

Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products: Workshop Summary Report

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Abstract

In April 2010 a workshop on the “Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products” was sponsored by the Product Quality Research Institute (PQRI) in coordination with Respiratory Drug Delivery (RDD) 2010. The objective of the workshop was to evaluate the current state of knowledge and identify gaps in information relating to the potential use of pharmacokinetics (PK) as the key indicator of *in vivo* bioequivalence (BE) of locally acting orally inhaled products (OIPs). In addition, the strengths and limitations of the PK approach to detect differences in product performance compared with *in vitro* and pharmacodynamic (PD)/clinical/therapeutic equivalence (TE) studies were discussed. The workshop discussed the relationship between PK and lung deposition, *in vitro* assessment, and PD studies and examined potential PK study designs that could serve as pivotal BE studies. It has been recognized that the sensitivity to detect differences in product performance generally decreases as one moves from *in vitro* testing to PD measurements. The greatest challenge in the use of PD measurements with some OIPs (particularly inhaled corticosteroids) is the demonstration of a dose–response relationship (for local effects), without which the bioassay, and hence a PD study, may not have sufficient sensitivity to detect differences in product performance. European authorities allow demonstration of *in vivo* BE of OIPs based solely on pharmacokinetic studies. This workshop demonstrated broader interest among discipline experts and regulators to explore approaches for the use of PK data as

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the key determinant of *in vivo* equivalence of locally acting OIPs. If accepted, the suggested approach (PK alone or in conjunction with *in vitro* tests) could potentially be applied to demonstrate BE of certain orally inhaled drugs.

Key words: pharmacokinetics, bioequivalence, pulmonary deposition, systemic absorption, central/peripheral ratio

Introduction

THIS ARTICLE SUMMARIZES the outcomes of the workshop on the "Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products" held in April 2010 in Orlando, Florida. The workshop was sponsored by Product Quality Research Institute (PQRI) in coordination with RDD 2010. Attendees from North America, Europe, Latin America, and Asia representing the pharmaceutical industry, academia, and regulatory bodies attended the workshop with the objective to evaluate the current state of knowledge and identify gaps in information relating to the potential use of pharmacokinetics (PK) as the key indicator of *in vivo* bioequivalence (BE) of locally acting orally inhaled products (OIPs). In addition, the strengths and limitations of the PK approach to detect differences in product performance compared with *in vitro* and pharmacodynamic (PD)/clinical/therapeutic equivalence (TE) studies were discussed.

The workshop began with a podium session during Respiratory Drug Delivery (RDD) 2010 to provide general knowledge on the use of PK with OIPs, which served as a framework for the remainder of the workshop. The first presentation addressed the issues related to the regulatory and scientific paradigms associated with demonstration of BE for inhaled products.⁽¹⁾ A presentation on utilizing clinical trial simulations discussed whether PK studies are able to determine the dose available to the lung, the pulmonary residence time, and the regional deposition.⁽²⁾ The clinical utility of the PK approach was explored using studies from the published literature where (1) PK data have proven to be in agreement with *in vitro* and/or clinical efficacy findings, and (2) where they were not in good agreement.⁽³⁾ Effective PK clinical trial designs were advocated and the importance of subject populations and study dose selection discussed.⁽⁴⁾ The final presentation reviewed the practical application of the European BE guidance, which provides for the possible demonstration of *in vivo* BE of OIPs based solely on PK evaluations.⁽⁵⁾

The workshop continued with three case study presentations that described the practical application of PK to demonstrate BE for two dry powder inhalers and a metered dose inhaler. The case studies were followed by moderated breakout sessions with focused discussions on the following selected topics:

- Pharmacokinetics and lung deposition
- Pharmacokinetics and *in vitro* assessment
- Pharmacokinetic and pharmacodynamic relationships
- Effective bioequivalence pharmacokinetic study designs

Each breakout session was held twice to allow for maximum discussion and input from workshop attendees. These sessions provided background information and clarification on the specific topics, as well as consensus or disagreement

on the usefulness of PK for establishing equivalence in local pulmonary delivery. The case study presentations and synopses from the breakout sessions are available online at the PQRI Website (www.pqri.org). This article presents a summary of the case study presentations and the breakout session discussions.

Background

The PQRI previously sponsored a 2-day workshop on "Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products," which reviewed recommendations for demonstrating BE in the development of OIPs.⁽⁶⁾ In that workshop, *in vitro* methods to demonstrate BE, biomarkers, imaging techniques, *in vivo* approaches to establish local delivery equivalence, and device design similarity were discussed. The workshop highlighted that the utility of PK studies for the evaluation of local pulmonary delivery equivalence warranted further discussion.

Inhalation products are considered complex drug-device combination products, with distinct performance characteristics and unique patient instructions for use and handling. Currently, PK studies alone are not universally accepted to assess BE of locally acting OIPs as it has been stressed that the sampling site for PK studies (plasma) is a compartment that is downstream of the site of action (the lung).⁽⁷⁾ Thus, PD endpoints have been suggested for testing pulmonary equivalence. Despite this, it is considered that PK might be able to provide key information (e.g., how much drug is deposited, where the drug is deposited, how long does the drug stay in the lung) for demonstration of BE of OIPs while being more discriminative of formulation performance than PD/clinical/TE studies.⁽²⁾

Regulatory considerations

The regulatory considerations for demonstrating BE of OIPs vary in the different global regions. In Europe, the EMA Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products⁽⁸⁾ recommends a stepwise approach using *in vitro* comparisons, followed by lung deposition studies (PK or imaging studies), and finally PD/clinical effect studies. At each step, if BE is demonstrated, no further studies are required.

In North America, the utilization of PK data in the demonstration of BE of OIP has evolved over time. The 1999 Health Canada guidance for second entry short-acting beta agonists (SABA)⁽⁹⁾ did not reference PK studies to establish equivalence, whereas the 2007 draft guidance for subsequent market entry of inhaled corticosteroids (ICS) recommends systemic exposure (PK) studies if the plasma levels are sufficient to enable reliable analytical measurement; otherwise, systemic exposure is determined in a PD study.⁽¹⁰⁾ Currently, Health Canada recommends BE studies comparing both

systemic exposure and local PD effect(s) to support BE of generic OIPs.

The U.S. Food and Drug Administration (FDA) Critical Path Opportunities for Generic Drugs⁽¹¹⁾ recognizes that the assessment of BE for locally acting products has presented unique scientific challenges to the approval of generic products. The FDA's Office of Generic Drugs (OGD) has previously issued revised, interim, or draft guidances for documentation of BE of pressurized metered dose inhalers (pMDIs)^(12,13) and locally acting aqueous nasal aerosols and sprays.⁽¹⁴⁾ Although there is currently no specific FDA guidance on the demonstration of BE for OIPs, based on the available information,^(15,16) a "Weight-of-Evidence" approach which incorporates qualitative (Q1) and quantitative (Q2) formulation sameness, *in vitro* testing for the evaluation of the comparative product performance, PK studies for the assessment of equivalent systemic exposure, and PD studies for the evaluation of equivalent local delivery, has been used to approve several ANDAs for CFC albuterol MDIs in the mid-1990s.⁽¹⁷⁾

U.S. definition of bioequivalence

The Code of Federal Regulations (CFR) 320.24(b) indicates that *in vivo* tests in humans measuring concentration–time profiles are considered to be the most sensitive approach in terms of accuracy, sensitivity, and reproducibility for determining bioavailability (BA) or BE. However, for drug products that are not intended to be absorbed into the bloodstream, which is the case with OIPs, BA, and/or BE may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site(s) of action. Therefore, the OGD currently recommends applicants conduct PK and PD/clinical studies for the demonstration of systemic and therapeutic (local action) equivalence, respectively. The greatest challenge in following this approach with some OIPs (particularly inhaled corticosteroids) is the demonstration of dose–response in PD studies, without which the study has no discriminative value for the determination of BE. The flat dose–response profiles of ICS represent a challenge and traditional clinical approaches, as well as PD models including exhaled nitric oxide⁽¹⁸⁾ and "asthma stability" evaluation,⁽¹⁹⁾ have not yet shown sufficient sensitivity necessary for BE studies.

