

Yashwant Pathak, Nazrul Islam

European Perspective on Orally Inhaled Products: In Vitro Requirements for a Biowaiver

Publication details
https://www.routledgehandbooks.com/doi/10.1201/9781003046547-48
Sunita Chaudhary, Dhaval Patel, Dasharath M. Patel, Jayvadan K. Patel
Published online on: 18 Oct 2021

48

European Perspective on Orally Inhaled Products: In Vitro Requirements for a Biowaiver

Sunita Chaudhary[1], Dhaval Patel[2], Dasharath M. Patel[3], and Jayvadan K. Patel[4]
[1]Arihant School of Pharmacy and Bio Research Institute, Gujarat, India
[2]Saraswati Institute of Pharmaceutical Sciences, Gujarat, India
[3]Graduate School of Pharmacy, Gujarat Technological University, Gandhinagar Campus, Gujarat, India
[4]Nootan Pharmacy College, Sankalchand Patel University, Gujarat, India

48.1 Introduction

The respiratory route is widely acceptable currently because it has a maximum absorptive area of up to 100 m^2 with good blood supply. Many diseases like asthma, asthmatic rhinitis, and many other respiratory diseases have their own adverse impact on the health of normal human beings (1). Globally, the occurrence of asthma is growing and chronic obstructive pulmonary disease (COPD) is widespread in 65 million people (2). In the European Union (EU), asthma is detected in 7% of the population and COPD in 6% is reported (3). Several kinds of medication are used to treat symptoms of COPD. Currently, inhaled products for the treatment of asthma are being developed (Trends in COPD pdf June 2013, accessed on Sept 2020) (4). Orally inhaled products have gained attention with increased interest in drug deposition in the lungs and alveoli. Devices which can give better targeting of drug in the lungs are largely favored, such as nebulizers, dry powder inhalers (DPIs), and pressurized metered dose inhalers (pMDIs). Use of orally inhaled products for asthma and pulmonary disease has created interest in the development of different combinations of available products and their generic versions.

Orally inhaled products (OIPs) have been successful in the development of some generic products, like Seretide®, Spiriva®, and Symbicort®, with annual revenues of US$10 billion. In the EU, there is an 8% death rate due to diseases of the respiratory system, and this creates a need for the development of safe and effective treatments. Repeatability in the workings of OIP and representing bioequivalence (BE) is difficult because the success of OIPs is mostly dependant on the mutual correlation of patient, device, and formulation. For the development of safe and effective generic products, it is important to develop appropriate approaches to demonstrate BE. One more complication observed at international level with regard to OIP is the testing and registration of new as well as generic products. In 2014, the IPAC-RS/UF conference was organized to provide information regarding the latest advancements regarding OIPs, such as metered dose inhalers (MDIs) and DPIs, and their market registration. At that conference many issues about OIPs were discussed, including the pharmacokinetic and pharmacodynamics aspects of generics and the criteria for acceptance after a demonstration of bioequivalence) (5). For complete and efficient development of an OIP, it is essential to have a through knowledge of formulation variables and their role in product performance for establishment of an *in vitro in vivo correlation* (IVIVC). IVIVC can be established successfully when in vitro and in vivo drug release prove similar in a scalable manner. IVIVC is generally proven by comparison with plasma concentrations. An IVIVC works well on oral formulations and there is much evidence that an in vitro test will not predict the result of a pharmacokinetics study, especially for orally inhaled formulations (6).

48.2 Regulatory Pathways in Europe

In the EU, the authorities responsible for regulation and approval of products follow a systematic methodology for granting of approval where equivalence is tested using in vitro equivalence, followed by pharmaceutical equivalence, and pharmacokinetic equivalence, which includes lung deposition studies, and further pharmacodynamic study that includes efficacy and safety study data. Thus in the EU, an in vitro study to establish equivalence is considered sufficient for approval of a product, but it may not be considered so in the United States (US).

In recent years, the EU as well as some other European countries have been advancing the regulations related to OIPs. Some substantial developments have materialized with regard to medical devices, bioequivalence, quality, and combination products (7).

The guidelines CPMP/EWP/4151/00 Rev.1 and EMEA/CHP/QWP/49313/ 2005 cover the overall necessities and specify the need for clinical and in vitro requirements for generics (Guideline on the requirements for clinical documentation for orally inhaled products pdf. February 2009, Accessed on December 2019) (8). In the EU, it is not compulsory to have complete equivalency between the generic product and reference product in every aspect, but a demonstration of bioequivalency with the reference product can be