Clinical pharmacology considerations

A fundamental consideration in clinical pharmacology is that there is a relationship between the concentration of the drug at its site of activity and its efficacy and/or toxicity. This is the basis of using PK approaches for demonstration of BE of drug products that act through the systemic circulation. If the active moiety of the drug reaches its sites of activity and toxicity from the systemic circulation, then the concentration in the systemic circulation determine the concentration at the sites of activity and toxicity. Therefore as depicted in Figure 1, two formulations of the same active moiety will be "bioequivalent" if their concentration–time profiles in the systemic circulation are equivalent, as their resulting concentrations at the sites of activity will then be the same, and their efficacy and safety will therefore be equivalent. Pharmacokinetic approaches have advantages

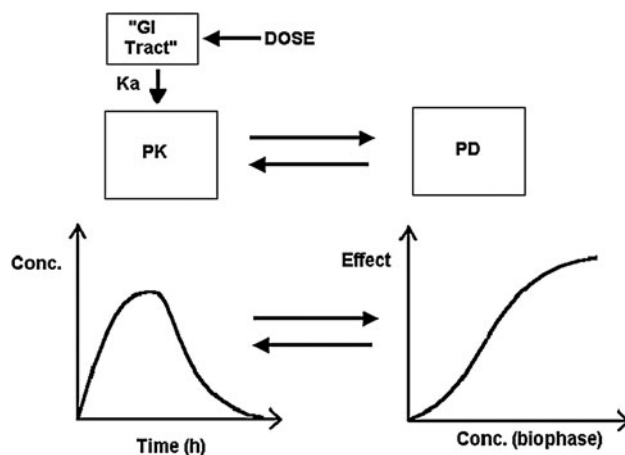


FIG. 1. The relationship between PK and PD.

over pharmacodynamic (biomarker or clinical) BE studies as drug concentrations can be generally measured with lower variability over a broad concentration range.

Pharmacokinetic studies alone for assessing the BE of locally acting drugs are not universally accepted due to the lack of evidence that pharmacokinetic studies can mirror the fate of deposited drug within the lung. Thus, in the case of locally acting products, two different studies (i.e., a PK study for evaluating the systemic exposure and a TE study showing that the local efficacy is the same) may be needed to demonstrate BE between two different formulations of the same locally acting moiety. The design of such TE studies should also assess the dose dependency of the therapeutic effect.

The concentration–response relationship at the site of activity for receptor mediated effects (Fig. 2) is generally S-shaped and saturable in nature. This nonlinear behavior with a steep dose–response only around the EC_{50} (the concentration inducing 50% of the maximum effect) limits the use of pharmacodynamic bioequivalence studies (TE studies) as differentiation between test and reference products delivering different amounts of drug will only be possible in the steep portion of the dose–response curve. Therefore, from a scientific point of view, BE should be assessed in the steep portion of the dose–response curve with the assessment being performed by projecting the efficacy of the test versus the reference on the dose scale (not the efficacy scale), as presented in Figure 2. BE studies, however, have to be performed at the dose of the innovator product, and this dose might be in the flat portion of the dose–response curve at which differences in the delivered dose will not translate into differences in effects (see Fig. 2).

PK approach

Pharmacokinetic tools might be a valuable alternative to clinical studies for assessing the pulmonary fate of OIPs if they can provide information on three key questions determining the local BE of inhalation drugs:

- What is the extent of pulmonary deposition?
- Is the drug deposited within the lung, that is, central/peripheral (C/P) ratio?

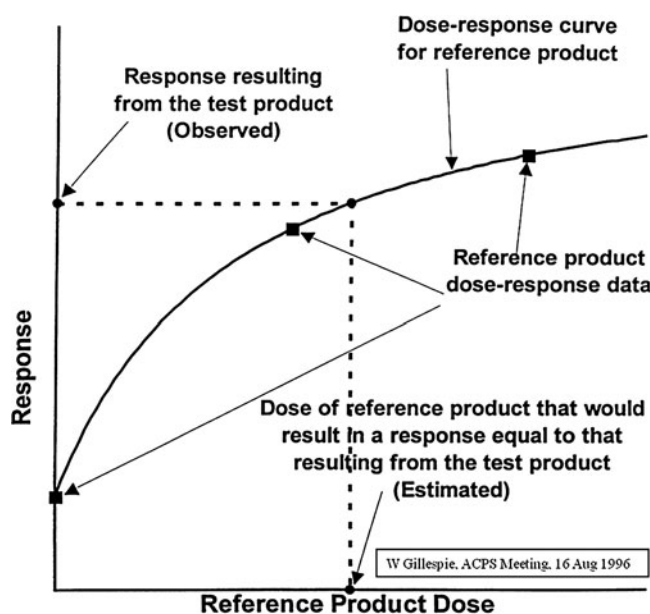


FIG. 2. Theoretical BE criteria on the dose scale.

- How long does the drug stay in the lung, that is, the systemic absorption rate?

For the use of PK studies for assessment of bioequivalence of OIPs, one needs to confirm that the systemic levels are reflective of drug concentrations at the site(s) of action in the lungs, and that the rate and extent of drug absorption into the plasma are directly related to the rate and extent of drug availability at the site(s) of action. Therefore, if systemic levels of OIPs can be shown to be directly related to the dose delivered to the lung (using a charcoal block or some other technique to block oral absorption) and the way in which it is deposited (i.e., discriminate C/P deposition ratio differences), systemic PK studies could potentially be used to replace PD/clinical/TE evaluation as a surrogate indicator for local delivery to the lung.

Summary of Case Study Presentations

Three presentations of case studies discussing the applicability of PK data for assessing BE are summarized. The case studies compared two different dry powder inhalers (DPIs) for a combination product, a series of studies comparing different DPIs and pMDIs containing a long-acting selective beta-2-adrenoceptor agonist, and a generic application applying the 2009 EMA guideline⁽⁸⁾ on the requirements for the demonstration of therapeutic equivalence between two inhaled products. For each of these presentations, data comparisons including *in vitro* assessments, PK and PD data, and clinical efficacy data were presented.

Salmeterol/Fluticasone Propionate DISKUS[®] versus Salmeterol/Fluticasone Propionate RPID[®]

Peter Daley-Yates, Ph.D., GlaxoSmithKline

The recent interest in updating and developing BE criteria for OIPs has led to a reappraisal of the practical and scientific issues in this area.^(3,8) This review of data from a case study

illustrates the difficulty in relying solely on laboratory data to assess the BE of inhaled drug products.⁽²⁰⁻²⁶⁾ In this example, two DPIs were studied—the DISKUS[®] inhaler and the Reservoir Powder Inhalation Device (RPID[®])—both containing the salmeterol 50 µg/fluticasone propionate (FP) 250 µg combination product (SFC 50/250).

The *in vitro* and clinical performance of the two combination dry powder formulations of SFC 50/250 showed conflicting results. The cascade impactor (CI) profiles at 60 L/min and clinical efficacy data indicated that the products were equivalent, whereas the PK data showed that systemic exposures to FP and salmeterol were approximately twofold greater for RPID compared to DISKUS. The clinical studies also found that SFC 50/250 from both products was well tolerated with no apparent difference in the incidence or profile of adverse events.^(20,24-26)

The differences observed in systemic exposure were unexpected as the two inhalers gave similar *in vitro* results when tested in the laboratory and contained essentially the same drug and lactose blend. There was a slightly higher FP emitted dose for particles at Stage 3 of the impactor for DISKUS, although this was not reflected in the PK data, which indicated lower systemic exposure for DISKUS. Stage 3 represents particles of 2.3–3.2 µm diameter, which are generally considered to be optimum for lung delivery, whereas particle sizes >5 µm are thought to deposit in the oropharyngeal region and have greater potential for oral absorption and systemic side effects. Particles <2 µm may penetrate deeper into the lungs and favor systemic delivery, but there were no notable differences between the two inhalers for finer particle fractions. Both inhalers appeared to show more similar particle size deposition profiles for salmeterol. The RPID appeared to show slightly higher deposition of FP particles in the coarser fractions in Stage 1 compared to DISKUS, but this did not explain the twofold difference in systemic exposure, particularly because the oral BA of swallowed FP is <1%.⁽²⁷⁾ The emitted dose of RPID SFC 50/250 using CI was also determined at a higher flow rate of 85 L/min and found to be 48.9 µg for salmeterol and 250.5 µg for FP (98 and 100% of label, respectively), an increase of no more than 7% of label claim over the reported 60 L/min values. The Fine Particle Mass (FPM) delivered by RPID SFC 50/250 at 60 L/min and 85 L/min was calculated to be 11.6 and 11.9 µg for salmeterol and 58.2 µg and 57.8 µg for FP, respectively, a change of no more than 0.6% of label claim. Based on these data and the previously reported lack of emitted dose flow dependency for the DISKUS, it is unlikely that flow rate dependency of the RPID at higher flow rates could account for the twofold difference in PK reported.⁽²²⁾

The limitations of the CI in applying quantitative measurements of particle size distribution to lung deposition patterns are well recognized.⁽²⁸⁻³⁰⁾ Cascade impactors generally use a metal induction port to represent the oropharyngeal region of the respiratory tract, but these ports are poor predictors of *in vivo* oropharyngeal deposition as they do not allow for the changing crossdimensional areas along the sections of the airway and the morphological features *in vivo* that influence airflow. In addition to these factors it is also possible that the differences in drug delivery between the two inhalers could be related to the subject/device interface such as the orientation of the mouthpiece leading to differences in throat versus lung deposition.⁽³¹⁾

In conclusion, despite the many similarities between the RPID and DISKUS SFC formulations, the clinical performance was influenced by other factors that were not clearly identified. Although *in vitro* tests and clinical efficacy endpoints found the two inhalers comparable, there was a lack of correlation between the *in vitro* FPM and *in vivo* PK data and between the PK data and the clinical efficacy data.

Formoterol Certihaler™ versus Formoterol Aerolizer™

Beverley Patterson, Ph.D., Novartis

Formoterol fumarate (FF) is a long-acting selective beta-2-adrenoceptor agonist. It is a racemic mixture of two enantiomers (R,R and S,S). Currently, no analytical method is available to determine the enantiomers in plasma. However, the enantiomers can be measured in urine using an enantiomer-specific, high-performance liquid chromatographic (HPLC) method. Due to the low doses in humans and the resulting extremely low systemic concentrations of formoterol, evaluation of PK at therapeutic doses has focused on urinary excretion as a surrogate of plasma PK. Recently, assays have been validated for plasma (LLOQ 1.45 pmol/L) and urine (LLOQ 17.4 pmol/L) expressed as the free base (unpublished data, Novartis), enabling determination of plasma PK following therapeutic doses.

The deposition of FF in human lungs for the Aerolizer (DPI) has been investigated.⁽³²⁾ Lung deposition was predicted to be 17.4% from *in vitro* measurements of particle size distribution by CI at different flow rates. In addition, the *in vivo* deposition was determined to be 19.6% by gamma scintigraphy with FF labeled with ^{99m}Tc, blended with lactose, and filled into capsules. The variability of lung deposition in this study was much higher than predicted. However, on average, the observed intrathoracic deposition was in good agreement to the values predicted using the *in vitro* model.

Three studies, the details of which are summarized in Table 1, were presented.^(33–35) In addition, a fourth study was also presented that focused on a fixed dose combination (Symbicort HFA pMDI and Formoterol HFA pMDI) with *in vitro* evidence for similar formulation performance.^(36,37)

The results from Study 1 and Study 2 demonstrated that the formoterol Certihaler™ and Aerolizer® have comparable PK and PD. All doses of FF delivered by Certihaler exhibited clinically relevant bronchodilatory effects that were similar to FF delivered via the Aerolizer. All doses of FF delivered via the Certihaler showed comparable onset of action within 3 min to FF delivered via Aerolizer. Considering urinary excretion of formoterol as a surrogate of systemic exposure, these studies demonstrate that systemic exposure to unchanged formoterol was similar between the Certihaler and the Aerolizer. Although formal statistical analysis to establish BE was not conducted, these results also suggest that PK BE could have been achieved. However, a formal BE study including charcoal block would have been required to test the hypothesis that both devices deliver similar drug amounts to the lung.

The results from Study 3, which compared delivery of 12 µg FF from a HFA pMDI and the Aerolizer, demonstrated comparable PK and PD between the devices. Formoterol delivered via HFA pMDI was dose proportional and similar to that of formoterol delivered via the Aerolizer.

In Study 4, *in vitro* data showed similarity of fine particle dose for FF from Symbicort (DPI) and HFA pMDI. However,

a definitive conclusion cannot be drawn for *in vitro* to *in vivo* PK/PD correlation due to the lack of identified published data. A PD correlation was established for FF doses of 4.5, 9, and 18 µg given either via Symbicort HFA (80/4.5 µg) or via Oxis Turbuhaler (4.5 µg) (with constant budesonide doses of total 320 µg). The average 12-h FEV₁ were similar, regardless of delivery device, among treatments with the same nominal FF doses. Mean FEV₁ values were significantly higher for treatments containing formoterol versus budesonide alone.

It is important to note that the formoterol Certihaler and HFA pMDI versus the Aerolizer results cannot be generalized for other compounds or devices. However, if *in vitro* characterization (with comparable methods) and *in vivo* PK show comparable results, they may provide an indication of comparable efficacy. Deposition characteristics should then be investigated simulating physiological flow profiles through the corresponding devices alongside the standard assessments. Appropriate *in vivo* PK, PD (efficacy), safety, and tolerability studies should be conducted.

Salbutamol (INN) MDI versus Salbutamol Originator MDI

Anders Fuglsang, Ph.D., Scientific Consultant (formerly of Sandoz/Aeropharm)

From 2003 to 2008 Sandoz developed a pMDI product containing salbutamol sulphate (known as albuterol sulfate in the United States) at a dose of 100 µg per actuation. The performance targeted that of a reference product manufactured by GlaxoSmithKline. To investigate equivalence in accordance with step 1 (*in vitro* evaluation) of the draft EMA BE guideline,⁽³⁸⁾ Sandoz used CI to compare the particle size distributions of the two formulations. A 90% confidence interval for the geometric mean Test/Reference ratio of select stage groupings was constructed and equivalence was to be concluded if the confidence interval was contained within 80–125%. At the time of study, the European guideline was only in draft but specified the tighter limits 85–118%. Sandoz entered a dialogue with EU regulators and successfully made a case for using the classical and somewhat broader BE limits. On four select stage groups, equivalence was proven within the tight limits (85–118%); however, equivalence at certain individual stages could not be shown. Therefore, a systemic exposure study was recommended. The study was a double-blind, double-dummy, crossover comparative PK study without charcoal administration. The study population consisted of 42 healthy adult volunteers.

The study followed a standard two-treatment, two-period, two-sequence design. An analysis of variance on log-transformed values peak plasma concentrations (C_{max}) or area under the concentration–time curve (AUC_{24h}) as assessed by noncompartmental analysis) was calculated and the residual used to construct a 90% confidence interval for the T/R ratios of C_{max} and AUC as primary endpoints, whereas safety parameters (blood glucose, potassium, tremor, and ECG) were secondary as was T_{max} .

The study established equivalence with the 90% confidence interval for AUC_{24h} being 93.1–108.2% and the 90% confidence interval for C_{max} being 101.1–119.2%. Data for T_{max} and safety parameters did not suggest product differences.

The combined pool of *in vitro* and *in vivo* data led regulators to issue approval. Although the relationship between

TABLE 1. FORMOTEROL CERTIHALER™ VERSUS FORMOTEROL AEROLIZER™ CASE STUDY DETAILS

Study	Objectives	Population	Dose/device	Parameters
Case Study 1 ⁽³³⁾ Multicenter, randomized, placebo controlled, double blind, double dummy, incomplete block crossover, dose finding study.	Optimal effective dose of formoterol fumarate delivered via the Certihaler in comparison with the Aerolizer. Dose proportionality of urinary excretion at steady state	Adults and adolescents with persistent asthma.	Placebo Certihaler versus Certihaler (5, 10, 15, 30 µg) versus Aerolizer (12 µg). twice a day for 4×1 week with a 1-week washout period	FEV ₁ -AUC 0–12 h, standardized for time Ae 0–12 (nmol) Ae 0–12 (% dose)
Case Study 2 ⁽³⁴⁾ Multicenter, randomized, placebo controlled, double blind, incomplete block crossover, dose finding study.	Optimal effective dose of formoterol fumarate delivered via the Certihaler in comparison with the Aerolizer. Dose proportionality of urinary excretion at steady state	Children aged 5 to 12 with persistent asthma.	Placebo Certihaler versus Certihaler (5, 10, 15, 30 µg) versus Aerolizer (12 µg). twice a day for 4×1 week with a 1-week washout period	FEV ₁ -AUC 0–12 h, standardized for time Ae 0–12 (nmol) Ae 0–12 (% dose)
Case Study 3 ⁽³⁵⁾ Randomized, multicenter, double-blind, double-dummy, placebo controlled, crossover, dose ranging study	Safety and efficacy of single doses of formoterol fumarate via pMDI in comparison to DPI and placebo. Single-dose PK (urinary excretion of unchanged formoterol)	Adolescent and adult patients with persistent asthma.	Formoterol fumarate delivered via an HFA pMDI (6, 12, and 24 µg) versus placebo and Aerolizer (12 and 24 µg)	FEV ₁ -AUC standardized for time Urine Ae 0–12 (nmol) Ae 0–12 (% dose)

in vitro data and *in vivo* outcomes is still unclear for many inhaled products, the study illustrates how PK can provide information on the drug delivery properties of inhalation products, and is a successful example of an application of the European stepwise approach to approval.