DOI: 10.1201/9781003046547-48

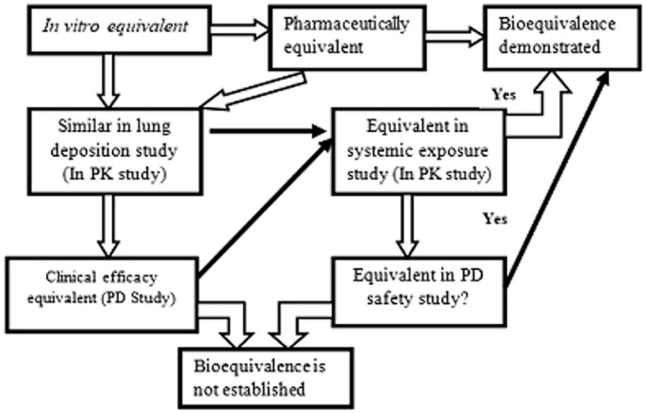

FIGURE 48.1 Diagram Representing EMA's Step-wise Approach for OIPs (10)

made by using pharmacokinetic and bioavailability studies (Guideline on the pharmaceutical quality of inhalation and nasal products pdf, March 2006, accessed on April 2015) (9). There is also specification for hybrid products which demonstrate equivalence by means of pharmacodynamic (PD) studies that can be waived from such kinetic and bioavailability studies. This classification focuses on the methods used to show therapeutic equivalence. During the study, the prescriber and patient are not informed about the approval of a generic product by pharmacokinetic study or as a hybrid which failed pharmacokinetic equivalence (1).

48.2.1 Bioequivalence Requirements in the EU

In the EU guidelines, there are systematic strategies for demonstration of therapeutic equivalence which use in vitro and in vivo data. In short, a study uses initially in vitro data intially for comparison, which is followed by pharmacokinetic data if required, and finally by any requirement for pharmacodynamics data. Figure 48.1 shows the systematic methodology to establish therapeutic equivalence for OIPs.

48.2.1.1 In Vitro Equivalence Testing

A European guideline highlights the main purpose of in vitro equivalence testing as being only for the establishment of therapeutic equivalence of OIPs. Use of in-vitro testing method is very effective for establishing equivalence of OIPs compared to the other strategies due to ease of operation and low variability between products. Generic products are approved depending upon in vitro data where it is found there is little variation with respect to the reference product, because changes from the reference product ire approved without the requirement of in vivo studies. The total aerolized dose administered to the lung and its aerodynamic particle size distribution (APSD) strongly affects the safety and efficacy of orally inhaled drug products (OINDPs). Consequently, the delivered dose and APSD are generally viewed as crucial quality attributes of inhaled products, and corresponding testing is required by regulatory guidance for characterization and quality control purposes (11).

48.2.1.1.1 Aerodynamic Particle Size Distribution

For in vitro characterization of OINDPs, ASPD and delivered dose are considered crucial attributes for quality. Depending upon the aerodynamic particle size of an aerosol, the location of deposition of particles in the lungs is decided. Specifically, the most effective range of particle size is 1 to 5 μm and particles larger than 5 μm have more impact on the oropharynx, if any particle smaller than 1 μm remains present in the air system. Larger particles will deposit at the back of the throat. Extremely small particles are directly exhaled instead of being deposited (European Pharmacopoeia 5.0: Chapter 2.9.18) (12). The cascade impaction method is used to determine APSD and the effect of different particle sizes on drug deposition in the lungs. Generally, for comparison of two OIPs, several methods are used, including inertial impaction methods, Marple-Miller impactor (MMI), Andersen cascade impactor (ACI), and next generation impactor (NGI). In Europe, USP, ACI, and MMI are recommended and NGI is specified in the *European Pharmacopoeia* (EP) (10).

For the in vitro comparison, selection of the stage is based on fine particle size and upper stage of the impactor which is relevant for measuring the safety and efficacy of the medicinal product when administered in vivo. The comparison should be done on at least four stages, which are expected. However, the amount of drug is limited and the quality of information may be degraded by division of the dose in to 4–5 stages. Depending upon the individual stage there is an in vitro acceptance range of ±15% for the aerodynamic particle size distribution (13).

However, the normally used impactor systems are not able to simulate sufficiently the anatomy of the the human respiratory system. When patients use the inhaler, the constant flow rate of the aerosol is not the same as that used in the impactor with respect to time (14). Another difference with the air pathways of the lungs is that the inlets of the impactor are of various diameters and lengths. This problem can be resolved by selecting a device with the proper mouth–throat geometry that closely resembles oropharyngeal deposition 15. If the composition is different qualitatively or quantitatively, then more broad in vitro testing is required with respect to the reference product (16). This study includes particle size distribution by laser diffraction (European Medicines Agency. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) pdf 2009, accessed on March 2015) (8).

In the EU, if suspensions have been evaluated by in vitro testing using crystallographic structure, drug particle size

distribution in suspension, and nebulized droplets, and have a qualitative and quantitative composition similar to the reference product, then the suspension for nebulization can be waived from in vivo studies (1).

Approval of pressurized metered dose inhalers (pMDIs) in solution is based on in vitro data in EU. In OIDP guidelines, there is a specific mention of in vitro requirements for pMDIs in suspension, but a description of a detailed test is not given. Hence, it is appropriate to accept in vitro tests for OIDP as per the US Food and Drug Administration (FDA) draft guidance for the industry (1).

48.2.1.1.2 Dose Content Uniformity

This is referred to as the amount of drug substance that is available to deliver the dose to a patient on a per-dose basis. Applicants can justify variation in the amount of dose delivered and also can justify the effects of the dose with regard to safety and efficacy of the product. The European Medicines Agency (EMA) specifies that there should be not more than a 15% difference in the targeted delivered doses of the test and reference products (17).

48.2.1.1.3 Dissolution, Permeation, Particle Clearance, and Tissue Exposure

Orally inhaled products deliver the inhaled drugs to the airways by local action and this generates a high localization of drug with improvement in the potency of the drug and the therapeutic value. When a drug has high water solubility, its molecular properties can influence the extent of tissue binding which ultimately it affects the local tissue concentration and therapeutic effects. For a compound with less solubility, material properties affect solubility and/or dissolution rate and this ultimately affects therapeutic value (18). When two formulations have similar aerodynamic particle size distributions with variation in systemic exposure, this gives a constant predicted difference in the dissolution rates of the two formulations. Even though there is a more significant effect of dissolution rate on therapeutic performance, there are no currently available regulatory guidelines on orally inhaled products and their in vitro testing. Forbes and colleagues (19) have discussed the problem of correlating in vitro dissolution data with the therapeutic and clinical performance of a product. The amount of drug dissolved is affected not only by the properties of the drug, such as surface area and solubility, which can be controlled externally, but also by physiological factors, like composition of the airway lining fluid, particle clearance rate, and permeability of the airway epithelium, all of which can vary between different regions of the lung (20).

48.2.1.1.4 In Vitro Dissolution

All pharmacopoeias specify dissolution testing as a standardized test of solid and semi-solid dosage forms, but due to the unavailability of a standardized method for measuring the dissolution behavior of OIPs, it is challenging to dissolve drug substance with poor solubility in a very limited volume of solvent, which results in poor dissolution behavior in physiological media. Thus, for systemic availability of drug from a DPI, the dissolution rate is a rate limiting step. Currently there is no available standardized in vitro test to explore the in vitro performance and characterization of DPIs (19). The FDA and the EMA recommend measuring the delivered dose and the APSD to determine the quality of the product, and this waives the dissolution testing.

Different techniques, like a modified twin stage impinger, flow through the cell, horizontal diffusion cell, Franz diffusion cell, and ethrough cell USP type IV and paddle type USP type II apparatuses with or without membrane holders, for substances using specified dissolution media are found in the literature. Selection of dissolution media is usually in the range of pH 6.8–7.4 for testing of inhaled products, and the media used can be saline phosphate buffer as well as simulated lung fluid (SLF). SLF is an aqueous solution containing mineral salts and sometimes surfactant, but no protein component or mucus. When orally inhaled products contain poorly soluble drug then it requires the presence of surfactant in the dissolution media. A surfactant that can be used in pulmonary formulations is phospholipid disaturated dipalmitoyl phosphotidyl choline (DPPC) in concentration of 0.02%, which is found in epithelial lung fluid (19). Preparation of DPPC solution is very difficult due to the unclear and lengthy method of preparation, which leads to the use of synthetic surfactants for comparison of in vitro dissolutions. In the pharma field, the FDA and EMA emphasize aerodynamic particle size distribution and delivered dose while there is no need of dissolution testing. As per the *European Pharmacopoeia*, dissolution is performed on particles collected from a cascade impactor in dissolution experiments (6).

SLF is more advantageous because it is a physiologically relevant media, with more complex composition, even with a low buffering effect sometimes, which makes it unsuitable for formulations that show a pH dependent drug release profile as well as a sustained release profile (21). It was observed that in SLF there is increase in pH within 24 hours from 7.4 to 8.8 (22). Son et al. studied the three dissolution media for the drug release profile of budesonide: phosphate buffered saline (PBS), phosphate buffer pH 7.4, and SLF. A similar drug release profile was shown in all three media (23).

48.2.1.2 Pharmacokinetics Approach

Previously in the EU, many inhaled products were approved mainly on the basis of in vitro data and pharmacokinetic data as shown in Table 48.1. EU considers pharmacokinetic bioequivalence studies as an acceptable methodology for analyzing the extent of lung deposition and the pattern of deposition after oral inhalation of products.

In EMEA guidelines, a pharmacokinetics study is performed for two main purposes: (1) to evaluate deposition of drug in the lungs in which there is an exclusion of absorption of active moiety from the gastrointestinal (GI) tract, and (2) to examine the safety of a molecule in a systemic route, where total systemic exposure in the lungs and GI tract should be investigated (1).