Summary of Breakout Sessions

The opinions expressed in the following discussions are those of individual scientists with insight and expertise on OIP, and do not necessarily reflect the opinions of the companies or regulatory agencies that employ them. The moderators and recorders (scribes) who authored this section have done their best to accurately reflect the lively discussion among the attendees that occurred in two separate breakout sessions. Inevitably, this summary cannot contain all the detailed opinions that were so graciously shared.

Session 1: Pharmacokinetics (PK) and Lung Deposition

Facilitators: Günther Hochhaus, Ph.D., University of Florida; Sau L. Lee, Ph.D., U.S. Food and Drug Administration; and Stephen Newman, Ph.D., Scientific Consultant; Scribe: Mei-Ling Chen, Ph.D., U.S. Food and Drug Administration

The purpose of this breakout session was to explore how PK data responds to changes in regional lung deposition,

address deficiencies in our knowledge of the relationship between PK and lung deposition, and discuss how the missing pieces of information might be obtained.

PK data from orally inhaled bronchodilators and corticosteroids can provide information about the total amount of drug deposited in the lungs, pulmonary residence time, and systemic exposure. The charcoal block PK method is able to quantify the mass of drug absorbed via the lungs for a range of drugs,⁽³⁹⁾ and this quantity has been shown to be numerically similar to the total lung deposition of terbutaline sulfate.^(40,41) The 30-min urinary excretion of albuterol and other drugs provides an index of pulmonary BA that allows two or more products to be compared.⁽⁴²⁾ However, it is also considered that the regional deposition pattern of drug within the lungs (and not just total lung deposition) is potentially relevant to the safety and efficacy of OIPs. The receptors for inhaled bronchodilators and corticosteroids are not distributed uniformly throughout the respiratory tract,⁽⁴³⁾ therefore, a difference in regional distribution between two products (e.g., an innovator and potential generic competitor) could result in differences in either efficacy or safety. Pharmacokinetic simulations⁽²⁾ suggest that differences in regional deposition are likely to affect parameters such as AUC (for slowly dissolving drug particles, a more central deposition results in lower AUC owing to more pronounced mucociliary clearance) and C_{max} (for particles that dissolve relatively quickly, faster absorption is observed in the peripheral lung). The hypothesis that PK studies can

identify differences in regional lung deposition between test and reference product needs to be investigated.

It was considered that existing data do not answer this question adequately. Studies involving QVAR HFA pMDI (Teva) versus CFC pMDI were suggested to provide the link between regional lung deposition and PK profiles, because they compared two aerosols with markedly different particle size distributions.^(44,45) However, those studies observed differences in both total lung deposition and regional lung deposition between the two products, so that it is difficult to judge which differences in PK profiles relate to changes in total lung deposition, and which to changes in regional lung deposition.

Radionuclide imaging methods can provide information relating to the regional deposition pattern of drugs within the lungs.⁽⁴⁶⁾ By themselves, these methods are not considered suitable by FDA for determination of BE between two inhaled products, the main reason being that it is necessary to radiolabel the products prior to their administration. Radionuclide studies generally involve the addition of the radionuclide ^{99m}Tc to a component of the formulation, in such a way that it traces the presence of drug across the full range of particle sizes. Although deposition can be quantified accurately by radionuclide imaging providing that the quality of the radiolabeling is sufficiently high, the act of radiolabeling per se could be considered to alter a product.⁽⁶⁾ However, it is possible that radionuclide imaging could be used to provide data that would strengthen the PK approach for showing BE between two inhaled products. Specifically, the breakout session considered whether lung deposition studies using radionuclide imaging could aid our understanding of what PK studies tell us about regional distribution of drugs within the lungs.

Radionuclide imaging using the two-dimensional method of gamma scintigraphy allows the lungs to be divided into between 2 and 10 zones,⁽⁴⁷⁾ from which indices such as the peripheral zone to central zone deposition ratio (P/C ratio), or its reciprocal (C/P ratio), can be determined. These indices are sometimes expressed relative to those of an inert radioactive gas (¹³³Xe or ^{81m}Kr). The P/C or C/P ratios respond to changes in factors such as particle size, which are known to influence regional lung deposition.⁽⁴⁸⁾ However, in gamma scintigraphy the lungs are compressed into only two dimensions, and both central and peripheral zones are likely to include a mixture of large conducting airways, small conducting airways, and alveoli. The information provided by gamma scintigraphic indices of regional lung deposition is hence limited, and P/C or C/P ratios are relatively insensitive to differences between treatment regimens.⁽⁴⁹⁾ The three-dimensional imaging technique of single photon emission computed tomography (SPECT) allows the distribution in the lungs to be examined with greater precision. Regional deposition can either be assessed from transverse, sagittal, and coronal sections through the lungs, or by considering the lungs as a series of concentric shells.⁽⁵⁰⁾ In the latter model, the large bronchi are contained in the innermost shells, whereas the alveolated regions of the lungs are contained in the outermost shells. Consequently, several studies have shown that SPECT imaging can detect expected differences in regional lung deposition between two products more effectively than gamma scintigraphy.^(51,52) It was considered that a comparative study or studies comparing PK data with

regional lung deposition data from SPECT would be a way of understanding better how PK data responds to changes in regional lung deposition.

It was considered that such a study or studies would be investigative in nature. They would be "one-time" studies, undertaken to enhance our fundamental understanding, and would not be a required part of the documentation obtained by individual sponsors wishing to make manufacturing changes or market a generic inhaled product.

The session attendees discussed the outline of a study design, and reached the following broad conclusions:

Objective. To compare in a crossover study the PK profiles of aerosolized drugs deposited centrally or peripherally within the lungs. The deposition pattern could be adjusted by varying the aerodynamic particle size distribution and/or the mode of inhalation. Importantly, these aerosols should be administered in such a way that total lung deposition is the same for central and peripheral deposition patterns, allowing the effects on the PK profiles of a change in regional lung deposition to be determined.

Radiolabeling. Drug formulations would be radiolabeled by the addition of compound containing ^{99m}Tc, probably ^{99m}Tc-diethylene triamine pentaacetic acid (DTPA). Appropriate radiolabeling validation testing⁽⁵³⁾ would be needed, especially for a drug formulated as a suspension rather than as a solution.

Administration. These aerosols could potentially be administered by a number of delivery systems, including nebulizers attached to a technology that allows breathing mode to be varied,⁽⁵⁴⁾ an aerosol bolus system that delivers aerosol to a predefined lung depth,⁽⁵⁵⁾ or as monodisperse pharmaceutical aerosols made by spinning disc generator and then inhaled from a large tank.⁽⁵⁶⁾ It was considered that use of monodisperse aerosols [geometric standard deviation (GSD) <1.22] would give "cleaner," but less realistic, data. The duration of administration should be as short as possible, in order to prevent significant loss of radiolabel from the lungs by absorption or mucociliary clearance before imaging.

Drugs. It was considered that both a rapidly dissolving drug (e.g., albuterol) and a slowly dissolving drug (e.g., fluticasone propionate) should be tested. Gastrointestinal uptake of drug would be minimized by the administration of activated charcoal at appropriate time points.