According to the EMA guidelines regarding orally inhaled drug products, demonstration of pharmacokinetic parameters such as maximum plasma concentration (Cmax) and area under curve (AUC) for each drug must be carried out to discover the

TABLE 48.1

EU Product Approvals Based on the EMA OIP Guidelines (24)

Products	Company	Year of Approval
Salmeterol HFA pMDI	Neolab Ltd	2011
Fluticasone/Salmeterol (FP/SM) DPI (Elpenhaler)	Pharos Ltd	2011
Fluticasone pMDI	Cipla Ltd.	2013
Ipratropium pMDI	Cipla Ltd.	2013
Fluticasone/Salmeterol pMDI	Cipla Ltd.	2014
Budesonide/Formoterol DPI (DuoResp Spiromax)	Teva Pharmaceuticals	2014
Lifsar (Fluticasone/Salmeterol DPI)	Winthrop Pharmaceuticals	2015
Sirdupla (Fluticasone/Salmeterol pMDI)	Mylan Ltd	2015
Bufomix (Budesonide/Formoterol DPI)	Orien Corporation	2014
Tiotropium Bromide DPI (Braltus or Gregal)	Teva Pharmaceuticals	2016

pMDI: pressurized metered dose inhaler; DPI: dry powder inhaler

bioequivalence of test and reference products (8). The AUC, or amount of drug available in blood from the lungs, determines the amount of dose targeted to lungs. In addition to AUC, the distribution pattern of a drug can be analyzed by Cmax and the time to achieve Cmax (Tmax). Depending upon the area of localisation of drug in the lungs, Tmax can be predicted. If drug is deposited in a peripheral area of the lung then it has shorter Tmax, and if drug from a DPI or solution in pMDI is deposited in the central lungs, then it has a longer Tmax. Sometimes a pharmacokinetic study can be used for analysis of both safety and efficacy of a drug because there is no absorption of drug in the intestine. In the European regulations, there is clear instruction about the consideration of AUC0-30 for measuring the efficacy of drug and AUC0-t for safety (1). The EMA recommends that there is no need to consider absorption of the active moiety from the GI tract in the case of orally inhaled products due to the pulmonary deposition and measurement of that amount via the lung and GI tract (safety) during a pharmacokinetic study. The EMA recommends an adult patient population, for safety purposes, in the selection of study subjects. For drugs with a narrow therapeutic window, the EMA recommends a range of 80–125% along with 90% confidence interval (CI) for ratio of the geometric means of AUC for test to reference. EMA has also increase Cmax ratio range 75–133% with 90% CI for highly variable drugs (24). Generally, pharmacokinetic parameters, including in vitro and in vivo as well as pharmacodynamics studies, are used to prove the bioequivalence of OIDPs. However, when in vitro data and pharmaceutical data are conflicting, then pharmacokinetic (PK) studies are required to prove the bioequivalence of inhaled drugs to ensure the substitutability of generics. There are some issues arising with regard to conducing PK studies to prove bioequivalence (25).

48.2.1.2.1 Dose Selection

A nasal drug delivery system delivers the drug locally; hence the systemic concentration of drug is minimum. Sometimes it is observed that a very low concentration is not detected by available bioanalytical techniques. This type of issue requires an increase in the dose of a drug or the need to develop a more sensitive bioanalytical method for drug assay. Selection of a higher dose is challenging for the safety of human volunteers. It may result in side effects like hypokalemia, tremors, and palpitations, such as in the case of salbutamol (26).

48.2.1.2.2 Subject Selection

To conduct a PK study, selection of human volunteers will be done on the basis of physiological condition and habits. Volunteers who are healthy nonsmokers are selected. There is special emphasis on selection of nonsmokers for the study for several reasons: (1) Regular smokers have chronic respiratory illnesses, which affect comparisons of PK parameters. (2) Regular smoking may induce some metabolic enzymes like CYP 1A1 and 1B1, which decrease the effectiveness of the drug. (3) Smokers have variations in mucocilliary clearance and variations in the pH of the local microenvironment (26). All these factors introduce variations intra-subject in crossover studies because the cumulative effects of these factors may create changes in the same individual at different time intervals. Screening of volunteers for respiratory diseases can be done by reviewing medical histories, checking X-rays, and doing pulmonary function testing (PFT). A spirometer is preferred to conduct PFT and peak flow meters (PFM) are used especially in non-hospitalized patients (27).

48.2.1.2.3 Subject Training

The use of PFM testing is one of the key parameters for measurement of proper performance of OIPs in terms of correct and continuous inhalation technique (26). The important points while providing training for inhalation are as follows: (1) Before starting inhalation, carry out complete exhalation. (2) Ensure complete seal of lip and mouthpiece. (3) Ensure complete coordination of actuation and inhalation as required for metered dose inhaler. (4) Instruct subject to breath slowly and deeply for 5–10 s. During inhalation device should be actuated. Then the breath should be held for 5–10 s followed by exhalation through the nose. (5) For DPIs, the energy required for inhaling and expelling drug is provided by the individual when the device is actuated. So initially there would be rapid and deep inhalation for 4–5 s, then breath-holding for 5–10 s, followed by exhalation through the nose (28).

48.2.1.2.4 Other Factors

i. ***Use of a spacer with an MDI***: By using a spacer with an MDI, we can avoid the need for coordination between inhalation and actuation, and this also avoids oropharynx deposition of active pharmaceutical ingredients (API). As per the EU guidelines, it is mandatory for the product to perform the PK studies with the spacer in order to receive approval of and licencing for the product. If the product can be used both ways, with or without the spacer, then the PK studies need to be performed in both cases (26).
ii. ***Use of charcoal block***: Generally the charcoal block method is used to eliminate drug oral absorption of a drug after a product has been orally inhaled. Administering a charcoal suspension at different time intervals can avoid the oral absorption from the inhaled drug, so the amount of drug available in systemic circulation gives an idea about the amount that was absorbed from the respiratory route (29). For all regulatory submissions, the use of a charcoal block is not compulsory for PK studies, but the EMA recommends two studies, one with the carbon block and one without. It also recommends validation of the method required for the administration of charcoal (30).

48.2.1.3 Pharmacodynamics Approach

The EMA specifies pharmacodynamics (PD) studies for safety purpose. According to the EU, if in vitro and PK studies fail to show equivalenc,e then PD studies are necessary for approvals. When there is a low concentration of drug in the plasma then the EMA also recommends a PD study. Advancement in analytical techniques, however, enables the detection of small amounts of drug in plasma and blood.

EMA highlights various recommendations for a variety of age groups. In adults, they recommend of assessment of the effect on the hypothalamic–pituitary–adrenal (HPA) axis. For children, safety data cannot be exactly predicted by extrapolating from the adult data in asthma. Finding PD equivalence uses two different tests to demonstrate systemic safety in children; for example, the systemic effect of inhaled corticosteroids can be assessed using the HPA axis, and the lower-leg bone growth rate is used as a surrogate marker for growth (8).

For the treatment of asthma and COPD, the main two class of locally acting inhalers are recommended like bronchodilators and corticosteroids. The bronchodilators are long-acting β2-agonists, short-acting β2-agonists, and anti-cholinergics, which are covered under the guidance of the EMA. The EMA also recommends bronchodilation and bronchoprotection studies. The EMA has not covered and specified a dose or criteria for acceptance of locally acting OIPs. PD studies give quantification information about the biological and physiological impacts of drug products and are used to scrutinize both safety and efficacy. Actually, this is very difficult to implement due to high levels of variability and sensitivity (17). Methacholine PD20 and an unspecific forced expiratory volume are accepted methods in the EU for locally acting OIPs. Variation in results can be reduced by crossover design, but as per European guidelines, parallel design is preferable. The time required for study and choice of primary and secondary endpoints are dependent on the therapeutic category of the test product (1).

Therefore, for European regulators, it is crucially important to demonstrate assay sensitivity. As per EMA guidelines, this requires analysis of relative potency and the response per dose. For new chemical entities, some EU reviewers preferred to use a response-scale analysis. By use of clinically related biomarkers, the pharmacological actions of the drug can be linked for successful identification of measurable results in a PD study. Using biomarkers enables a successful demonstration of the dose–response relationship that can be carried out with a representative dose. If the test and reference products show similarity clinically, that indicates that both have similar efficacy if a change in dose is rigorously associated with a measurable response. It is challenging to demonstrate the bioequivalence of orally inhaled corticosteroids based on clinical data because it gives a narrow dose response with a long time to show effect for local action. The EMA recommends different PD studies at different intervals (23).

To study the bioequivalence (BE) of inhaled corticosteroids for the treatment of asthma, the EMA recommends that quality of life be validated by using questionnaires and also by examining patient variables like exhaled nitric oxide (eNO) and sputum eosinophil. Moreover, different studies like parallel double blind or randomized studies are recommended, and a crossover design can also be used as an alternative method of measurement if needed. The EMA recommends a comparison of two different doses of test and reference substances, depending upon their dose response curve, and the selection of dose is from the sharp portion of the dose–response curve (17).

48.3 Biowaiver for OIDP in the European Union

In the European Union, PK studies are used to demonstrate bioequivalence, but under the following criteria, these studies can be waived.

48.3.1 Criteria 1

If two formulations are identical in quantity and quality, in the case of nebulized solution, the approval of a product can be granted without in vitro testing. However, if the composition of both formulations is different, then in vitro testing is necessary. Bioequivalence studies of nebulizers containing budesonide are based on in vitro data, which ensures similarity in particle size distribution in suspension and aerodynamic particle size distribution of the nebulized droplets (6).

48.3.2 Criteria 2

Products that remain in solution at the time of administration like oral solutions, effervescent tablets, and injectable solutions, if some terms and conditions are met, like absence of excipients which change the motility of the GI tract and stability of the preparation.

48.3.3 Criteria 3

As per BCS some classes of drug products can be biowaived by comparing drug release profiles, if there are differences in some key excipients that can affect absorption which can be avoided. However, the drugs that can be biowaived by the EMA for class I and III drugs are slightly different (Guideline on the Investigation of Bioequivalence. 20-1-2010, accessed in June 2020) (31).

48.3.4 Criteria 4

If bioequivalence is proved with the most effective dose, then additional strengths do not require testing to show bioequivalence. In such cases, the strength of the test product must fulfill all requirements of qualitative and quantitative composition, having used similar procedures for manufacturing, and the same dissolution profile is obtained.