Imaging. SPECT imaging of the lungs would be carried out immediately after administration using a gamma camera system with two or three rotating heads. At the present time, there are efforts to standardize methodology for radionuclide imaging studies, being made under the auspices of the International Society for Aerosols in Medicine (ISAM) and PQRI. It is envisaged that the agreed standardized SPECT methodology would be used in these one-time studies.

Endpoints. The regional distribution pattern in the lungs would be determined, either from transverse sections through the lungs, or by division of the lungs into concentric shells. Differences in PK parameters, including AUC and T_{max} , would be assessed over a period up to 12 h. If the PK

profile is similar for both central and peripheral deposition patterns, then this would suggest that PK data are relatively insensitive to factors that influence regional lung deposition. Conversely, if a difference in PK profiles is seen then the data would aid our understanding of likely difference in PK profiles that could arise as a result of differences in regional lung deposition in a BE study.

Study population. Healthy volunteers were considered to be suitable for these one-time studies to assess the relationship between regional lung deposition and PK profiles. Data in healthy subjects would probably be more discriminatory than data in patients, avoiding the inherent variability associated with using patients expressing a continuum of disease states. It would be important to ensure that the study was adequately powered.

Other options. The addition of a further study leg involving intravenous administration of the test drug was seen as an option, as this could allow absolute BA to be determined. However, it would be important that these additions to the study design should not compromise the main study objective.

A key practical issue not resolved was who would fund these one-time studies. It was considered that should PK methods be deemed acceptable for demonstrating BE between two inhaled products, then it could be in the interests of a consortium of companies to undertake the work.

As indicated above, the objective of the proposed study is exploratory. The absence of such studies should not impact considerations for acceptance (where applicable) of PK data as an indicator of *in vivo* BE of OIPs.

Session 2: Pharmacokinetics (PK) and In Vitro Assessment

Facilitators: Wallace P. Adams, R.Ph., Ph.D., U.S. Food and Drug Administration; Martin Oliver, M.R.Pharm.S., Vectura; and Guirag Poochikian, Ph.D., Poochikian Pharma Consulting Scribe: Svetlana Lyapustina, Drinkler Biddle and Reath

The objective of this session was to consider the importance of a relationship between *in vitro* data and PK in the establishment of BE, and whether *in vitro* data alone or in combination with PK data can adequately predict the regional lung deposition of an OIP.

From the breakout sessions there was no consensus that *in vitro* data plus PK data alone can establish BE. Factors limiting the usefulness of *in vitro* data include determination of the Aerodynamic Particle Size Distribution (APSD) by CI at a constant flow rate rather than guided by the inhalation flow profile, and use of a CI induction port such as the USP induction port^(57,58) commonly used for quality control (QC) testing, but that is not a physiologically realistic model of the human throat. Thus, studying APSD at multiple flow rates in the range reflective of the target population is necessary for BE, as APSD varies with flow rate. A physiologically relevant induction port for dose entry into the impactor was also considered important. Hypothetically, if *in vitro* measurements can be refined via the use of human throat casts and inhalation profiles that are reflective of the population, then an *in vitro* APSD measurement may result in an improved

in vitro-in vivo relationship, which would be more relevant to the patient.⁽⁵⁹⁾ For example, in a recent presentation at RDD 2010,⁽⁶⁰⁾ the CI flow rate was held constant, and yet an inhalation profile was used to fractionate the aerosol prior to entrance into the CI. The above considerations would be too complicated for QC purposes, but could provide the basis for a useful BE test assuming reproducibility issues associated with human throat casts could be adequately addressed.

Furthermore, clinical performance depends not only on the particle deposition (which is characterized via APSD under defined conditions) but also on the physicochemical properties of the active pharmaceutical ingredient (API) and the formulation characteristics. Establishing a system for OIPs similar to the Biopharmaceutics Classification System (BCS) developed for immediate release solid oral dosage forms⁽⁶¹⁾ would be useful, although such a system would need to include, besides solubility and permeability characteristics, the influence of the device and patient's inhalation model.

A question was raised that if an *in vitro in vivo* correlation (IVIVC) were established for a drug product, then a PK study would not be needed, and under this scenario whether BE could be concluded based on the demonstration of *in vitro* equivalence alone. Questions were also raised, but could not be answered in this session, as to what tests would be needed if an innovator introduced a change to their product (e.g., a change in the valve or filling method of a pMDI, or a change in the flow pathway of a DPI). It is not clear whether PK results would detect such a change, and more importantly, to what extent such a change would be relevant to the *in vivo* drug performance. The session also discussed the challenge that batch-to-batch variability in reference products can pose for establishing BE, especially for some parameters which change during the product's shelf life.

Another area of discussion addressed the relationship between QC tests and *in vitro* tests for equivalence. Even though these types of tests serve different purposes, they both need to be linked to clinical performance in order to be meaningful. Similarly, discussing specifications was viewed as important in the context of BE. Comments were made concerning drug product specifications and *in vitro* BE criteria and whether these two are consistent with each other.

The session attendees agreed that a number of *in vitro* tests should be considered for equivalence determinations in addition to CI and delivered dose uniformity. Physicochemical characterization is important—both of the API and of the excipients—because they can interact and change the performance characteristics of the product. In addition, spray pattern and plume geometry, surface properties, and device resistance are relevant for *in vitro* comparisons. Furthermore, comparable product performance should be confirmed over the product's shelf life as well as through-container life (e.g., a single-dose study at beginning and end of an inhaler unit). The product's age should be considered when making *in vitro* comparisons.

Session attendees from generic firms noted that matching the physicochemical properties of the API and excipients of the reference product may be important but is also challenging, as USP monographs do not contain sufficient information about their properties and drug product specifications.

It was suggested that *in vitro* links to PK should be established on a product-by-product basis. Specific require-

ments for such a linkage thus depend on the drug product formulation and device design. It was also suggested that in some instances, with a highly sensitive bioanalytical method and a rapidly dissolving drug with a well-controlled PK study design, it may be possible to provide good BE evidence by a range of *in vitro* tests combined with the PK data. There was an understanding that dissolution testing of inhaled drugs is a still-evolving area, and that currently there are no standardized tests predictive of the drug's fate in the lung. For example, it was mentioned that lung residence time (e.g., 1 vs. 24h) might dictate for which products the dissolution characteristics would be important to match for BE. Many physicochemical factors affect dissolution, such as lipophilicity of the API, particle size, geometry, surface area, API-excipient associations, and physiological conditions of the lung including mucus and other factors, which may potentially impact the PK of a product.

A comment was made that replicating the deposition pattern in the lung was important, although the connection between lung deposition and safety/efficacy is still poorly understood (e.g., a recent study showed that the spread in Peripheral-to-Central ratio within a study, using healthy volunteers and the same batch, was many-fold⁽⁶²⁾). It was also mentioned that no *in vitro* tests could be identified that would be predictive of regional lung deposition, and that data on monodisperse particles have been contradictory and far removed from realistic aerosols and inhalation patterns. Furthermore, local adverse effects would not be captured with PK or *in vitro* data. For these and other reasons, the general consensus was that currently *in vitro* testing alone is insufficient to establish equivalence of OIPs.

In summary, the main conclusions were:

- *In vitro* data alone are not sufficient to establish BE.
- Ideally, establishing a relationship between *in vitro* testing and PK is desirable. This relationship would need to be demonstrated for a specific product under consideration.
 - There was no consensus among the attendees in this session that a combination of *in vitro* data and PK data can establish BE because of the lack of a relationship between *in vitro* testing and PK. Studies establishing a relationship between PK and regional lung deposition (see previous session) could also address the lack of systematic data to relate *in vitro* to PK data.
- APSD is accepted as a critical BE parameter
 - Testing needs to be made more patient relevant (better throat models, more realistic airflow profiles, realistic ranges of pressure drop).
 - There is low probability that current compendial test platforms (e.g., USP induction port, cascade impactor operated at constant flow rate) will be able to achieve broadly useful IVIVC, but in the future some specific solutions may be found.

The following areas were considered in need of further discussion and consideration:

- There is a lack of systematic data to relate *in vitro* performance to PK data.
- A BCS approach for OIPs might be useful although it is unclear how device characteristics could be included.
- Ideally, even for QC purposes, an *in vitro* test should be relevant to the *in vivo* performance. However, it is noted

that in practice all QC tests recommended by the regulatory agencies are not proven for their relevance to *in vivo* performance.

- Variability in the reference listed drug may influence both *in vitro* and PK comparisons.
- The question of what constitutes clinically significant differences in any of the tests needs to be answered by clinicians before tests and standards are set.
- USP should be requested to update API monographs to include physicochemical properties of OIPs, as well as a new inlet design for cascade impactors.

Session 3: Pharmacokinetic (PK) and Pharmacodynamic (PD) Relationships

Facilitators: Hartmut Derendorf, Ph.D., University of Florida; Murray P. Ducharme, Pharm.D., Cetero Research; and Sandra Suarez Sharp, Ph.D., U.S. Food and Drug Administration; Scribe: Myra Herrle, Ph.D., Novartis

The goal of this session was to discuss the ability of the PK approach to detect differences in product performance in comparison with PD/clinical studies with the ultimate goal of gaining a consensus on the possibility of considering *in vitro* and PK studies as the only ones needed for the demonstration of BE of OIPs. The key questions asked of the session attendees and a summary of the discussion are provided below.

1. Does a study with a PD endpoint have better discriminating power than a PK study to distinguish between the performance of two formulations of the same active ingredient (in terms of equivalence/inequivalence)?

During the session it was discussed whether PD methods are sensitive enough for establishing BE of OIPs. It was pointed out that reproducible, clinically relevant, and sensitive PD biomarkers are currently a prerequisite for this approach. Where this may be possible for the evaluation of beta-agonists, this approach may currently not be possible for the evaluation of ICS. None of the currently explored or proposed PD measures/markers (such as eNO suggested for ICS by FDA, bronchitis eosinophilia suggested for ICS by Health Canada, or airway resistance parameters) have been shown at this time to have sufficient sensitivity and reproducibility to allow one to detect exposure differences at the sites of activity that are comparable to the typically accepted BE ranges (e.g., 90% confidence intervals around the geometric mean ratios of the test to reference exposure measures to be completely within 80–125%). As mentioned above, it is preferable to employ equivalence metrics to the respective exposure measures instead of the PD measures because of the large discriminating power of the former. Using the latter, should the evaluation be performed where the maximum response is obtained, further increases in exposure will not lead to further changes in the response. However, one would not consider two products to be BE if they produce the same response but with different exposures at the sites of activity. In short, these PD methods will only discriminate between two different formulations if huge differences exist.

There was some debate related to how fast drugs were absorbed. It was argued that the lungs are so well perfused that they should not be considered a “topical” organ like the

skin, for example, and that therefore once the corticosteroids existed in a solution at the site of activity that they would almost immediately appear in the systemic circulation. The debate appeared to be related to the rate at which different corticosteroids become solubilized at the site of action versus the actual absorption process. This debate, however, was not considered by the attendants to be directly relevant to the issue at hand and was therefore not pursued.

2. *What are the facts suggesting that differences in concentrations in the lungs (via a TE study) may not lead to differences in systemic concentrations and vice versa?*

Two different formulations of an ICS would have the same efficacy and toxicity if their concentrations at the sites of efficacy and toxicity (e.g., the "biophase") in the lung are the same. As it is not technically feasible to sample directly from the lungs, these concentrations are not possible to obtain experimentally. As shown in Figure 3, a TE study looks at endpoints that are indicators of potential differences or similarities at that location. On the other hand, a PK study indicates potential differences or similarities in terms of systemic concentrations. What is not completely known at this point is the link between the systemic concentrations and the concentrations at the biophase. Recognizing that both types of study (e.g., the TE or the PK study) may be imperfect at discriminating between two formulations of inhaled corticosteroids in terms of concentrations of the active moiety at the biophase, the session attendees were asked to comment on the following two key questions: (a) What are the facts suggesting that a clinical marker for potential differences in concentrations in the lungs (e.g., via a TE study using eNO or other marker) may not lead to differences in systemic concentrations? (b) What are the facts suggesting that differences in systemic concentrations may not lead to differences in the clinical marker for potential concentrations in the lungs (via a TE study using eNO or other marker)?

The audience was not aware of any study or data suggesting that question (a) above could happen. There was a case presented for budesonide (Flexhaler)⁽³⁾ in which it was reported that the products were equivalent based on PK measurements but were not equivalent based on a PD endpoint. It was argued that the products compared in the PK studies were different than those compared in the PD study, and therefore, the conclusions being presented were inadequate. An absence of data does not mean that the scenario in question (a) does not exist, but the reverse is also true. Indeed, it would be impossible to obtain data suggesting question (a) above if a PK study would be discriminative of what happens at the biophase.

The discussion then focused on the proposal to use systemic exposure measures (C_{max} , AUC) to assess pulmonary exposure. It was pointed out that there is also no known example in which two products would have been shown to be equivalent based on their PK while performing differently



FIG. 3. Relationship between TE studies and PK studies.

in any of their PD properties. On the other hand, two products that are not equivalent based on their systemic exposure could not be considered bioequivalent in general because they would present different systemic safety profiles even if their local exposure would be equivalent.

Small differences in pulmonary exposure are likely to result in respective systemic exposure changes in C_{max} and AUC. It was felt that if two products with negligible oral bioavailability show equivalent *in vitro* performance and equivalent systemic PK that it would be reasonable to assume that their pulmonary exposure could also be considered equivalent. This would suggest that systemic concentrations may reflect sufficiently what is and has happened at the site of activity or biophase. Some people felt, however, that this statement needs to be supported by data.

There was also a debate about the uncertainty of determining if differences in concentrations in the lungs (via a TE study) would lead to differences in systemic concentrations (especially for inhaled glucocorticoids) due to the current lack of a sensitive PD/clinical endpoint.

Other topics discussed that were not directly relevant to this session but considered to be important were:

- the lot to lot variability in the reference product and its implication on having favorable BE results;
- the basis for having $\pm 20\%$ acceptance versus other equivalence limits in general PK studies;
- whether or not the usual goalpost of equivalence need to be similar for these products;
- the importance of conducting or not conducting a replicate design;
- the problems and issues related to device similarity;
- the need to use or not use charcoal block in PK studies;
- the concerns about the potential utility of eNO as a PD marker.

Many of these issues were discussed in Session 4, thus were only briefly entertained. No consensus was reached on these issues.

3. *The audience was asked if they felt that for ICS and inhaled bronchodilators, a properly conducted PK study would suffice to prove BE without the TE with PD marker.*

The consensus among the attendees for both sessions was yes. The design of such a study was not a goal of the current session and is yet to be determined. What is considered as "properly" designed/conducted PK study is discussed separately in the next section.

Session 4: Effective Bioequivalence Pharmacokinetic (PK) Study Designs

Facilitators: John Davis, Ph.D., Pfizer; Bing V. Li, Ph.D., U.S. Food and Drug Administration; Partha Roy, Ph.D., U.S. Food and Drug Administration; and Tushar Shah, M.D., Teva Pharmaceuticals; Scribe: Susan M. Holmes, M.S., GlaxoSmithKline

The objective of this session was to identify the important factors and considerations in the design of BE PK study for OIPs. These factors include the possible means of distinguishing drug absorption between the pulmonary route and the nonpulmonary route, appropriate subject population,

key PK metrics, and BE acceptance criteria, statistical approaches, and additional considerations for multiple strength OIPs. The key questions asked of the session attendees and a summary of the discussions are provided below.

1. *How to distinguish drug absorption from the pulmonary route and from the nonpulmonary (e.g., gastrointestinal) route?*

A problem inherent in the use of PK methods as a means of assessing the delivery of drugs to the lungs is that systemic drug levels can result not only from drug absorbed through the lungs, but also from drug which is absorbed via nonpulmonary routes, especially absorption through the gastrointestinal (GI) tract due to the swallowed fraction and buccal absorption following oral inhalation. The audience agreed unanimously that separation of nonpulmonary absorption from pulmonary absorption is key to interpreting systemic exposure following oral inhalation. The audience concurred that for drugs with measurable oral BA, activated charcoal block method is regarded as the most suitable approach for distinguishing drug absorption between lung and nonpulmonary routes. It was also felt that for drugs with negligible (e.g., <1%) oral BA, conducting a charcoal block study may not be necessary as it is assumed that the amount of the drug in the systemic circulation is a direct result of the fraction of the drug reaching the lungs.