When a comparison of test and reference products is carried out using data from in vitro studies, then in vivo studies can be waived, but when a product is available in different strengths and BE is proven with one strength in an in vivo study, the product is also considered proven for equivalence (Community Code Relating to Medicinal Products for Human Use pdf. 2001, accessed in August 2020) (32).

In the case of orally inhaled products available in multiple strengths, the EMA emphasizes in vitro testing for both test and reference products in all possible strengths. When the formulation shows in vitro dose linearity, then an individual dose of drug substance is sufficient to establish bioequivalence clinically, and it is generally preferable to select the minimum dose at different levels, which will enhance the sensitivity of the study. Selection of the dose for study also depends upon the type of study. For PD studies, dose selection should be the minimum in order to obtain maximum sensitivity of drug assay as much possible, as per guideline specification. Conversely, for PK studies, the selected dose for study is highest to get the maximum plasma levels because it gets low systemic exposure (Legal basis for products for local use pdf. December 2012, accessed in January 2020) (33).

Suppose testing reveals that the test and reference product and linearity relationship does not exist, then bioequivalence of the test product to the reference product will have to be recognized with a different product strength and maybe by all possible product strengths. Because it will be necessary to modify the test product so that it becomes similar to the reference product for comparison of their therapeutic equivalence. If, by using different strengths of the test and reference products, it is not possible to show proportionality in vitro, then a bracketing approach is used to establish equivalence. In the bracketing approach, dose strengths are selected from the most similar to the most different for in vitro testing (8).

Therefore, in the design and development of a generic product which acts systemically, the manufacturer should always consider a biowaiver if possible, otherwise it will be necessary to perform a PK bioequivalence study. However, in the legislation of the EU, the focus is on product approvability, whereas interchangeability is not covered in the regulations. Hence PK differences between products are not considered to be clinically significant, so products are considered as therapeutic equivalents based on the PD, and the product can be approved as a hybrid. On the other hand, those generics having bioequivalence based on PK and that waived PD to demonstrate are considered as generic.

48.4 Criteria for the In Vitro Comparison

Based on Committee for Medicinal Products for Human Use (CHMP) guidelines, comparative in vitro data obtained with an above-mentioned method may be acceptable when the test product is compared with the reference product. The following criteria should be satisfied:

i. The product must have similar API in its different forms, like hydrates, solvates, salts, esters.
ii. Product should be pharmaceutically similar like inhaler, metered dose inhaler, dry powder inhaler.
iii. Performance of product, behavior of aerosol particles, and dissolution characteristics should not be influenced by differences in crystalline or amorphous forms.
iv. Product performance, like delivered dose uniformity, aerosol particle characteristics, and inhalation compatibility of the patient should not be influenced by any difference in excipients, and they must not affect change safety of the product (25).
v. The inhaled volume coming through the device must enable a sufficient amount of drug into the lungs, and should be similar (within 15%) to the reference.
vi. The same amount of active substance should be released from both test and reference product.
vii. The inhalation device has the same resistance to airflow (within 15%) compared to reference (8).

48.5 Case Studies of Orally Inhaled Drug Products

48.5.1 Case Study of Glycopyrronium and Formoterol Fumarate

Bevespi Aerosphere was the first medicine in its category to be approved by the European Commission (EC); it contains glycopyrronium and formoterol fumarate in a pressurized metered-dose inhaler (pMDI) for treatment of COPD. It also acts as bronchodilator. This product offers a new choice of device in the inhaler category. Bevespi Aerosphere is to be taken two times a day, a fixed dose, which offers dual action as a bronchodilator containing glycopyrronium which acts as an antagonist of a long-acting muscarinic and formoterol fumarate, which act as agonists of β2. In a phase III trial program, approval of this product was done based on the efficacy and safety of Bevespi Aerosphere and it involved more than 5000 patients in a study (Bevespi Aerosphere approved in China for patients with COPD, May 2020, accessed on August 2020) (34).

48.5.2 Case Study of Fluticasone Furoate/ Vilanterol DPI

This is a combination of fluticasone furoate and vilanterol, available in a fixed dose that contains corticosteroids and a long-acting β2 adrenoreceptor agonist (LABA), which is branded as Relvar or Revinty, and its once-daily dose is delivered via a dry powder inhaler (DPI). The EU approves fluticasone furoate/vilanterol DPI for the treatment of asthma in adults and adolescents. It was observed in this study that a once-daily dose of fluticasone furoate/vilanterol improved pulmonary function and is more effective that a twice-daily dose. It was also observed that fluticasone furoate/vilanterol is more effective compared to fluticasone propionate. With the additional consideration of the frequency of dose administration, fluticasone furoate/vilanterol provides more patient compliance due to the one daily dose where other combinations available for asthma require doses twice a day (35).

48.6 Summary

Approval of an orally inhaled drug product can be allowed in the European Union based on its in vitro data if it follows the step-wise approach of the CHMP plus fulfillment of certain conditions. This step-wise approach can be successfully applied to solutions for nebulization as well as pMDI and suspension for nebulization because variations in the dissolution profile of the suspension depends upon its particle size distribution and surface properties, which can be compared by crystallography. For OIDP, it is essential to demonstrate a comparison of in vitro data as a part of the establishment of equivalence with more than one strength of the same reference product, and it is also necessary to demonstrate similar flow rates from the devices for the test and reference products for the pharmacokinetic data to be accepted.

REFERENCES

1. Lee L, Bhawana S, Alfredo G, Gustavo M, Ying L, Sarah L, Shuguang H, Juliet R, Abhijit V, Jaideep G, Shrinivas P, and Svetlana L. Regulatory considerations for approval of generic inhalation drug products in the US, EU, Brazil, China, and India. *The AAPS Journal*. 2015; 17(5): 1285–1304. doi: 10.1208/s12248-015-9787-8.
2. Global Initiative for Asthma (GINA). "Global burden of asthma." http://www.ginasthma.org/local/uploads/files/GINABurdenReport_1.pdf. Accessed 26 Nov 2014.
3. World Health Organization. Burden of COPD. http://www.who.int/respiratory/copd/burden/en/. Accessed 26 Nov 2014. 3. "Asthma and Allergy Foundation of America. Asthma facts and figures." https://www.aafa.org/display.cfm?sub=42&id=8. Accessed 26 Nov 2014.
4. American Lung Association. "Trends in COPD (Chronic bronchitis and emphysema): morbidity and mortality." 2013. http://www.lung.org/finding-cures/our-research/trend-reports/copd-trendreport.pdf. Accessed 26 Nov 2014.
5. Hochhaus G, Craig D, Martin O, Sau L, and Svetlana L. Current scientific and regulatory approaches for development of orally inhaled and nasal drug products: overview of the IPAC-RS/University of Florida Orlando Inhalation Conference. *The AAPS Journal*. 2015; 17(5): 1305–1310. doi: 10.1208/s12248-015-9791-z.
6. Frohlich E, et al. Biological obstacles for identifying in vitro-in vivo correlations of orally inhaled formulations. *Pharmaceutics*. 2019; 11(7): 316, 1–19. 10.3390/pharmaceutics11070316
7. Dina Al-Numani D, et al. Rethinking bioequivalence and equivalence requirements of orally inhaled drug products. *Asian Journal of Pharmaceutical Sciences*. 2015; 10(6): 461–471. 10.1016/j.ajps.2015.08.006.
8. Committee for Human Medicinal Products (CHMP). "European Medicines Agency: 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 use in the treatment of asthma in children and adolescents."22-1-2009. London, European Medicines Agency (EMA). Available at www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003504.pdf. Accessed on January 20, 2019.
9. European Medicines Agency. "Guideline on the pharmaceutical quality of inhalation and nasalproducts." http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf, 2006. Accessed on 08.07.15
10. Evans C, David C, Tim C, Eva A, Richard A, Dale C, Sanjeeva D, Myrna D, Eng P, William D, Anders F, Afredo G, Michael G, Robert H, Gu¨ nther H, Susan H, Paul L, Svetlana L, Parameswaran N, Dennis OC, David P, Ilse P, Colin R, Dennis S, Gur J, Marjolein W, and Patricia W. Equivalence considerations for orally Inhaled products for local action—ISAM/IPAC-RS European Workshop Report. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2012; 25(3): 118–123. 10.1089/jamp.2011.0968.
11. Sandell D. "Review of the EMEA guidelines' in-vitro equivalence criteria for cascade impaction data." [internet]. 2010 [cited 2019 Apr 30]. 2010. Available from: https://ipacrs.org/assets/uploads/outputs/Sandell.pdf. Accessed 11 June 2019.
12. Preparations for inhalation: Aerodynamic assessment of fine particles. European Pharmacopoeia 5.0: Chapter 2.9.18.
13. Andersen AA. New sampler for the collection, sizing, and enumeration of viable airborne particles. *Journal of Bacteriology*. 1958; 76(5): 471–484. PMID: 13598704.
14. Khoubnasabjafari M, Elaheh R, Morteza S, Vahid J, Lan C, Donghao C, Hak-Kim C, and Abolghasem J. A new hypothesis to investigate bioequivalence of pharmaceutical inhalation products. *DARU Journal of Pharmaceutical Sciences*. 2019; 27(1): 517–524. doi: 10.1007/s40199-019-00250-x.
15. Newman SP and Chan HK. In vitro/in vivo comparisons in pulmonary drug delivery. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2008; 21(1): 77–84.
16. MacNeish CF, Meisner D, Thibert R, Kelemen S, Vadas EB, and Coates AL. A comparison of pulmonary availability between ventolin (albuterol) nebules and ventolin (albuterol) respirator solution. *Chest*. 1997; 111(1): 204–208. 10.1378/chest.111.1.204