Validation of the charcoal block method was the topic of intense discussion. Only few attendees within the two sessions had experience with conducting charcoal block studies. Questions were raised whether all grades and types of activated carbon are the same or whether adsorption efficiency of activated charcoal is dependent on physicochemical properties of the charcoal, that is, particle size, absorptive surfaces, etc. The general understanding seems to be that because it is typically used in large excess, these attributes may not be critical. It may be important to find out the impact of gastric pH and food on the adsorptive efficiency of the charcoal. The applicability of this method for the regulatory purpose of determining BE in the context of lung delivery may still be in question due to lack of unequivocal evidence for complete blockage of absorption of the drug from nonpulmonary routes. According to some in the audience, the efficiency of charcoal block also may vary among subjects within the same study, and hence may render BE evaluation less robust. Therefore, in view of some uncertainties around the charcoal block method, some session attendees continued to hold the view that the current FDA weight-of-evidence approach seems an appropriate compromise. However, the majority agreed that there is enough prior knowledge among the members to rely on this method to accurately delineate pulmonary absorption of the inhaled product. The EMA now accepts PK data from charcoal block studies for regulatory filings to assess pulmonary deposition.⁽⁸⁾ Future experience from European submissions may be able to address the reliability of the method.

The audience also wondered whether a decision tree, similar to the BCS approach for oral drugs, can possibly be created in order to determine the situations when a PK study with charcoal block needs to be conducted. Many in the audience felt that a testing paradigm needs to be developed to establish an IVIVC for inhaled drugs, which may eventually help obviate the need for PK studies with charcoal block.

In conclusion, the general consensus for now was that charcoal block is a useful tool to block GI absorption of OIPs and therefore can be used effectively to measure drug absorption exclusively via the pulmonary route. However, the charcoal block method needs to be adequately validated when it is used for regulatory purposes. It was also generally agreed that a separate PK study without charcoal block should be conducted in conjunction with a charcoal block study in order to determine total systemic exposure as a result of both pulmonary and nonpulmonary drug absorption.

2. *Which subject population should be considered as appropriate in PK BE study design for OIPs?*

The choice of study population in PK BE study for OIPs was discussed. For most orally administered drugs, a healthy subject population is chosen for BE study because it is sensitive and discriminating. For oral dosage forms, the physical processes of drug absorption are usually the same in patients as they are in healthy subjects. It was mentioned that such might not be the case for OIPs where, depending upon drug distribution within the lungs, local efficacy, and/or safety can be variable.

For OIPs, the question discussed was whether there is any evidence that the presence of lung disease changes the relative exposure of the same drug from two different OIPs. Healthy subjects are to be used if the disease has no effect on relative BA between two OIPs. Patients may be used under the circumstances where the disease changes the relative systemic exposure of the two OIP formulations. It was discussed that for a given formulation, healthy subjects exhibit comparatively higher absolute systemic exposure compared to asthma patients due to difference in C/P deposition. This difference would not be an issue when evaluating BE if the relative systemic exposure between the two OIPs is the same on the healthy subjects and patients. There was a great deal of uncertainty expressed by the audience in applying this principle for all drugs and for all indications. Unlike oral medications, drug delivery is an important factor while determining therapeutic equivalence between two OIPs. Drug delivery to the lungs often depends on patient-device interaction, and that may differ between the innovator and the generic products. Some in the audience expressed the opinion that to compare two drug products and establish that one can be substituted for another without any clinical differences, the BE study should be conducted in the population for which the products are intended to be used.

It is generally accepted that healthy subjects present a more controlled and simplified system, and using a patient population for the determination of BE between two OIPs adds a level of complexity that may be often difficult to overcome. In the case of ICS, the audience debated whether or not PK results from an asthma population can be applicable to the chronic obstructive pulmonary disease (COPD) population and vice versa. The patient population is usually exposed to concomitant medications, and hence data may be more variable. The audience wondered whether there are any reports of studies conducted to compare two OIPs in both healthy subjects and patient population. Some pointed out that for completeness, PK studies should be conducted in both healthy subjects and patients.

In conclusion, the majority agreed that healthy subjects offer a reasonable population for comparative data, and hence should be used for BE evaluation of OIPs. However, in situations where disease has an impact on relative exposure between two products, PK data may be needed in patients in lieu of or in addition to healthy subjects.

3. *What PK metrics should be considered as the relevant or key parameters in BE determination for OIPs? What BE acceptance criteria are appropriate in evaluating the BE of OIPs?*

Over the years, FDA has recommended C_{\max} and AUC as the means of quantifying systemic exposure in BE studies.⁽⁶³⁾ Similar concepts are being debated to see how the same PK metrics can be applied to compare active drugs delivered at the pulmonary site of drug action from different inhaled products. From the discussion, it is generally perceived that both C_{\max} and AUC are the PK measures of choice to quantify the pulmonary available dose. Other parameters such as Mean Residence Time (MRT) and T_{\max} may also act as supportive data. It is mentioned that differences in regional distribution as reflected in the C/P deposition might be captured in a standard BE design using PK measures of C_{\max} and AUC. Centrally deposited, slowly dissolving drugs tend to be more efficiently removed by mucociliary clearance, resulting in smaller C_{\max} and AUC compared to peripherally deposited and fast dissolving drugs.

Some session attendees argued that AUC reflects not only drug absorption but also clearance. However, considerations for clearance are not relevant to BE evaluation as the same active ingredients are monitored, and hence, systemic clearance is assumed to remain unchanged because it is independent of dose, delivery, and the product formulation. Getting accurate estimates of C_{\max} and T_{\max} or some measures of early exposure is challenging because lung absorption is generally rapid for many drugs, and plasma levels sometimes fall on the borderline of analytical limitation. Therefore, such measures can exhibit large variability (both inter- and intraindividual). To overcome limits of detection, PK studies are often conducted by administering supratherapeutic doses, that is, several puffs of the medication. In these cases, initial blood sampling may be difficult to optimize in order to capture a true C_{\max} and T_{\max} after inhalation of multiple puffs which need some length of time to be completed.

Some session attendees stressed the need to look at the additional PK parameters rather than focusing on PK measures of C_{\max} and AUC only. The audience debated the importance of considering early exposure measurements such as T_{\max} and MRT as alternate or additional PK measures to establish equivalent drug concentration at the pulmonary site of drug action. However, the majority viewed these measures to be less robust. The majority also concluded that C_{\max} is the most sensitive and robust parameter to test for differences in the absorption rate. Overall, a consensus has been reached that C_{\max} and AUC are the most appropriate PK parameters for most inhaled drug products and indications. For some specific cases, partial AUC may also be considered.

4. *What study design is recommended for assessing the BE of OIPs? What statistical approach should be utilized?*

FDA generally recommends the standard two-formulation, two-period, two-sequence crossover design for conventional oral dosage forms to demonstrate BE. Single-dose studies are preferred over multiple-dose studies because they are generally more sensitive in assessing release of the drug substance from the drug product into the systemic circulation. The audience agreed that such thinking is also applicable for OIPs. However, unlike oral drugs, the issue of blinding was raised in the discussion and some attendees thought that this may be important to consider for OIPs. Because delivery of the drug product from an OIP is intimately connected to the device, open-label design may impact the patient handling of the device and therefore the delivery efficiency of the drug product. However, if this is the case, one can also argue that open-label studies may be more important as it captures a real-life clinical use situation. Moreover, it is difficult to guess how trial participants will interact with a test device compared to an approved reference product and how that will impact the delivery of the drug to the lungs. However, blinding is operationally not easy considering the fact that a double-dummy design needs to be implemented to achieve an adequate double-blind. In the end, no consensus was reached regarding blinding. There was some discussion regarding the inclusion and exclusion criteria for the PK studies. It is generally agreed that the same set of criteria typically employed in studies for oral drugs can be implemented with few exceptions as needed. Lung function data is often collected in PK studies when conducted in the patient population for OIPs as part of screening to ensure that subjects with compromised lung function do not participate in these trials. However, this type of screening would not be necessary with studies conducted in healthy volunteers. Everybody agreed that smokers needed to be excluded from these studies.

The audience discussed the statistical approaches used in the assessment of BE. Statistical analysis for AUC and C_{\max} is based on the principle of average BE that involves the two one-sided tests procedure to determine whether the average values for AUC and C_{\max} for the test and the reference products were comparable. This involves the calculation of a 90% confidence interval for the ratios of the averages for the test and the reference products that are required to fall within the 80–125% limits to conclude BE. The audience generally thought that these BE limits can be applied for OIPs. When the variability of the reference product is documented to be high, a reference scaling approach can be a reasonable alternate to establish BE.

5. *What additional considerations should be taken in the cases of multiple strength OIPs?*

The members of the audience floated the idea of “bio-waiver” when considering multiple strengths. The session attendees wondered whether adopting qualitatively (Q1) and quantitatively (Q2) the same inactive ingredients between the test and reference products, would provide the necessary confidence to waive the BE studies of the bracketed strengths. Some mentioned that without an established IVIVC and BCS-like classification, a pathway for bio waiver may not be feasible. For complex dosage forms and delivery systems such as OIPs, formulation proportionality in terms of dose delivered to the patient is not easy to achieve. In addition, the delivery device may be different for different

strengths, and the dynamics of powder inhalers may also be different for different strengths. However, it is possible that in the future, a more abbreviated testing scheme may be crafted for intermediate or lower strengths, once the critical attributes of the product are understood. At this moment, the majority agreed that BE PK studies need to be conducted for all product strengths in addition to documenting comparability *in vitro*.

Workshop Conclusions

This workshop reviewed the current approaches and made recommendations for considerations for using PK as a main tool to establish local delivery BE of OIPs for NDAs, ANDAs, and postapproval changes. The outcomes represented the current scientific understanding and highlighted the areas in which further work is needed. Using the presentations from RDD 2010⁽¹⁻⁵⁾ and the case studies as a framework, in-depth discussions from the breakout sessions identified areas of consensus and areas where additional scientific understanding is needed.

In Session 1, it was generally agreed that regional lung deposition is relevant with respect to safety and efficacy of OIPs. Although the use of 3D imaging was regarded as unsuitable for routine bioequivalence studies, it was believed that it is an important technique within an exploratory study to assess whether PK can identify differences in the regional deposition. The design considerations for a study utilizing imaging to understand how PK profiles respond to changes in regional deposition within the lung were outlined. The objective of the proposed lung deposition study is to fill certain gaps in knowledge; such studies cannot be part of the BE testing paradigms partly due to necessary "alteration" of the reference product for radiolabeling. The study results would be used to validate the possible use of PK in demonstrating equivalence of local delivery for OIPs. However, funding was recognized as being a major barrier to conducting such a one-time investigational study.

The Session 2 attendees agreed that *in vitro* data alone is not sufficient to establish BE. Moreover, there was no consensus in Session 2 that a combination of *in vitro* data and PK data can establish BE because of the lack of a relationship between *in vitro* testing and PK. Ideally, a relationship between *in vitro* testing and PK is desirable, and this relationship would need to be demonstrated for each specific product under consideration. Studies establishing a relationship between PK and drug deposition should also include *in vitro* approaches as this would generate needed systematic data to relate *in vitro* to PK data. APSD was generally accepted as a critical BE parameter. However, to achieve a broadly useful IVIVC, the *in vitro* testing needs to be made more patient relevant (e.g., better throat models, more realistic airflow profiles, realistic ranges of pressure drop). There is low probability that current compendial test platforms will be able to achieve such IVIVCs; however, some specific cases may emerge.

There was consensus by the Session 3 attendees that PK is more discriminative than PD in part because the difference between the low and high dosing regimen in equivalence studies using clinical or PD endpoints generally are typically two- to fourfold, whereas a standard PK study conventionally can assume equivalence with relative bioavailabilities

of ± 20 percent. In addition, for ICS, no PD marker is currently recognized as optimal. The session attendees were unaware of any data suggesting that differences in concentrations in the lungs (via a TE study) would not result in differences in systemic concentrations. It was generally agreed that TE studies using PD endpoints for certain drugs (e.g., ICS) may lack sensitivity to differentiate between two formulations in terms of local concentrations at the site of action. On the other hand, systemic PK data may provide information on potential differences in pulmonary deposited dose, pulmonary residence time, and information on the C/P deposition ratio (at least for slowly dissolving drugs). Thus, PK can be more discriminative. The ultimate question is: do systemic concentrations reflect comparative drug delivery to the site(s) of activity in the lung? There was consensus by the session attendees that for ICS and inhaled bronchodilators, a properly conducted PK study may be a reasonable approach to establish BE without the TE study with PD marker. However, what constitutes a "properly conducted study" broadly applicable to OIPs remains to be determined.

In Session 4, blocking buccal and GI absorption when these routes contribute significantly (e.g., >1%) to overall systemic levels was judged to be necessary by the attendees. Charcoal block is commonly used. However, validation of the charcoal block is necessary, but not commonly performed. There was a consensus that use of healthy volunteers is more discriminating than patients; making the BE conclusion more robust. For PK studies, the standard metrics (e.g., AUC, C_{max}) using traditional acceptance criteria (e.g., a 90% confidence interval and BE limits of 80–125%) were judged to be appropriate. Single-dose, crossover studies using average (not population) BE was preferred. Appropriate protocol rigor should be utilized to ensure adequate sampling to correctly obtain C_{max} and early AUC time point data. Finally, every dosage strength offered should be subjected to BE PK study.

Currently, OGD typically requests *in vitro*, PK, and PD/clinical studies for demonstrating BE for the approval of multisource OIPs. In the case of development/postapproval changes for innovator OIPs, the information required depends on the complexity of the change and should be discussed with the Agency. Generally, for minor changes (such as those defined as Level 1 according to the SUPAC guidances⁽⁶⁴⁻⁶⁶⁾), comparative *in vitro* information may be sufficient. Complex changes (such as those defined as Level 3 according to the SUPAC guidances) require comparative bioavailability data and PD/clinical studies. It has been recognized, though, that the sensitivity to detect differences in product performance generally decreases as one moves from *in vitro* testing to PD/efficacy measurements. The greatest challenge in following this approach with some OIPs (particularly inhaled corticosteroids) is the demonstration of a dose-response relationship in PD studies, without which the bioassay has no value in the determination of BE. The workshop demonstrated that a greater willingness seems to exist among discipline experts and regulators to explore approaches to address the gaps in knowledge necessary for the acceptance of PK data as the key determinant of *in vivo* equivalence of locally acting OIPs. If accepted, the suggested approach (PK alone or in conjunction with *in vitro* tests) could potentially be applied to demonstrate BE of certain orally inhaled drugs.

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List of Abbreviations

ANDA	Abbreviated new drug application
API	Active pharmaceutical ingredient
APSD	Aerodynamic particle size distribution
AUC	Area under the concentration-time curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
C/P	Central to peripheral ratio (inverse of P/C)
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CI	Cascade impactor; cascade impaction
C _{max}	Maximum plasma concentration
CMC	Chemistry, manufacturing, and controls
COPD	Chronic obstructive pulmonary disease

DPI	Dry powder inhaler
DPTA	Diethylenetriamine pentaacetic acid
EEG	Electroencephalogram
EMA	European Medicines Agency
eNO	Exhaled nitric oxide
EU	European Union
FDA	Food and Drug Administration
FEV ₁	Forced expired volume in the first second
FF	Formoterol fumarate
FP	Fluticasone propionate
FPM	Fine particle mass
GSD	Geometric standard deviation
HFA	Hydrofluoroalkane
HPLC	High-performance liquid chromatography
ICS	Inhaled corticosteroids
INN	International Nonproprietary Name
ISAM	International Society for Aerosols in Medicine
IVIVC	<i>In vitro-in vivo</i> correlation
MRT	Mean residence time
NDA	New Drug Application
OGD	Office of Generic Drugs, FDA
OIP	Orally inhaled product
P/C	Peripheral to central ratio (inverse of C/P)
PD	Pharmacodynamics
PK	Pharmacokinetics
pMDI	Pressurized metered dose inhaler
PQRI	Product Quality Research Institute
QC	Quality control
R	Reference drug product
RDD	Respiratory drug delivery
RPID	Reservoir powder inhalation device
SABA	Short-acting beta-agonist
SFC	Salmeterol xinafoate/fluticasone propionate combination product
SPECT	Single photon emission computed tomography
SUPAC	Scale-up and post-approval changes
T	Test drug product
T _{max}	Time to reach maximum plasma concentration (C _{max})
TE	Therapeutic equivalence
USP	United States Pharmacopeia