17. Lu D, Lee SL, Lionberger RA, Choi S, Adams W, Caramenico HN, Chowdhury BA, Conner DP, Katial R, Limb S, Peters JR, Yu L, Seymour S, and Li BV. International guidelines for bioequivalence of locally acting orally inhaled drug products: similarities and differences. *The AAPS Journal*. 2015; 17(3): 546–557. 10.1208/s12248-015-9733-9.
18. Backman P, Adelman H, Petersson G, and Jones CB. Advances in inhaled technologies: understanding the therapeutic challenge, predicting clinical performance, and designing the optimal inhaled product. *Clinical Pharmacology & Therapeutics*. 2014; 95(5): 509–520. 10.1038/clpt.2014.27.
19. Forbes B, Per B, David C, Myrna D, Bing V, and Beth M. In vitro testing for orally inhaled products: developments in science-based regulatory approaches. *The AAPS Journal*. 2015; 17(4): 837–852. 10.1208/s12248-015-9763-3.
20. Riley T, David C, Jan A, Andrea C, Agnes C, Andrew C, Monisha D, Janet M, Jolyon M, Maria R, Nastaran S, Terrence T, and Svetlana L. Challenges with developing in vitro dissolution tests for orally inhaled products (OIPs). *AAPS PharmSciTech*. 2012; 13(3): 978–989. doi: 10.1208/s12249-012-9822-3.
21. Radivojev S, Zellnitz S, Paudel A, and Fröhlich E. Searching for physiologically relevant in vitro dissolution techniques for orally inhaled drugs. *International Journal of Pharmaceutics*. 2019; 556: 45–56. 10.1016/j.ijpharm.2018.11.072.
22. Gunther A, Schmidt R, Nix F, Yabut-Perez M, Guth C, Rosseau S, Siebert C, Grimminger F, Morr H, Velcovsky HG, et al. Surfactant abnormalities in idiopathic pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis. *European Respiratory Journal*. 1999; 14: 565–573.
23. Son YJ, Horng M, Copley M, and McConville JT. 2010. Optimization of an in vitro dissolution test method for inhalation formulations. *Dissolution*, pp. 6–13.
24. Usmani OS, Molimard M, Gaur V, Gogtay J, Pal Singh GJ, Malhotra Gngfh and Derom E. Scientific rationale for determining the bioequivalence of inhaled drugs. *Clinical Pharmacokinetics*. 2017; 56(10): 1139–1154. 10.1007/s40262-017-0524-6
25. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden BJ, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *Journal of Allergy and Clinical Immunology*. 1999; 104(6): 1215–1222. 10.1016/S0091-6749(99)70016-3.
26. Thakkar K, Mhatre S, Jadhav M, Goswami S, and Shah R. Pharmacokinetic studies for proving bioequivalence of orally inhaled drug products—critical issues and concepts. *Frontiers in Pharmacology*. 2015; 6(117): 1–4. 10.3389/fphar.2015.00117.
27. Silvestro L, Savu SR, Savu SN, Tudoroniu A, and Tarcomnicu I. Development of a sensitive method for simultaneous determination of fluticasone propionate and salmeterol in plasma samples by liquid chromatography-tandem mass spectrometry. *Biomedical Chromatography*. 2012; 26: 627–635. 10.1002/bmc.1708.
28. Loke YK and Singh S. Risk of acute urinary retention associated with inhaled anticholinergics in patients with chronic obstructive lung disease: systematic review. *Therapeutic Advances in Drug Safety*. 2013; 4: 19–26. 10.1177/2042098612472928.
29. Fowler SJ and Lipworth BJ. Pharmacokinetics and systemic β2-adrenoceptor-mediated responses to inhaled salbutamol. *British Journal of Clinical Pharmacology*. 2001; 51(4): 359–362.
30. Scott JE. The pulmonary surfactant: impact of tobacco smoke and related compounds on surfactant and lung development. *Tobacco Induced Diseases*. 2004; 2: 3. 10.1186/1617-9625-2-1-3
31. Committee for Medicinal Products for Human Use (CHMP). "Guideline on the Investigation of Bioequivalence."20-1-2010. London, European Medicines Agency (EMA). Available at www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed on June 25, 2020.
32. Directive 2001/83/EC of the European Parliament and of the Council of 6 April 2001 on the "Community Code Relating to Medicinal Products for Human Use." *Official Journal of the European Communities L*. 2004; 311: 67–128.
33. Co-ordination Group for Mutual Recognition and Decentralised Procedures—Human. CMDh Questions & Answers. Generic Applications. Legal basis for products for local use." 12/2012. Available at www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh-272-2012-Rev0-2012_10.pdf. Accessed January 2, 2020.
34. https://www.astrazeneca.com/media-centre/press-releases/2020/bevespi-aerosphere-approved-in-china-for-patients-with-copd.html https://www.astrazeneca.com/media-centre/press-releases/2020/bevespi-aerosphere-approved-in-china-for-patients-with-copd.html. Accessed on 20 June 2020.
35. Deeks ED, Lyseng-Williamson KA, and Syed YY. Fluticasone furoate/vilanterol dry-powder inhaler in asthma: a guide to its use in the EU. *Drugs & Therapy Perspectives*. 2017; 33: 153–159.